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EDITORIAL

Why more attentions to fetus in cases of intrahepatic cholestasis of pregnancy?

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a peculiar disease in middle-late pregnancy with the pathological characteristics of hepatic capillary bile duct silts and is accompanied by clinical presentations of pruritus and bile acid (BA) elevation in serum. Maternal outcomes for patients diagnosed with ICP are usually good. However, fetal outcomes can be devastating with high frequencies of perinatal complications. Patients with ICP generally have an early delivery due to fetal complications. The current hypothesis is that ICP has higher frequencies of fetal complications due to high concentrations of BA which has toxic cellular effects to many organs. In lungs, it destroys the AT-II cells, decreasing phospholipids synthesis leading to the alveolar capillary permeability to increase and pulmonary surfactant to decrease. In heart, cholate can cross into the fetal compartment and causing fetal arrhythmias and decreased contractility. In the nervous system, high BAs can cause nerve cell denaturation and necrosis, mitochondria edema and membrane dissolve. In the placenta, high BA concentration can cause edema of the villous, decrease number of villous, intervillous thickening and balloon formation. In addition, high total BA can result in chorionic vein constriction and impaired fetal adrenal function.

Key words: Intrahepatic cholestasis of pregnancy; Bile acid; Perinatal outcome; Fetal lung; Fetal heart

Core tip: Fetal outcomes for patients diagnosed with intrahepatic cholestasis of pregnancy can be devastating with serious complications. Advances in our understanding of the reasons that can cause severe fetal complications, such as sudden fetal death, slowed fetal lung maturity, perinatal nervous system injury, distress, and neonatal asphyxia, will provide some hints towards the basic etiology of this disorder. We look forward to a time that early diagnosis will be made and laboratory tests will be carried out to monitor these fetal conditions. I would suggest that more attention should be paid to the fetus which contributes to improve fetal outcomes.

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a maternal metabolic disease affecting up to 5% of pregnancies[1]. It occurs in the second and third trimester, and is characterized by intense pruritus and an elevation in serum bile acid (BA) concentrations. Maternal outcomes for patients diagnosed with ICP are usually good. However, fetal outcomes can be devastating with complications of pre-

mature delivery, fetal distress, neonatal asphyxia, neonatal respiratory distress syndrome, neonatal multi-system damage, and fetal death[2,3]. Thus, early recognition, treatment, and timely delivery are imperative. From the maternal viewpoint, the main symptom is the intense pruritus, which may become intolerable leading to an early delivery[4]. On the fetal viewpoint, it is more concerning since the high risk of perinatal complications which can result in fetal demise. Thus, many doctors would advocate induction at 37 wk[5].

SEVERE INFLUENCES OF ICP TO FETUS

Sudden fetal death

One of the most worrisome aspects of ICP is the possibility of sudden fetal death[6]. Possible explanations for sudden fetal death are taurocholate crossing into the fetal compartment and causing fetal arrhythmias and decreased contractility[7]. Other studies have noted an increased P-R interval in human fetuses affected by ICP[8]. Intrauterine fetal demise is also associated with ICP, especially when the total BA (TBA) level is critically elevated, but it rarely occurs prior to 36 weeks' gestation. With the risk for sudden fetal death, it becomes a dilemma how to monitor and when to deliver. Since fetal death rarely occurs before 36 weeks' gestation, many doctors favor delivery when it reaches to 37 wk gestation[9].

Lung maturity

ICP usually accompanied with slowed lung maturity. It is associated with fetal distress, neonatal asphyxia, neonatal respiratory distress syndrome, and cholic acid pneumonia[10]. In Glantz's study, fetal asphyxia was related to BA concentration with the critical level of 40 mmol/L or greater[11]. The pulmonary pathological changes consist with neonatal pulmonary hyaline membrane disease, light transmittance of the lung reducing, swelling, widely atelectasis, diffuse pulmonary hyaline membrane disease[12,13]. In one of our case control studies, amniotic fluid surfactant and lamellar body was significantly decreased and fetal lung area/body weight ratio was significantly reduced in ICP patients. In addition, fetal blood TBA showed a negative correlation to the surface active substances-phospholipids production. In Shi *et al*[14] study, cholic acid can cause a dysfunction in the synthesis of surface active substances in the lung. He found that high BA can lead to immature fetal rat lung with the pulmonary morphological changes of smaller alveolar cavities, thickening alveolar intervals, local atelectasis, and most cells fall off from the wall. Furthermore, pulmonary tissue was found to have heavy density and diffuse bleeding lesions.

Nervous system

Severe and moderate ICP can cause perinatal nervous system injury and the severity of injury is associated with the TBA level. Pathological changes include immaturity of the hepatoencephalic barrier and presents with endothelial holes, thinning of the base membrane leading to an increase in permeability[15]. Animal experiments demonstrated that high BAs can cause nerve cell denaturation and necrosis, mitochondria edema and membrane damage[16]. By measuring umbilical artery blood pH, lactic acid, and color Doppler on fetal cerebral artery blood flow, it was found that ICP can cause fetal acidemia and reduced fetal cerebral blood flow[17].

Fetal distress and neonatal asphyxia

ICP has higher frequencies of fetal distress and neonatal asphyxia. It is considered these may be associated with the pathological changes in the placenta. The morphology of placentas from the rodent model of ICP is markedly abnormal. Human and rodent studies have shown that transplacental transfer of BAs is impaired in ICP. High BA concentration results in placental alteration with increased syncytial knots, reduced collagen, edema of the villous, decreased number of villous, intervillous thickening and balloon formation[18]. Geenes found that ICP placentas have an increase in the number of syncytial knots, and that these can be reproduced in an *in vitro* model exposed to the BAs taurocholic acid and taurochenodoexycholic acid[19]. Ding studied the morphologic ultrastructure of human placental syncytial cells and reported that ICP placenta has impaired cellular organelle, resulting in the abnormal physiological function of syncytial cells, and affecting the synthesis and transportation functions of the placenta[20].

Vascular system

In addition, high TBAs can increase the intracellular calcium concentration resulting in chorionic vein constriction and can lead to the increase of placental circulation resistance[21]. It can cause fetal adrenal dysfunction and influence the production of vascular aldosterone and corticosterone[22].

LABORATORY MONITORING OF ICP

Many laboratory abnormalities can be seen in ICP. The most specific and sensitive marker of ICP is TBA levels greater than 10 μmol/L[23]. In addition, the cholic acid level is significantly increased while the chenodeoxycholic acid level is mildly increased, resulting in an elevation in the cholic/chenodeoxycholic acid level ratio[24,25].

Recommended laboratory studies for the diagnosis of ICP include monitoring total serum BA levels, cholic acid, chenodeoxycholic acid (to evaluate the cholic/chenodeoxycholic acid ratio), total bilirubin, transaminases, GGT, PT, PTT, and INR. These laboratory studies are used in conjunction with physical examination and symptoms to make a diagnosis of ICP. Once a diagnosis of ICP has been made, TBA levels can be followed every 2-3 wk to guide therapy and timing of delivery. In addition, coagulation studies and transaminase levels should be monitored to measure progression of the disease.

MANAGEMENT OF FETUS

More attention should be placed on the fetus. Tests for the fetus, including umbilical artery Doppler studies, bio-

physical profile, and nonstress tests, should be performed to reduce the risk of stillbirth[26]. One study demonstrated that increased fetal testing and scheduled induction with documentation of fetal lung maturity in patients with ICP lessened perinatal mortality rates compared with patients who were not tested[27]. Delivery should be induced at 37 wk. If deliver prior to 37 wk occurs, amniocentesis for fetal lung maturity is necessary. If meconium is present at the time of amniocentesis, delivery is indicated regardless of the fetal lung maturity results. Delivery should proceed without an amniocentesis if the fetal monitoring is nonreassuring.

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EDITORIAL

Mirabegron, a novel, non-antimuscarinic drug for the overactive bladder: An up-to-dated review

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Abstract

Mirabegron opened a new era in the treatment of overactive bladder (OAB). For the first time physicians dealing with OAB have an effective alternative to the pharmacological mainstay of the therapy for this disorder, the antimuscarinic drugs. This first-in-class, potent β3-adrenoceptors agonist has recently received approval by regulatory authorities in Japan, United States and Europe, based on the favourable efficacy-tolerability profile demonstrated in multiple randomized, multinational, controlled trials, both short and long-term. There is substantial consistency through the studies in reporting the cardiovascular safety of treatment with mirabegron. The main advantage of mirabegron is the placebo-like incidence of classic adverse effects caused by antimuscarinics, dry mouth and constipation, that is expected to improve long-term adherence of patients to treatment. Mirabegron can be used in patients with contraindications to antimuscarinics and in those who discontinued previous antimuscarinic therapy. Herein, we reviewed the published literature on mirabegron, focusing on the rationale of β3-agonism for OAB treatment and on the preclinical and clinical evidence of efficacy and safety available on this new pharmacological principle.

Key words: Mirabegron; β3-adrenoceptor agonist; Antimuscarinics; Overactive bladder; Urinary incontinence

Core tip: Mirabegron is a first-in-class, potent β3-adrenoceptors agonist that has been proven effective in the treatment of overactive bladder (OAB) based on multiple randomized multinational trials. The safety-tolerability profile of treatment with mirabegron has been extensively studied. The placebo-like incidence of classic adverse effects caused by antimuscarinics should improve long-term adherence to treatment with this new drug. Mirabegron can be an alternative in patients with contraindications to antimuscarinics or that discontinued previous antimuscarinic therapy. An updated review of the rationale of β3-agonism for OAB treatment and evidence of efficacy and safety of mirabegron is presented.

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INTRODUCTION

Overactive bladder (OAB) is a syndrome characterized by the key symptom of urinary urgency, with or without urinary incontinence, usually associated with urinary frequency and nocturia[1]. Detrusor muscle overactivity (DO) is often, but not always, the underlying condition[2]. The differential diagnosis with stress or mixed urinary incontinence, based on clinical examination and urodynamic investigations, is of utmost importance in order to plan the more appropriate therapeutic strategy[3].

The prevalence of OAB is high in western countries and increases with age[4]. This bothersome and multifac-

torial bladder disorder that significantly impairs patient's health-related quality of life (HRQL), is also associated to significant comorbidities[5] and high socioeconomic costs[6].

The treatment of OAB is aimed to achieve symptom relief and improvement of HRQL. First-line treatment relies mainly on lifestyle advice and bladder training, functional electrical stimulation, clean intermittent catheterization and pharmacological treatment. Neuromodulation, intradetrusor botulinum toxin injection and surgery represent more invasive, second-line treatment options.

Antimuscarinics are the mainstay in the pharmacological treatment of OAB[7]. However, these drugs are merely symptomatic and patients with unsatisfactory response due to lack of efficacy are frequent. Moreover, antimuscarinics are not completely bladder-selective causing bothersome adverse effects (AEs), including dry-mouth, nausea, constipation and central nervous system AEs. Because of these limitations, long-term adherence to treatment with antimuscarinics is low[7-10].

The limitations of antimuscarinics prompted the research of novel pharmacological principles with a distinct mechanism of action and aimed to improve bladder storage phase symptoms, without affecting the voiding phase, and with a better tolerability profile[11]. Among innovative peripherally acting compounds, several selective β3-adrenoceptors (β3-ARs) agonists have undergone clinical proof-of-concept studies including ritobegron (also known as KUC-7483 and as KUC-7322 for its active metabolite), solabegron (also known as GW427353) and mirabegron (also known as YM178).

Mirabegron reached the final stages of pharmacological development and has been recently granted marketing approval in Japan, United States (Myrbetriq™) and Europe (Betmiga™). The drug is formulated as Oral Controlled Absorption System (OCAS) tablets. OCAS is a hydrophilic gel-forming matrix tablet, a modified release system (also referred as extended-release or prolonged-release) that allows a release of drug from the tablets for an extended period, with more steady absorption, and avoids high peak-to-trough fluctuations in plasma concentration and the considerable food effect of immediate-release formulations. The drug product is available in two dosage strengths of 50 mg (recommended to-be-marketed, once daily dose, orally with or without food) and 25 mg (for patients with severe renal or moderate hepatic impairment).

Thereafter we reviewed experimental and clinical data on mirabegron by searching English-language full papers and abstracts published by May 2013 in MEDLINE, clinicaltrials.gov, controlled-trials.com, clinicaltrialsfeeds.org, and proceedings of international scientific meetings.

RATIONALE OF β3-AGONISM FOR OAB TREATMENT

The fixation of noradrenalin to β-ARs activates the molecular pathway of cyclic adenosine monophosphate (cAMP) that is the most important mediator of detrusor muscle compliance and relaxation in mammalian species, although there is evidence suggesting that a cAMP-independent, potassium channels-mediated mechanism may play an important role[12-15].

β1-, β2- and β3-ARs have been demonstrated in both animal and human urinary bladder, although, β3-ARs represent the far most abundant subtype in the human bladder[16,17]. β3-ARs have been found to be highly and preferentially expressed on bladder tissues including urothelium, interstitial cells, and detrusor smooth muscle[12,18-21].

Detrusor muscle relaxes in response to β-AR agonists in a dose-dependent manner and human studies showed that this effect is mediated mainly through β3-AR[17,22-25]. Targeting β3-ARs has a significant effect on reducing spontaneous uncoordinated detrusor contractile activity in human bladder[23]. Interestingly, preliminary research showed that 49% of patients with idiopathic DO have a tryptophan 64 arginine mutation of the β3-AR gene that may be a useful genetic marker[26].

Animal studies demonstrated that both non-selective and selective β3-AR agonists were able to increase bladder capacity and inhibit neurogenic or experimentally-induced DO and bladder outlet obstruction (BOO)-associated OAB, without changing voiding detrusor pressure or increasing residual volume[17,21,27-30].

Although β3-ARs on detrusor muscle cells were believed to be the main site of action of β3-AR agonists in treating OAB, the main *in vivo* effect of these compounds could be on the afferent side of the micturition reflex, by a direct inhibition of afferent nerves or of the myogenic/urotheliogenic mechanisms involved in the promotion of afferent activity. In fact, there is evidence that selective β3-AR agonists can (1) inhibit the bladder filling-induced activity of mechanosensitive Aδ-fibers (and C-fibers at higher doses inducing retention) in rats[31], and (2) reduce autonomous bladder non-voiding contractions of myogenic origin[27] that can generate localized microcontractions facilitating afferent nerves activity[32]. It has been also reported that a direct influence on urothelial functions, such as the release of NO and urothelial-derived inhibitory factor, can contributes to the promotion of detrusor relaxation *via* the inhibition of C-fiber activity[33-35]. Finally, experiments in spinal cord transected rats showed that β3-AR agonists can directly inhibit bladder afferent activity[36].

As the main effect of β3-AR agonists *in vivo* remains unclear, so the detailed mechanism of action by which these drugs exert their beneficial effect in DO and OAB has not been completely established and further studies are needed. However, taken together, the available experimental evidence supports β3-AR agonism as a novel pharmacological principle intended for the treatment of OAB, including storage symptoms secondary to BOO[37,38].

PRECLINICAL EVIDENCE ON MIRABEGRON

Mirabegron is a novel, once-daily, orally active, first-in-class, potent and selective β3-AR agonist. Cellular studies

showed that mirabegron stimulates the intracellular cAMP accumulation by acting with full agonistic activity and high efficacy on human β3-ARs; on the other hand, its efficacy on β1- and β2-ARs was very low (446 times less selective for these receptors in Chinese hamster ovary cells)[30,39].

Affinity for human β3-AR did not appear to be altered by several gene variants of the receptor[40]. Studies on isolated strips of human detrusor muscle demonstrated an efficacy of mirabegron comparable to that of isoprenaline, a non-selective β3-AR agonist[30]; this efficacy of mirabegron was maintained in isolated detrusor strips obtained from control patients and patients with BOO or BOO-associated DO[41]. More interestingly, mirabegron induced a dose-dependent reduction of the frequency of rhythmic bladder contractions when given intravenously to urethane-anesthetized rats; however, unlike anticolinergics, it did not significantly decrease the contraction amplitude[30]. In rat model of bladder dysfunctions, mirabegron was effective in improving storage-phase urodynamic parameters, without affecting voiding-phase parameters, such as micturition pressure, threshold pressure and residual volume; this pharmacological profile should decrease the risk of causing urinary retention[39,42,43]. While mirabegron reduced the frequency of non-voiding bladder contractions, anticolinergics mainly reduced their amplitude[44].

In vivo experiments also showed that, during bladder filling, mirabegron can directly inhibit in a dose-dependent manner the mechanosensitive bladder afferent nerves firing of both Aδ- and C-fibers, that was more remarkable for Aδ-fibers[45]; in this study, mirabegron also inhibited both bladder microcontractions and Aδ-fibers activity at doses that do not decrease bladder pressure, suggesting a possible additional action of β3-AR agonists as therapeutic agents for OAB or other bladder sensory disorders.

The aforementioned findings prompted several trials aimed to investigate efficacy, safety, tolerability and discontinuation rate of mirabegron in the clinical setting of OAB patients. In particular, the development of mirabegron by Astellas Pharma Inc. (Ibaraki, Japan) involved an extensive clinical development and clinical pharmacology programs including 41 studies[46].

CLINICAL EVIDENCE OF EFFICACY

Proof-of-concept and dose-finding studies

Mirabegron has been extensively studied in more than 10000 individuals and about 40 clinical studies have been performed over the last 10 years. Safety and efficacy in OAB patients were evaluated in 5 global, 12-wk trials: two phase Ⅱ (Clinicaltrials.gov number: NCT01604928 and NCT00337090) and three pivotal phase Ⅲ (NCT00689104, NCT00662909, NCT00912964) studies that compared mirabegron with placebo and with tolterodine (a commonly prescribed oral anti-muscarinic agent). A further safety study (NCT00688688) evaluated long-term (12 mo) results.

A proof-of-concept, randomized, double-blind, parallel group, phase Ⅱa dose-ranging trial (BLOSSOM trial, NCT01604928) was conducted in six European countries including 260 OAB patients that were assigned to four treatment arms: placebo (n = 66), mirabegron 100 mg *bid* (n = 65), mirabegron 150 mg *bid* (n = 65), and tolterodine 4 mg extended-release (ER) once-daily (n = 64), for a 4-wk period[47]. With regard to mean micturition frequency, mirabegron was significantly superior to placebo and tolterodine: 2.2 micturitions/24 h *vs* 1.2 micturitions/24 h for both doses (adjusted $P \leqslant 0.01$ for both comparisons). Compared with placebo, mirabegron was also superior with respect to mean volume voided per micturition, mean number of incontinence episodes, nocturia episodes, urgency incontinence episodes, urgency episodes per 24 h and HRQL variables. No difference in efficacy was observed between the 100 and 150 mg twice-daily doses, leading to the conclusion that a total daily dose of 200 mg provides maximum therapeutic efficacy.

An European, dose-finding, phase Ⅱb randomized trial (DRAGON trial, NCT00337090) enrolled 919 OAB patients (mean age 57.2 years, 89.3% female) assigned to six study arms: placebo (n = 166), mirabegron 25 mg (n = 167), 50 mg (n = 167), 100 mg (n = 168), 200 mg (n = 166) and tolterodine 4 mg ER (n = 85), for a 12-wk period[48]. In this study a once-daily OCAS formulation of mirabegron was used. Statistically significant, dose-dependent reductions in the mean number of micturitions per 24 h (primary endpoint) were seen with mirabegron 50 (-2.1), 100 (-2.1) and 200 (-2.2) mg, compared with placebo (-1.4). Mirabegron significantly increased mean volume voided per micturition and decreased mean number of urgency and urgency incontinence episodes per 24 h, level of urgency (at doses of 100 and 200 mg) and nocturia episodes (at doses of 50 mg): about half of the incontinent patients in each mirabegron group was dry at the end of treatment. Similarly to previous studies evaluating antimuscarinics[49], the difference in response *vs* placebo was evident after 1 wk of treatment and the maximum effect was achieved and sustained from 8 to 12 wk. Although the study was not powered for head-to-head comparison with tolterodine, the authors observed that the magnitude of improvements in efficacy outcomes in the mirabegron groups was within the same range as that of the tolterodine group.

Randomized large-scale pivotal trials

Based on the aforementioned results, three subsequent large-scale, phase Ⅲ, randomized studies were conducted by Astellas (Table 1)[50-52]. Efficacy analyses of these studies were based on two co-primary efficacy endpoints: (1) the change from baseline to endpoint in the mean number of incontinence episodes per 24 h; and (2) the mean change from baseline to endpoint in the mean number of micturitions per 24 h.

An European-Australian multicentre, randomised, double-blind, parallel-group, placebo and active controlled phase Ⅲ trial (SCORPIO trail, NCT00689104) enrolled 1978 OAB patients (mean age 59.1 years, 72.2% female)

Table 1 Coprimary efficacy variables in 12-wk phase Ⅲ pivotal randomized controlled trials

Trials	Patients (*n*)	Arms (*n*)	Change from baseline in incontinence episodes/d[1] (FAS-I)	Change from baseline in micturitions/d[1] (FAS)	Ref.
SCORPIO	1978	Placebo (494)	-1.17	-1.34	[50]
		Mirabegron 50 mg (493)	-1.57[a]	-1.93[a]	
		Mirabegron 100 mg (496)	-1.46[a]	-1.77[a]	
		Tolterodine 4 mg ER (495)	-1.27 (NS)	-1.59 (NS)	
ARIES	1328	Placebo (454)	-1.13	-1.05	[51]
		Mirabegron 50 mg (442)	-1.47[a]	-1.66[a]	
		Mirabegron 100 mg (433)	-1.63[a]	-1.75[a]	
CAPRICORN	1302	Placebo (433)	-	-	[52]
		Mirabegron 25 mg (433)	-0.40[a]	-0.47[a]	
		Mirabegron 50 mg (440)	-0.42[a]	-0.42[a]	
Pooled analysis	3542	Placebo (1328)	-1.10	-1.20	[53]
		Mirabegron 50 mg (1324)	-1.49[a]	-1.75[a]	
		Mirabegron 100 mg (890)	-1.50[a]	-1.74[a]	

[a]$P < 0.05$ *vs* placebo. [1]Mean adjusted changes from baseline to final visit. FAS: Full analysis set; FAS-I: Full analysis set-incontinence (all FAS patients with ⩾ incontinence grade at baseline); NS: Not significant; ER: Extended release.

that were assigned to four arms: placebo, mirabegron 50 mg, mirabegron 100 mg or tolterodine slow-release (SR) 4 mg once-daily, for a 12-wk period (Table 1)[50]. Compared to placebo, statistically significant reductions were observed with 50 and 100 mg of mirabegron in both co-primary efficacy measures. Although improvements in both co-primary endpoints were also observed with tolterodine SR, they did not reach statistical significance. Compared with placebo, all active treatment groups achieved statistically significant improvements from baseline in mean volume voided per micturition; the mirabegron 50 mg group achieved a statistically significant improvement also in the mean number of episodes with urgency (grade 3 or 4) per 24 h. No statistical comparison with tolterodine SR was performed in this study, however the magnitude of effect with mirabegron was at least as good as that observed with tolterodine SR.

Another multicentre, randomised, double-blind, parallel-group, placebo-controlled phase Ⅲ trial (ARIES trial, NCT00662909) was conducted in the United States and Canada[51]. This study enrolled 1328 OAB patients (mean age 60.1 years, 74.3% female) randomly assigned to three treatment arms: placebo, mirabegron 50 mg, mirabegron 100 mg once-daily, for a 12-wk period (Table 1). Compared to placebo, statistically significant decreases from baseline were observed with 50 and 100 mg mirabegron in the number of incontinence episodes and in the number of micturitions per 24 h. Significantly greater improvements *vs* placebo were observed for both mirabegron treatment groups also in mean level of urgency, mean number of urgency incontinence episodes per 24 h, mean number of urgency episodes (grade 3 or 4) per 24 h and mean number of nocturia episodes per 24 h.

The third pivotal phase Ⅲ study is an European-North American, randomized, double-blind, placebo-controlled trial (CAPRICORN trial, NCT00912964), including 1306 eligible patients (mean age 59.0 years, 68.7% female) randomly assigned to receive placebo, mirabegron 25 mg or mirabegron 50 mg, for a 12-wk period (Table 1). The results of this trial, submitted to regulatory authorities by Astellas and presented as meeting abstract, are still unpublished in peer-review journals[52]. Both mirabegron 25 and 50 mg groups demonstrated statistically significant improvements for the co-primary efficacy endpoints, providing evidence that the lower dose also results in a clinically meaningful benefit, although greater efficacy was observed with mirabegron 50 mg.

Recently, a pooled analysis of data from the above-mentioned three pivotal randomised phase Ⅲ studies has been reported as abstract; the efficacy of mirabegron (50 or 100 mg) was compared with placebo (Table 1)[53]. This pooled analysis demonstrated similar statistically significant and clinically meaningful improvements for mirabegron 50 and 100 mg compared with placebo based on co-primary efficacy endpoints; the reduction with mirabegron of the micturition frequency per 24 h and the number of incontinence episodes per 24 h compared with placebo was of about 0.55 and 0.40, respectively.

Long-term efficacy data

A multinational randomised, double-blind, parallel group, active-controlled, phase Ⅲ trial has been conducted in North America, Europe and other countries (TAURUS trial, NCT00688688) assessing long-term safety (primary outcome) and efficacy of mirabegron. In this study 2444 OAB patients were randomised to three study arms: mirabegron 50 mg (n = 812) and 100 mg (n = 820) and tolterodine SR 4 mg (n = 812), once daily for 12 mo[54]. The study was not designed to demonstrate a statistically significant difference in efficacy between treatment groups and was not placebo-controlled. The authors reported that, for both doses of mirabegron, improvements in OAB symptoms were observed by month 1 and were maintained throughout the follow-up period, as measured by the change from baseline for mean number of micturitions per 24 h, mean number of incontinence episodes per 24 h and mean volume voided/micturition[54]. Overall, data from this safety study provide evidence

demonstrating the durability of effect for mirabegron in the treatment of OAB and support the results of previous studies showing that the β3-AR, unlike other β-AR subtypes, is not prone to desensitization[55].

QUALITY OF LIFE MEASURES AND TREATMENT SATISFACTION

In the DRAGON trial[48], the International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB) and the ICIQ-OABqol questionnaires were used for HRQL assessment. Dose-dependent improvements from baseline to the end of treatment were observed with the ICIQ-OAB questionnaire and were statistically significant *vs* placebo for all mirabegron groups. Improvements from baseline to the end of treatment were also observed with the ICIQ-OABqol questionnaire, although only the comparison between the mirabegron 200-mg group and placebo was statistically significant. Patient-reported benefit was also evaluated with the question "has the treatment been of any benefit to you?" ("no", "yes, a little", or "yes, very much"). The percentage of patients classified as "responders" (improvement of ≥ 1 category from baseline) at the end of treatment was 59.0%, 65.0%, 65.8% and 70.8% for the mirabegron 25-mg, 50-mg, 100-mg, and 200-mg groups, respectively, compared with 51% for placebo and 55% of the tolterodine groups.

All three active treatment groups (mirabegron 50 and 100 mg, tolterodine ER 4 mg) demonstrated a statistically significant improvement from baseline to final visit compared with placebo on the three HRQL measures used in the SCORPIO trial[50]: OAB-Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), and Treatment Satisfaction-Visual Analog Scale (TS-VAS).

These results were replicated in the ARIES trial[51]; both mirabegron treatment groups demonstrated significantly greater improvements from baseline to final visit *vs* placebo in OAB-q (symptom bother, HRQL total score and dimensions of coping, concern and sleep), TS-VAS and PPBC.

In the CAPRICORN trial both mirabegron groups (25 and 50 mg) demonstrated statistically significant improvements *vs* placebo for the TS-VAS; for the OAB-q, the mirabegron 50 mg group demonstrated statistically significant improvements *vs* placebo in the Symptom Bother scale[52].

Long-term data on both doses of mirabegron, 50 and 100 mg, also showed numerical improvements on the OAB-q (symptom bother and HRQL total score), PPBC scale, and TS-VAS, similar to those seen using a well-established antimuscarinic treatment for OAB[54].

SUBPOPULATION ANALYSES

Clinical data in specific subpopulations of OAB patients are still scant in published literature.

With regard to the influence of gender, it must be noted that most of patients enrolled in phase Ⅲ trials were females and limited data are available on the efficacy of mirabegron in males, especially in those with benign prostatic hyperplasia (BPH). A non-randomized study, focusing on males, reported that mirabegron was effective in male patients with OAB and improved not only OAB symptoms, but also voiding symptoms in BPH men, without increasing post-voiding residual urine[56]. In this study, with a small number of participants, a greater improvement of urgency urinary incontinence based on OAB Symptom Questionnaire was observed in BPH patients treated with α1-blocker compared to those not treated with α1-blocker, suggesting that combining mirabegron with α1-blocker might benefit males with wet OAB. Accordingly, pooled pivotal trial efficacy data reported by the FDA showed that mirabegron 50 mg and 100 mg were effective for both male and female subjects, although a larger reduction *vs* placebo in mean number of incontinence episodes was observed in female subjects compared to male subjects; however, it was suggested that this observation could be due to a lower baseline level of incontinence in males, overlapping symptomatology with male co-morbid conditions (*e.g.*, BPH), increased mirabegron exposure in females, or some combination of all 3 factors[57]. The same document reports that mirabegron 50 and 100 mg did not appear effective in decreasing the mean number of incontinence episodes in men with BPH[57]. In a phase Ⅱ, double-blind, parallel-group, placebo-controlled urodynamic study (NCT00410514) including 200 men with LUTS and BOO, Nitti *et al*[58] reported that 50 and 100 mg mirabegron do not adversely affect Q_{max}, detrusor pressure at Q_{max} and bladder contractility index, and are well tolerated in these patients. However, because of the limited number of men with BPH included in available studies, it is not possible to draw meaningful conclusions.

A non-randomized, active-controlled study reported that mirabegron is effective for those whose OAB is unresponsive to antimuscarinic drugs, although its effectiveness was less in these patients compared to newly diagnosed OAB patients[56]. In this study, 38.4% of OAB patients did not respond to mirabegron as well as to antimuscarinics; as noted by the authors, this subject deserves further elucidation. Accordingly, a post-hoc analysis of the SCORPIO trial[59] showed that both mirabegron 50 and 100 mg once-daily were effective in improving both mean number of incontinence episodes and micturitions per 24 h *vs* placebo, not only in antimuscarinic-treatment-naïve patients but also in those patients who failed prior OAB antimuscarinic therapy, regardless of the reason for discontinuation.

With regard to the effect of the age, the pooled data from the three pivotal randomised studies were analysed in the OAB population aged ≥ 65 years in order to investigate the benefit of mirabegron in elderly OAB patients[60]. Approximately 38% of patients were ≥ 65 years of age (placebo n = 504; mirabegron 50 mg n = 499; mirabegron 100 mg n = 340). Mirabegron 50 and 100 mg re-

sulted in reduction in incontinence episodes per 24 h and micturitions per 24 h in patients ≥ 65 years of age, with an adjusted mean difference *vs* placebo of -0.66 and -0.68, respectively, and of -0.62 and -0.75, respectively. These results are of great value, given the increasing prevalence of OAB with age and the common adverse events associated with antimuscarinics in the aging population[7].

SAFETY, TOLERABILITY AND DISCONTINUATION

There is substantial consistency through the studies in reporting safety and tolerability of treatment with mirabegron.

Despite a small increase in pulse rate, mirabegron demonstrated good safety and tolerability in the BLOSSOM trial[47]. An incidence of treatment-emergent adverse effects (TEAEs) of 39.2% with mirabegron *vs* 36.4% with placebo and 48.4% with tolterodine has been reported. AEs in the mirabegron group were mild or moderate in intensity, the most commonly reported class of TEAEs being gastrointestinal disorders (13.8%), followed by headache (6.9%), with a lower incidence compared to tolterodine group (23.4%, 9.4%, respectively). Treatment-related dizziness and palpitations were more common with mirabegron compared to placebo and tolterodine. Of note, no episodes of acute urinary retention were reported. Discontinuation rates due to AEs were 4.6% and 7.7% with mirabegron 100 and 150 mg, respectively, 1.5% with placebo and 3.1% with tolterodine.

In the DRAGON trial, one or more TEAEs were reported by 43.8%-47.9% of patients in the mirabegron groups (25, 50, 100 and 200 mg) *vs* 43.2% in the placebo group[48]. Again, the most common reported TEAEs were gastrointestinal disorders (7.2%-8.3% with mirabegron *vs* 5.3% with placebo), including constipation, dry mouth, dyspepsia and nausea. Of note, the incidence of dry mouth, reported to be an important factor for determining persistence with antimuscarinic agents[10], was higher with tolterodine ER 4 mg (3.5%) than with mirabegron (1.8% to 3.0%, depending on dose). Again, no episodes of acute urinary retention were reported with mirabegron. A statistically significant, dose-dependent increase from baseline in mean pulse rate *vs* placebo was detected with 100 and 200 mg mirabegron (1.6 and 4.1 bpm, respectively, AM; 2.7 and 4.7 bpm PM); however, this change in pulse rate was not associated with an increase in cardiovascular AEs and no differences between treatment groups were observed in ECG parameters and blood pressure. Discontinuation owing to AEs was low at 3.0% with placebo, 2.4%-5.3% with mirabegron, and 1.2% with tolterodine.

An incidence of TEAEs similar across the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine SR groups (43.3%, 42.8%, 40.1% and 46.7%, respectively) was reported in the SCORPIO trial[50]. The most common TEAEs in this study were hypertension (7.7%, 5.9%, 5.4% and 8.1%), dry mouth (2.6%, 2.8%, 2.8% and 10.1%), headache (2.8%, 3.7%, 1.8% and 3.6%), and nasopharyngitis (1.6%, 2.8%, 2.8% and 2.8%). At the final visit, mirabegron was associated with small dose-dependent, not clinically meaningful increases in pulse rates compared with placebo, that were similar to those seen with tolterodine; the overall incidence of adjudicated cardiovascular events was similar in placebo- and mirabegron-treated patients, and slightly higher in tolterodine-treated patients. The discontinuation rate owing to TEAE was low, at 2.6%, 4.9%, 3.2%, and 4.4%, respectively.

The ARIES trial[51] confirmed a similar incidence of TEAEs across placebo, mirabegron 50 mg and 100 mg groups (50.1%, 51.6% and 46.9%, respectively). In this study, the incidence of hypertension was 6.6%, 6.1% and 4.9%, and headache 2.0%, 3.2% and 3.0% in the placebo, mirabegron 50 mg and 100 mg groups, respectively. An increase incidence of urinary tract infections was noted with mirabegron 50 mg (12%) and 100 mg (16%), compared with placebo (8%). Changes in laboratory assessments, vital signs, physical examination, ECG and post-void residual volume were small and consistent across treatment groups. No AEs of QTc prolongation and no proarrhythmic events were observed. Discontinuation rates due to AEs were 3.8%, 4.1% and 4.4% in the placebo, mirabegron 50 mg and 100 mg groups.

In the CAPRICORN trial, common TEAEs included hypertension in 5.3%, 6.9%, and 7.0%, and headache in 2.1%, 0.9% and 0.9%, in the placebo, mirabegron 25 mg and mirabegron 50 mg groups, respectively[52].

In compliance with abovementioned studies, long-term safety and tolerability have been confirmed by the results of the TAURUS trial (Table 2)[54]. The most frequent TEAEs were hypertension, dry mouth, constipation and headache, which occurred at a similar incidence across all treatment groups, while the incidence of dry mouth was more than three fold higher in the tolterodine group. A higher incidence of neoplasms (benign, malignant, and unspecified including cysts and polyps) was seen in the mirabegron 100 mg group (1.3%) compared with mirabegron 50 mg (0.1%) or tolterodine ER 4 mg (0.5%), but was not considered to be treatment-related. Discontinuations due to AEs were comparable across treatment groups, occurring in only 6.4%, 5.9%, and 6.0% of patients on mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg, respectively.

ONGOING STUDIES AND AWAITED RESULTS

Several studies are ongoing in order to evaluate efficacy and safety of mirabegron in selected groups of patients or in comparison with other drugs. Some of these studies are still recruiting patients, while others have been completed and their results should be published on peer-review journals. Many studies are also ongoing focusing on several pharmacokinetic features of mirabegron and pharmacological interactions.

A randomized, phase Ⅱ, double-blind, factorial, paral-

Table 2 Most frequent (> 2% in any treatment group) treatment emergent adverse events and adverse events of interest[1] *n* (%)

MedDRA (v.9.1), preferred term	Mirabegron 50 mg (*n* = 812)	Mirabegron 100 mg (*n* = 820)	Tolterodine ER 4 mg (*n* = 812)
Any AE	485 (59.7)	503 (61.3)	508 (62.6)
Hypertension	75 (9.2)	80 (9.8)	78 (9.6)
Urinary tract infection	48 (5.9)	45 (5.5)	52 (6.4)
Dry mouth	23 (2.8)	19 (2.3)	70 (8.6)
Nasopharyngitis	32 (3.9)	35 (4.3)	25 (3.1)
Headache	33 (4.1)	26 (3.2)	20 (2.5)
Influenza	21 (2.6)	25 (3.0)	28 (3.4)
Constipation	23 (2.8)	25 (3.0)	22 (2.7)
Back pain	23 (2.8)	29 (3.5)	13 (1.6)
Dizziness	22 (2.7)	13 (1.6)	21 (2.6)
Diarrhea	15 (1.8)	24 (2.9)	16 (2.0)
Sinusitis	22 (2.7)	18 (2.2)	12 (1.5)
Arthralgia	17 (2.1)	19 (2.3)	16 (2.0)
Tachycardia	8 (1.0)	19 (2.3)	25 (3.1)
Cystitis	17 (2.1)	11 (1.3)	19 (2.3)
Adverse events of interest			
Corrected QT interval prolongation[2]	3 (0.4)	2 (0.2)	3 (0.4)
Hypertension[2]	89 (11.0)	83 (10.1)	86 (10.6)
Cardiac arrhythmia[2]	32 (3.9)	34 (4.1)	49 (6.0)
Urinary retention	1 (0.1)	1 (0.1)	3 (0.4)
Acute urinary retenction	0	1 (0.1)	1 (0.1)
Hypersensitivity	45 (5.5)	44 (5.4)	42 (5.2)
Sincope/seizure	1 (0.1)	0	1 (0.1)
Hepatotoxicity[2]	17 (2.1)	19 (2.3)	15 (1.8)

[1]In the safety analysis set; [2]Definition based on standardized medical dictionary for regulatory activities (MedDRA) query. Adverse event not based on standardized MedDRA queries were predefined. Reprinted from reference[54], with permission. AE: Adverse Event; ER: Extended release.

lel-group, active and placebo-controlled, multicenter, dose-ranging study (SYMPHONY trial, NCT01340027) has been conducted to evaluate efficacy, safety and tolerability of six dose combinations of solifenacin and mirabegron compared to mirabegron and solifenacin monotherapies in the treatment of OAB.

The BEYOND trial (NCT01638000) is an ongoing double-blind, randomized, multi-center, phase Ⅲ study of mirabegron *vs* solifenacin in 1692 subjects with OAB treated with antimuscarinics and dissatisfied due to lack of efficacy.

A post-marketing study (NCT01745094) is recruiting patients in order to evaluate safety and efficacy of concomitant use (add-on-therapy) of mirabegron in patients with OAB under treatment with solifenacin.

CONCLUSION

After 30 years of predomination of antimuscarinics, a new compound, with a novel mechanism of action, is for the first time available in the pharmacological armamentarium aimed to treat OAB. Mirabegron has proven effective across multiple randomized controlled trials, both short and long-term, and showed a favourable safety profile with a placebo-like dry mouth incidence. Mirabegron can be used for patients with contraindications to antimuscarinics and its effectiveness has been confirmed in patients who discontinued previous antimuscarinic therapy. Although the tolerability profile of mirabegron offers the potential to improve adherence to OAB treatment, this optimal efficacy-tolerability balance is to be demonstrated in clinical real-world every day practice.

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EDITORIAL

Female urinary incontinence during pregnancy and after delivery: Clinical impact and contributing factors

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Abstract

Urinary incontinence (UI) is a common condition affecting adult women of all ages and it could have a negative influence on quality of life. The etiology of UI is multifactorial, but some of the most important risk factors are obesity and ageing, as well as adverse obstetric events. Pregnancy and delivery *per se* have been implicated in the etiology of UI. Although several studies have demonstrated a direct association between UI and vaginal delivery in short, medium and long-term, the role of childbirth on the risk of UI remains controversial. The mechanical strain during delivery may induce injuries to the muscle, connective and neural structures. Vaginal birth can be associated with relaxation or disruption of fascial and ligamentous supports of pelvic organs. Parity, instrumental delivery, prolonged labor and increased birth weights have always been considered risk factors for pelvic floor injury. Also genetic factors have been recently raised up but still there are not appropriate guidelines or measures to reduce significantly the incidence of UI. The role of pelvic floor muscle training (PFMT) in the prevention and treatment of UI is still unclear. However, PFMT seems to be useful when supervised training is conducted and it could be incorporated as a routine part of women's exercise programmes during pregnancy and after childbirth.

Key words: Urinary incontinence; Pregnancy; Delivery; Cesarean section; Forceps; Episiotomy; Obesity; Collagen; Pelvic floor muscle training

Core tip: The mechanical strain during delivery may induce injuries to the muscle, connective and neural structures. Vaginal birth can be associated with relaxation or disruption of fascial and ligamentous supports of pelvic organs. Parity, instrumental delivery, prolonged labor and increased birthweight have always been considered risk factors for pelvic floor injury. Also genetic factors have been recently raised up but still there are not appropriate guidelines or measures to reduce significantly the incidence of urinary incontinence.

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INTRODUCTION

Pelvic floor dysfunctions include a wide range of anatomic and functional disorders (*e.g.*, hypo-function: urinary incontinence, fecal incontinence and pelvic organ prolapse; hyper-function: defecatory dysfunction, sexual

dysfunction and voiding dysfunction). In women over 45 years old, prevalence of urinary (urge or stress) incontinence ranges from 17% to 45%, anal (faecal or flatus) incontinence (AI) from 0.5% to 17%, and urogenital prolapse between 20% to 30%. These prevalences could be therefore underestimated since most of the epidemiological investigations are obtained by self-report which could confound the real incidence of pelvic floor dysfunctions[1-4] (Table 1).

Epidemiological evidences demonstrate that adverse obstetric events are related to pelvic floor dysfunction. Lower urinary tract symptoms (LUTSs) during pregnancy and postpartum have been associated to physiological and anatomical changes of pregnancy. LUTSs were present in 63.8% of Brazilian pregnant women, and the main risk factors were multiparity and pre-pregnancy LUTSs, smoking, constipation, and regular coffee consumption[5]. However, those symptoms are transient and disappear some months after delivery and they do not request further investigations.

According to the most recent definition of the International Continence Society (ICS), urinary incontinence (UI) is defined as "the complaint of any involuntary leakage of urine". Although UI is not a life threatening status, it is a common, annoying and expensive condition, and it deeply affects a woman's quality of life[6]. In a subset of population, UI during pregnancy has been reported to be 19.9% among nulliparous and 24.1% among primiparous women[7]. In the last years, clinicians and health researchers have extensively investigated the factors influencing prevalence of UI in order to ameliorate the management and treatment of affected patients. However, accurate prevalence data are difficult to obtain from the literature since noteworthy differences among the studies in terms of methodologies[8,9]. The fact that UI is more common in women than in men indicates the contribution of factors such as pregnancy to UI.

PREVALENCE OF UI DURING PREGNANCY AND AFTER DELIVERY

It is well known that, during pregnancy, women can experience urogynaecological problems which includes not only urinary incontinence, but also urinary tract infection, filling and voiding disorders, pelvic organ prolapse and AI[10]. The development of these conditions determinate physiological changes that occur in pregnancy but it can be also linked to previous pregnancies. In fact, during pregnancy, supporting structures are supposed to be overloaded due to the fetus weight and the progressive growth of the uterus, both in weight and size[11,12]. Additionally, pregnant uterus increases the angle between the bladder neck and urethra, which can participate to urinary symptoms. Hormonal changes due to pregnancy can also cause changes in tissue, in the support and in the continence mechanism[7,13].

During pregnancy and after delivery, both UI and AI are frequent complaints. The cumulative incidence during pregnancy was 39.1% and 10.3%, respectively[14]. According to a recent systematic review, it has been reported a prevalence of UI at the first trimester of 8.3%, at the second of 31.8% and at the third of 34.8%[14]. The most prevalent type of UI is the stress urinary incontinence (SUI), affecting up to 79.2% at the third trimester which is prompted by a physical movement or activity, such as coughing, sneezing, running or heavy lifting, that puts pressure (stress) on the bladder[15,16]. In a systematic review of population-based studies, in order to investigate the prevalence of UI within the first year postpartum, during the first 3 mo postpartum, the pooled prevalence of any postpartum incontinence was 33% in all women. The mean prevalence was double in the vaginal delivery group (31%) compared to the cesarean section group (15%)[17].

Table 1 Pelvic floor dysfunctions

Hypo-function	Hyper-function
Urinary incontinence	Voiding dysfunction
Fecal incontinence	Defecatory dysfunction
Pelvic organ prolapse	Sexual dysfunction

RISK FACTORS OF DEVELOPING UI DURING PREGNANCY AND AFTER DELIVERY

Risk factors of developing UI after delivery have been related to the characteristics of mother and baby themselves. Pregnancy per se has been reported to be a risk factor for postpartum UI especially if the incontinence started during the first trimester[18,19]. That is supported by the increase in the rate of SUI with an increased number of abortions, which suggests that pregnancy by itself may have promoting effects on UI.

It has been found that the main risk factors of UI in pregnancy are maternal age more than 35 years[20], pregestational maternal body mass index (BMI) and family history of UI[16]. The prevalence of UI increases with maternal age and there is an annual increase in UI prevalence of 3% per year[21]. Moreover, the first delivery is considered to exert the greatest increase in risk for UI, even if subsequent deliveries contribute to a further increase in the risk of UI[22].

The relationship between maternal weight and subsequent development of incontinence has been diffusely investigated. Higher pregestational BMI is known to be associated with postpartum UI[23]. It has been demonstrated an increased risk of UI (8%) proportionally to the increase of BMI unit, and this risk is not related to the type of delivery, vaginally or by caesarian section[21]. Pregnant women at term with body weight equal or more than 75 kg appear to double the risk of SUI[24]. UI during pregnancy and still persistent at 3 mo is usually associated to women with higher BMI[25]. The Norwegian Mother and Child Cohort Study studied 12679 primiparous

women, continent before pregnancy, at weeks 15 and 30 of pregnancy and 6 mo postpartum. Weight gain greater than the 50th percentile weeks 0-15 was weakly related with higher incidence of UI at week 30 when compared with weight gain less than or equal to the 50th percentile. In addition, weight increase greater than 50th percentile during pregnancy was not associated with higher incidence of UI, 6 mo postpartum[26].

Most of the interest is given to the impact of obstetric factors on UI after childbirth. In women who delivered vaginally, the risk of incontinence increases with increasing fetal birthweight (especially for children with birthweight ⩾ 4000 g[25,27,28], and probably in women who received oxytocin[28]. Shoulder dystocia and associated obstetrical maneuvers for its relief have not detrimental effects on perineum and do not increase UI incidence after delivery[29]. The vaginal delivery of two successive fetuses does not seem to be a cause of SUI as compared to cesarean, although its rate was higher in the "twin" group (40%) than in the "singleton" group (20%) which appears to be related to total intrauterine weight[30].

Another important contributing factor in developing UI after delivery is the presence of urinary leakage before pregnancy[23]. Thus, previous UI was a significant risk factor for period prevalent UI during pregnancy, explaining 34% and 83% of pregnancy UI for nulliparous and primiparous, respectively[7]. In addition, in nulliparous women prepregnancy UI is a strong herald for the increased prevalence of UI 4-12 years postpartum[21].

Cesarean section seemed to be followed by less postnatal UI than vaginal delivery[28,31]. It has been found that the risk is 67%-71% higher after vaginal delivery than after caesarean section[21], but this advantage given by cesarean delivery seems to disappear after the second cesarean section[16]. A systematic review reported that cesarean section reduced the risk of postpartum SUI from 16% to 10%, and the number needed to prevent SUI is 15 in 6 cross-sectional studies. In the same report, from the analysis of 12 cohort studies, the incidence of SUI in cesarean section patient decreased from 22% to 10% and the number needed to prevent SUI was 10%[31]. Nevertheless, a prospective multicenter study do not show a significant difference of risk for bothersome UI between women delivered by one or more vaginal deliveries and women delivered by one or more caesarean sections[32].

Concerning the type of cesarean sections, it has been found no difference in the prevalence of UI, or UI persisting for more than 10 years[21], between women delivered by acute or elective caesarean section (elective caesarean is defined as the caesarean section performed before the onset of labour, while caesarean section performed during labour are denoted as acute caesarean sections). That one indicates that it is the later stages of delivery, when the fetus passes through the pelvic floor that leads to the increased risk of UI. However, it should be clear that one has to perform eight or nine caesarean sections to avoid one case of UI. Moreover, operative delivery by caesarean section also involves a degree of risk for morbidity and mortality over and above that of vaginal delivery.

One area of considerable controversy is the role of episiotomy and spontaneous perineal lacerations[33]. Almost 80 years ago, episiotomy was proposed as a strategy to prevent spontaneous lacerations and to thereby reduce "pelvic relaxation". However, more recent studies have suggested that episiotomy may increase the odds of pelvic floor disorders. Thus, the role of episiotomy is uncertain. Episiotomy is not significantly associated with any of the pelvic floor disorders considered. In contrast, women who had experienced multiple spontaneous perineal lacerations were significantly more likely to have prolapse to or beyond the hymen, and were significantly less likely to have overactive bladder (OAB)[34]. In 2005, a systematic review concluded that the effect of episiotomy on the development of pelvic floor disorders remains unknown[35].

Also controversial is the association between operative delivery and pelvic floor disorders. While some research has suggested that operative delivery substantially increases the odds for pelvic floor disorders[23,28,36], other research suggests that operative birth is not a strong predictor of urinary incontinence[19,37-39] or pelvic organ prolapse[40]. Recently, it has been demonstrated that women with at least one forceps delivery are more likely to report stress incontinence, OAB, AI, prolapse symptoms and prolapse to or beyond the hymen on examination, although this association is statistically significant only for OAB[34]. Preventing obstetric trauma needs changes in current obstetric practice: reduction in the episiotomy rate, use of vacuum extractor in preference to forceps.

Anal sphincter injuries showed a significantly higher risk of fecal incontinence 10 wk after delivery in women with these injuries, as well as in women with a second-stage labor of more than 50 min[41].

MOLECULAR AND GENETIC MECHANISMS

Pelvic floor disorders, such as SUI and pelvic organ prolapse, may have common pathophysiological processes related to pelvic floor tissue laxity and loss of support. Those changes could be relevant most of all during period of important modifications, such as pregnancy and delivery. However, the molecular mechanisms responsible for tissue changes in UI are poorly understood yet. Lin *et al*[42] have studied 22000 genes from the urethral tissue of a parturition-induced stress urinary incontinence (SUI) rat model. The expression of 42 urethral genes was different between continent and incontinent rats. Genes important in inflammation, collagen breakdown, and smooth muscle inhibition are upregulated in the urethras from rats with parturition-related incontinence.

Using the same model, muscle, collagen Ⅰ/Ⅲ and reticular fibers in the urethra of SUI rats were also significantly decreased, besides fragmentation and disorganization. Transforming growth factor (TGF) beta 1, metal-

loproteinase (MMP) 9, and phosphorylated Smad2 were expressed significantly higher in parturition-associated SUI than in continent rats[43]. Birth appears to activate elastin expression by TGF-beta 1 signals while estrogen interferes with this mechanism, resulting in improper assembly of elastic fibers. The TGF-beta family also contributes in the regulation of myometrial activation at term integrating mechanical and endocrine signals for successful labor contraction[44].

In humans, there is a three-fold prevalence of SUI among first-degree relatives of female patients with SUI[45] which suggests a genetic factor involved in the predisposition of connective tissue injury. Allen-Brady *et al*[46] have studied the relationship between predisposing gene and pelvic flood disorders, including UI, on chromosome 9q21. In a large sample of twins, it has been demonstrated a genetic component for the aetiology of SUI, although environmental factors equally contributed to variation liability[47]. Further research into the genetic basis of UI may provide a comprehensive understanding of the biological basis of the disorder.

PREVENTION OF URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY

Most pregnant women had no information about pelvic floor, and a little number of women could only localize to the region. Several studies have demonstrated that antenatal pelvic floor muscle training (PFMT) taught in a general exercise class, during pregnancy, could be helpful in the prevention of postpartum UI in primiparous women without UI during pregnancy[48]. The utility of regular pelvic floor muscle exercises is due to the ability of the muscles that support the pelvic organs, to become stronger and to help to use the muscles more effectively. Pregnant and postpartum women who do PFMT have significantly less urine leakage[49], even if PFMT does not affect labor and birth outcomes or complication rates[50,51]. In addition, PFMT applied in pregnancy is effective in the treatment and prevention of urinary incontinence during pregnancy, and this effect may persist to postpartum period[50,52].

On the other hand, an Australian prospective randomised controlled trial, among women 3 mo after delivery, has compared women which had PFMT or a usual postpartum care[27]. At 3 mo after delivery, the prevalence of UI was respectively 31% and 38%. After one year, there was no significant difference in continence status between both groups[53]. Even if there was no significant difference in continence status, women in the intervention group were more motivated than those in the control group in practicing pelvic floor exercises at adequate frequencies.

In conclusion, there are no specific techniques or treatments to prevent the development of postpartum UI but there are correct behaviors to follow that severely limit the incidence of postpartum UI. A good management of pre-pregnancy BMI and weight gain during pregnancy, proper management especially of the second and third stage of labor, fetal weight < 4.0 kg, and finally a good awareness of their own pelvic floor and its training to strengthen those muscles, constitute the elements on which we can work to significantly reduce the possibility of developing UI after pregnancy.

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FRONTIER

Individualized misoprostol dosing for labor induction or augmentation: A review

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Abstract

Cesarean birth rates are greater than 20% in many developed countries. The main diagnoses contributing to the high rate of cesarean births in nulliparous women are dystocia and prolonged labor. Traditionally, a policy of vaginal dinoprostone for the treatment of unripe cervix or early amniotomy with oxytocin administration for a ripened cervix has been associated with a modest reduction in the rate of cesarean births due to arrest disorders. However, the course of vaginal dinoprostone is tedious and oxytocin should be administered through an infusion pump, which may be inconvenient in certain settings. Because misoprostol has powerful uterotropic and uterotonic effects, and has become a common agent used in the practice of obstetrics and gynecology, the United States Food and Drug Administration removed the absolute contraindication of the drug during pregnancy from its label in April 2002. However, excessive uterine contractility resulting in tachysystole or fetal distress is always a concern with the oral or vaginal use of fixed-dosage misoprostol. Therefore, misoprostol should be administered with caution to ensure that fetal hypoxia does not occur. A pilot trial examining the use of very small, frequent, titrated oral misoprostol dosages administered every 2 h was first conducted by Hofmeyr *et al* in 2001. Given women's different metabolisms and responses to misoprostol, another method of titrating individualized oral misoprostol with dosing administered every hour relative to uterine response was then developed by Cheng in 2006. Based on previous studies, this titration method is potentially an ideal alternative to traditional dinoprostone, oxytocin or the previously established misoprostol dosing method for labor induction or augmentation.

Key words: Cervix; Misoprostol; Oxytocin; Labor induction; Labor augmentation

Core tip: Avoiding uterine tachysystole and fetal hypoxia is the critical consideration when implementing labor induction or augmentation with misoprostol. Titrated oral misoprostol is potentially an ideal alternative to traditional dinoprostone, oxytocin or the previously established misoprostol dosing method for labor induction or augmentation.

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BIOGRAPHY

Shi-Yann Cheng received his MD degree from National Yang-Ming University, Taipei, Taiwan. He completed an extensive 5-year obstetrics residency in Taiwan in the Department of Obstetrics and Gynecology, Veteran General Hospital, Kaohsiung. He is presently the Director of the Department of Obstetrics and Gynecology and Medical Education and Research at Medical China University Beigang Hospital and Lecturer in the School of Medicine

at Medical China University, Taichung, Taiwan. His research interests cover clinical obstetrics and interdisciplinary collaborative care education, and his most notable contribution is the development of the concept of labor induction with titrated misoprostol solution with a focus on dosing interval and uterine responses according to the pharmacokinetics of misoprostol. His CV lists 16 peer-reviewed publications, 2 book chapters, prestigious medical education devotion awards, and presentations at national and international meetings.

INTRODUCTION

There are many indications for term labor inductions and more than 15% of all gravid women require aid in cervical ripening. A labor course longer than that of spontaneous labor is the most commonly encountered problem associated with labor induction. Additionally, prolonged spontaneous labor in nulliparous women is another common problem that can result in a negative birth experience[1,2] and can be associated with a non-reassuring fetal heart rate (FHR) resulting in emergency cesarean delivery[3,4]. Considering the root cause of these problems, the unripe cervix is the greatest barrier to spontaneous birth, which results in great concern and unnecessary cesarean deliveries. Therefore, overcoming an unripe cervix is a critical issue. Misoprostol, a synthetic prostaglandin E1 analogue, was initially used to treat peptic ulcers caused by prostaglandin synthetase inhibitors. Because misoprostol has been used off-label for a variety of indications in the practice of obstetrics and gynecology, including medication abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage, the absolute contraindication of the use of misoprostol during pregnancy was removed from the label by the United States Food and Drug Administration in April 2002[5]. Because misoprostol has powerful uterotropic and uterotonic effects, many studies have been conducted since 1992 to learn how to administer the drug while taking into consideration safety during labor induction[6-9]. Fetal hypoxia resulting from uterine tachysystole is always an obstetrical concern[10-16]. The recommended dosage of misoprostol is 50 μg every 4 h *via* the oral route or 25 μg every 4 h *via* the vaginal route[17] until adequate labor commences, but the induction duration is prolonged. Because the risk of inducing fetal hypoxia is incurred by using a fixed dosage of misoprostol, a pilot trial using very small, frequent, titrated oral misoprostol doses every 2 h was first conducted by Hofmeyr *et al*[18,19] in 2001. It was concluded that this new approach to oral misoprostol administration was successful in minimizing the risk of uterine hyperstimulation, which has been a feature of misoprostol use for labor induction, at the expense of a somewhat slower response in women with intact membranes and unfavorable cervices[19]. Given women's different metabolic rates and responses, another method of titrating individualized oral misoprostol with dosing administered every hour relative to uterine response was developed[20-23]. It was observed that a higher success rate of vaginal delivery within 24 h, not accompanied by a higher rate of uterine hyperstimulation, was achieved using the 1-h oral misoprostol titration method (Table 1). According to the results of titration studies, misoprostol is the ideal candidate agent for labor induction and augmentation due to its convenience of administration and cervical ripening characteristics.

PRINCIPLE OF TITRATED ORAL MISOPROSTOL ADMINISTRATION

After misoprostol is absorbed, it undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and is detectable in the blood plasma[26]. Because misoprostol's effects on and toxicity to the uterus based on serum concentrations of misoprostol acid at term are unknown, the rationale for titrated administration stems from the proven efficacy and pharmacokinetics of misoprostol, and the extreme inter- and intra-individual variation in uterine sensitivity[20]. To avoid uterine hyperstimulation and shorten the labor course, misoprostol should be administered in small, frequent doses (one dose per hour, generally) titrated against the uterine response. This approach is analogous to the conventional, titrated use of oxytocin. Currently, misoprostol is available as an oral tablet of 100 or 200 μg and is water-soluble. Oral administration is easier and has greater acceptability among women than vaginal administration. Because the drug absorption is more rapid and more predictable, with a peak serum concentration after oral administration of 34 min and a half-life of 20-40 min[26], a 1-h interval between oral administrations and an increase in dosage of 20 μg every 4 h from the initial 20-μg dosage were determined to be optimal, based on a mathematical model that takes these drug characteristics into consideration[20]. This method maintains a virtually steady serum level of misoprostol acid, thus avoiding large fluctuations and increases the peak serum concentration of the 20-μg absorptive misoprostol dose every 4 h by a factor of 1.33. This mathematical model is described in Table 2.

CLINICAL PHARMACOLOGY OF MISOPROSTOL

Misoprostol does not affect the hepatic mixed-function oxidase enzyme systems. In patients with varying degrees of renal impairment, there is an approximate doubling of the $T_{1/2}$, peak serum concentration (C_{max}), and area under the serum concentration curve compared with those of normal patients, but no clear correlation between the degree of impairment and area under the serum concentration curve has been shown. No routine dosage adjustment is recommended in older patients or patients with renal impairment[27,28]. Misoprostol does not produce clinically significant effects on the serum levels of prolac-

Table 1 Comparison of titrated oral misoprostol in labor induction between studies

Ref.	Year	No. of women	Initial dosage (μg)	Dosing interval	Efficacy	Adverse effects	Cesarean rate (%)
Hofmeyr *et al*[18]	2001	25	20	q2h	72% VD within 32 h	8% UH	20.0
Hofmeyr *et al*[19]	2001	346	20	q2h	62% VD within 24 h	4% UH	16.0
Matonhodze *et al*[24]	2003	176	20	q2h	60.2% VD within 24 h	4% UH, 8% UT	14.0
Cheng *et al*[20]	2006	77	20	q1h	93.5% VD within 24 h	0% UH, 9.1% UT	3.9
Bricker *et al*[25]	2008	375	20	q2h	76% VD within 24 h	2% UH, 5% UT	14.0
Cheng *et al*[21]	2008	101	20	q1h	94.1% VD within 24 h	0% UH, 6.9% UT	4.0
Ho *et al*[22]	2010	112	20	q1h	94.6% VD within 24 h	0% UH, 7.1% UT	3.6
Souza *et al*[23]	2010	30	20	q1h	80% VD within 24 h	13.3% UT	20.0

VD: Vaginal delivery; UH: Uterine hyperstimulation; UT: Uterine tachysystole.

Table 2 Mathematical model of titrated oral misoprostol

	Times $t = 34 + 60n$, $n = 0, 1, 2, 3, \text{---}$ (min)				
Dosage (mcg)	34	94	154	214	274
20	P				
20		$P(1/4^0 + 1/4^1)$			
20			$P(1/4^0 + 1/4^1 + 1/4^2)$		
20				$P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3)$	
40					$P + P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3 + 1/4^4)$
…					

Set the function C = f(t), where C: Concentration of misoprostol acid (pg/mL) in plasma; t: Times during the whole process, $t = 34 + 60n$ (min), when taking misoprostol at $n = 0, 1, 2, 3, \text{---}$ (h); T_{max} (the time to peak plasma concentration of misoprostol acid after absorption): 34 min; $T_{1/2}$ (the half-life of misoprostol acid): 30 min as determined by a pharmacokinetics study. When $n = 0$, intake 20 μg, $t = 34$ min, set the peak plasma concentration of misoprostol acid, C = P; When $n = 1$, intake 20 μg, $t = 34 + (60 \times 1) = 94$ min, and $C = P(1/4^0 + 1/4^1)$; When $n = 2$, intake 20 μg, $t = 34 + (60 \times 2) = 154$ min, and $C = P(1/4^0 + 1/4^1 + 1/4^2)$; When $n = 3$, intake 20 μg, $t = 34 + (60 \times 3) = 214$ min, and $C = P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3)$; When $n = 4$, intake 40 μg, $t = 34 + (60 \times 3) = 214$ min, and $C = P + P(1/4^0 + 1/4^1 + 1/4^2 + 1/4^3 + 1/4^4)$ and so on. Therefore, C = f(t) is a convergent series in which the upper limit = P/(1 - 1/4) + P/(1 - 1/4) + --- = (4/3)P + (4/3)P + ---.

tin, gonadotropin, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones, creatinine or uric acid. Furthermore, gastric emptying, immunological competence, platelet aggregation, pulmonary function and the cardiovascular system are not modified by the recommended doses of misoprostol[28]. Therefore, the use of misoprostol is not contraindicated in patients with renal disease, severe anemia, systemic lupus erythematosus, hypertension or heart disease.

RISKS OF MISOPROSTOL ADMINISTRATION

Uterine rupture is an unwanted risk of labor regardless of whether a woman has had a previous caesarean delivery. Most studies suggest that the use of misoprostol in women with a previous caesarean delivery increases the frequency of uterine scar disruption, either described as uterine dehiscence or overt uterine rupture[29-31]. There are even sporadic reports of uterine rupture in women without prior cesarean surgeries[32,33]. Grand multiparity appears to be a risk factor for uterine rupture in the presence of misoprostol, although there is a report of uterine rupture in a primigravida[34]. Therefore, the indications for labor induction or augmentation must be carefully evaluated prior to misoprostol administration.

PREPARING ORAL MISOPROSTOL SOLUTIONS AND GUIDELINES FOR ADMINISTRATION

Misoprostol is manufactured as an oral tablet and is water-soluble. The uterine activity produced by an oral solution is faster and stronger than that produced by an oral tablet or when administered *via* the rectal or vaginal route[35]. One 200-μg tablet of misoprostol may be dissolved in 200 mL of drinking water in a medicine bottle. The misoprostol solution needs to be used completely within 24 h after preparation or discarded. Women are induced with one basal unit of 20 mL of misoprostol solution (1 μg/mL) prepared as described above. The determined volume of misoprostol solution is poured according to the obstetrician's discretion at each dosing, following the guidelines of labor induction[21] or augmentation[22]. Initially, the determined volume may be given upon request by an obstetrician according to the guidelines when regular uterine contractions are not achieved. Once regular uterine contractions are achieved, the obstetrician is called to visit the patient and make a decision regarding the next dose or dosage adjustment, if any. Such individualized administration of misoprostol decreases the accidental fetal hypoxia resulting from uterine hyperstimulation. The flowchart of administration is shown in Figure 1. The

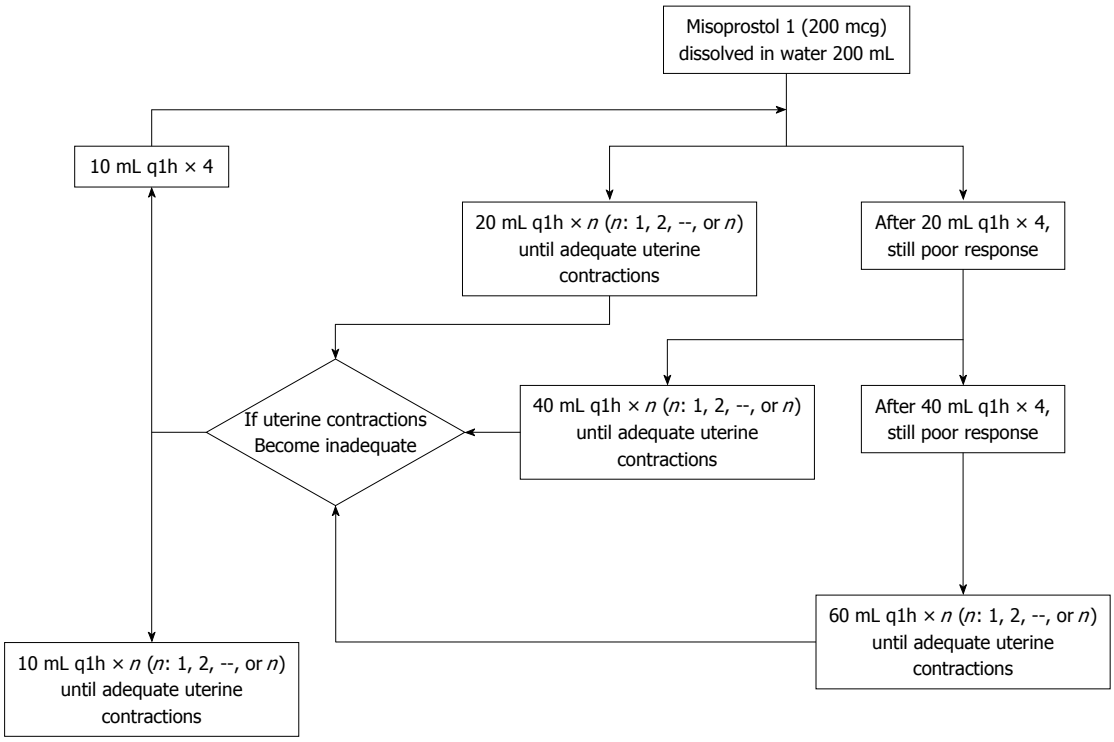

Figure 1 Flowchart of misoprostol administration.

general misoprostol administration guidelines are as follows: (1) An initial dose of 20 μg/h is administered and repeated hourly until adequate uterine contractions are achieved. If contractions do not occur after 4 doses, the dosage is increased to 40 μg/h and repeated hourly until uterine contractions are achieved, for a maximum of 4 more doses. If the response still remains poor after 8 h, the dosage can be increased to 60 μg/h until adequate contractions occur or a maximum cumulative dosage of 1600 μg is reached; (2) Adequate uterine contractions are defined as 3 or more contractions in a 10-min period, over 30-min windows. Once uterine activity is adequate for a 1-h period, no further misoprostol is administered; (3) If the contractions subsequently become inadequate, hourly doses of misoprostol solution are started at 10 μg/h and can be increased to 20 μg/h, and perhaps 40 μg/h, based on uterine responsiveness. This process is repeated until adequate uterine contractions occur or a maximum cumulative dosage of 1600 μg is reached; (4) FHR and uterine activity are continuously monitored throughout the active phase of the labor course; (5) Induction failure is defined as not entering the active phase of labor after 36 h of misoprostol treatment, with a maximum cumulative dosage of 1600 μg. Failure to progress is defined as cervical dilation or fetal descent without any progress for 3 h after entering the active labor phase; (6) Intravenous magnesium sulfate (4 g over 30 min) or any other tocolytic agent available should be given at the physician's discretion if uterine hyperstimulation occurs; (7) When the cervix achieves a Bishop score of 9, the artificial rupture of the membrane can be performed at the physician's discretion; (8) The active phase is defined as the achievement of adequate uterine contractions with a cervical dilatation of greater than 3 cm; (9) Supplemental oxytocin can be used at the physician's discretion when uterine contractions are inadequate or when entering into the active phase of labor with a favorable cervix (Bishop score > 8) because of poor response to misoprostol; and (10) Cesarean delivery is offered to all patients after induction failure, after failure of labor to progress, or when non-reassuring FHR patterns occur.

INDICATIONS AND CONTRAINDICATIONS FOR MISOPROSTOL ADMINISTRATION

The indications for labor induction with titrated oral misoprostol are the same as those for labor induction with oxytocin, including post-term pregnancy, preeclampsia, diabetes mellitus, oligohydramnios, intrauterine fetal growth restriction, and abnormal antepartum fetal surveillance results. However, to avoid adverse events, it is important for practitioners to be alert to contraindications, including a non-reassuring FHR pattern, uterine scarring, grand multiparity (≥ 5), any contraindication for labor or vaginal delivery or both, suspected placental abruption with an abnormal FHR pattern, and hypersensitivity to misoprostol or prostaglandin analogues.

ADVERSE EFFECTS AND TERATOGENICITY OF MISOPROSTOL

In published case reports[36-38], accidental overdosing with misoprostol resulted in pyrexia, hypoxia and rhabdomy-

olysis; all occurred with a single drug intake at a dosage exceeding 3000 μg. These adverse effects are signs of misoprostol toxicity and can be easily monitored when administering misoprostol. The other common side effects are nausea, vomiting and diarrhea, but these side effects rarely occur in the course of labor induction or augmentation with titrated oral misoprostol. Furthermore, these side effects are easily relieved by medication.

First trimester exposure to misoprostol is associated with facial paralysis[39], limb defects or vascular disruption defects[40,41] in newborns. In the Latina American Collaborative Study of Congenital Malformations of 4673 malformed infants and 4980 control infants, increased frequencies of transverse limb defects, ring-shaped constrictions of the extremities, arthrogryposis, hydrocephalus, holoprosencephaly and bladder exstrophy, but not Mobius syndrome, were observed in the infants exposed to misoprostol in utero[42]. There are no known reports of teratogenicity upon misoprostol ingestion when taken after the first trimester.

EFFICACY OF TITRATED ORAL MISOPROSTOL

The 1-h interval between titrated oral misoprostol administration based on pharmacokinetics has been proven to be effective in previous studies. One randomized controlled trial of titrated misoprostol compared titrated oral with vaginal misoprostol for labor induction[21]. Women between 34 and 42 wk of gestation with an unfavorable cervix (Bishop score ≤ 6) and an indication for labor induction were randomly assigned to receive titrated oral or vaginal misoprostol. The titrated oral misoprostol group received a basal unit dose of 20 mL of misoprostol solution (1 μg/mL) every hour for 4 doses, then with titration based on individual uterine responses. The vaginal group received 25 μg every 4 h until attaining a more favorable cervix. Vaginal delivery within 12 h was the primary outcome. The data were analyzed on an intention-to-treat basis. Titrated oral misoprostol and vaginal misoprostol were given to 101 (48.8%) and to 106 (51.2%) women, respectively. Completed vaginal delivery occurred within 12 h in 75 (74.3%) women in the titrated oral group and 27 (25.5%) women in the vaginal group ($P < 0.01$; RR = 8.44; 95%CI: 4.52-15.76). Four women (4.0%) in the titrated oral group and 18 (17.0%) women in the vaginal group underwent cesarean deliveries ($P < 0.01$; RR = 0.20; 95%CI: 0.07-0.62). The incidence of hyperstimulation was 0.0% in the titrated oral group compared with 11.3% in the vaginal group ($P < 0.01$; RR = 0.08; 95%CI: 0.01-0.61). Although more women experienced nausea (10.9%) in the titrated oral group ($P < 0.01$; RR = 27.07; 95%CI: 1.57-465.70), fewer infants had Apgar scores of less than 7 at 1 min in the titrated oral group compared with the vaginal group ($P < 0.01$; RR = 0.10; 95%CI: 0.01-0.76). The conclusion was that titrated oral misoprostol was associated with a lower incidence of uterine hyperstimulation and a lower cesarean delivery rate than vaginal misoprostol for labor induction in patients with unfavorable cervix.

Another randomized controlled trial compared oral titrated misoprostol with intravenous oxytocin for labor augmentation in women at 36-42 wk of gestation with spontaneous onset of active labor[22]. Women meeting the general selection criteria of having regular contractions, an effaced cervix dilated between 3 and 9 cm, and inadequate uterine contractions (2 or fewer contractions every 10 min) during the first stage of labor, were randomly assigned to titrated oral misoprostol or intravenous oxytocin. The augmentation-to-vaginal delivery interval and occurrence of vaginal delivery within 12 or 24 h were the primary outcomes. The data were analyzed on an intention-to-treat basis. Of the 231 women, 118 (51.1%) and 113 (48.9%) were randomized to titrated oral misoprostol and titrated intravenous oxytocin, respectively. The median interval from the start of augmentation to vaginal delivery was 5.22 h (3.77-8.58 h, 25th-75th percentile) in the misoprostol group, and 5.20 h (3.23-6.50 h, 25th-75th percentile) in the intravenous oxytocin group ($P = 0.019$). Complete vaginal delivery occurred within 12 h for 92 (78.0%) women in the misoprostol group and 97 (85.8%) women in the oxytocin group ($P = 0.121$; RR = 0.91; 95%CI: 0.80-1.03). There were no significant differences between the 2 groups who delivered vaginally within 24 h. Twelve (10.2%) women in the misoprostol group and 13 (11.5%) women in the oxytocin group underwent cesarean deliveries ($P = 0.744$; RR = 0.88; 95%CI: 0.42-1.85). The side effects and neonatal outcomes also did not differ between the two groups. The conclusion was that labor augmentation with titrated oral misoprostol or intravenous oxytocin resulted in similar rates of vaginal delivery within 12 and 24 h.

A retrospective review of the medical records of all patients between 37 and 42 wk of gestation with a Bishop score ≤ 6 who underwent labor induction with titrated oral misoprostol solution[43] has also been conducted. The women were allocated into two groups: nulliparous and multiparous. The women received one basal unit of misoprostol solution (20 mL, 1 μg/mL) every hour for four doses; additional doses were titrated based on individual uterine responses. The latent and active phase intervals and occurrence of vaginal delivery within 12 h were the primary outcomes. Of the 112 women included in the study, 49 (43.8%) nulliparae and 63 (56.2%) multiparae underwent labor induction with titrated oral misoprostol solution. Although fewer women delivered vaginally within 12 h in the nulliparous group than in the multiparous group (42.9% *vs* 85.7%; $P < 0.01$; RR = 0.54; 95%CI: 0.39-0.76), there was no significant difference between the two groups regarding vaginal delivery within 24 h (87.8% *vs* 100.0%; $P = 0.09$; RR = 0.96; 95%CI: 0.90-1.02). Four (8.2%) women in the nulliparous group and none (0.0%) of the women in the multiparous group underwent caesarean deliveries ($P = 0.02$; RR = 1.09; 95%CI: 1.00-1.18). All induction durations, including the latent and active phases, were significantly shorter in the multiparous

group ($P < 0.01$). Induction failure did not occur in any patient in either of the groups. There was no instance of hyperstimulation, which was defined as tachysystole or hypertonus with a non-reassuring FHR pattern, although tachysystole, defined as the presence of at least 6 contractions in 10 min over at least 2 10-min windows, occurred in 4 (8.2%) nulliparous women and 4 (6.3%) multiparous women. Hypertonus, defined as a single contraction lasting more than 2 min, did not occur in either group. None of the neonates in either group had Apgar scores of < 7 at 1 min. The conclusion was that titrated oral misoprostol solution was a promising method of labor induction for both nulliparous and multiparous women.

SUMMARY AND FUTURE PROSPECTS

Cesarean birth rates are greater than 20% in many developed countries[44]. The main diagnoses contributing to the high rate of cesarean births in nulliparous women are dystocia and prolonged labor. Traditionally, a policy of vaginal dinoprostone for the treatment of an immature cervix or early amniotomy with oxytocin administration for mature cervices for the prevention of a delay in labor progress is associated with a modest reduction in the rate of cesarean births[45]. However, the course of vaginal dinoprostone or misoprostol is tedious, and excessive uterine contractility resulting in fetal distress is always a concern with the oral or vaginal use of fixed-dosage misoprostol. Oxytocin administration through the intravenous route needs to be under the control of an intravenous pump and may be inconvenient in certain settings. Because titrated oral misoprostol solution is easier to administer than titrated intravenous oxytocin, it is worth conducting these treatment regimens for labor induction or augmentation. In addition, misoprostol offers several advantages over dinoprostone and oxytocin, including a longer shelf life, stability at room temperature, and easy administration. It is an ideal alternative to traditional dinoprostone or oxytocin for labor induction or augmentation. In consideration of inter- and intra-individual variations of drug response during the dosing course, it is reasonable that the titrated oral misoprostol solution may replace fixed-dosage misoprostol *via* the vaginal or oral route for labor induction or augmentation. In addition, the use of titrated oral misoprostol is superior to the traditional use of vaginal misoprostol in completing vaginal deliveries to reduce the cesarean rate, based on previous randomized controlled trials[21]. However, further studies are needed to determine the minimal plasma misoprostol concentration necessary to induce a uterine response during labor induction at term and to validate the mathematical model of titrated oral misoprostol. This information will help ensure the obstetric use of misoprostol.

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Folic acid supplementation: The new dawn for postmenopausal women with hot flushes

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Abstract

Hot flushes, experienced by 75% of menopausal women, are associated with estrogen deprivation. Estrogen was shown to ameliorate hot flushes by interacting with monoamine neurotransmitters in the brain; reducing noradrenaline and increasing serotonin. Hormone replacement therapy (HRT), the first treatment option, causes concerns over possible increased risks particularly breast cancer. Folic acid is involved in the biosynthesis of serotonin and nordrenaline, which is responsible for its effects on mood and cognition, and degrees of folate inadequacy, not severe enough to produce megaloblastic anaemia, were found to be associated with depression and cognitive malfunctioning. Also, increased age was observed to relate to reduced serum and cerebrospinal fluid folic acid levels. There is emerging evidence that folic acid supplementation ameliorates hot flushes by the same mechanism as estrogen. To explore this hypothesis, a multi-centre, double-blind, placebo-controlled randomized is being set up to compare the effect of 5 mg folic acid *vs* placebo in reducing the frequency and severity of hot flushes in postmenopausal women, and on the blood level of serotonin and noradrenaline. If folic acid supplementation is demonstrated to be effective, this will be a turning point in the clinical practice since it represents a cheap, safe and well-tolerated alternative to HRT.

Key words: Folic acid; Hot flushes; Menopause; Noradrenaline; Serotonin

Core tip: Hormone replacement therapy usage by postmenopausal women with hot flushes causes concerns over possible increased risks particularly breast cancer. The improved longevity of women in general and breast cancer survivors in particular, and the limited success shown by the non-hormonal alternatives made it imperative to find a therapy that is effective and safe. It is hypothesized that folic acid supplementation may ameliorate hot flushes by the same mechanism as estrogen supplementation, *i.e.*, by reducing noradrenaline and increasing serotonin neurotransmitters. This article discusses the rationale, potential role, mechanisms of action and safety issues related to its use in these women.

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CURRENT DILEMMA

Hot flushes, the most characteristic menopausal symptom, are experienced by up to 75% of menopausal women, and in half of them symptoms are severe enough to seek medical advice[1]. Hot flushes are associated with estrogen deprivation and they are the most commonly reported side effect of the selective estrogen receptor modulators[2]. Therefore, hormone replacement therapy (HRT)

is the first treatment option[3]. However, the perception of the risks and benefits of HRT had changed since the publication of Women's Health Initiative Trial in 2002[4], and an increasing number of women are seeking alternatives for conventional HRT because of the concerns over possible increased risks particularly breast cancer[3]. In addition, there is evidence that non-hormonal mechanisms play an important role in the pathophysiology of hot flushes[3,5].

Treatment of breast and endometrial cancer frequently results in the loss of ovarian function and menopausal symptoms. Symptoms of iatrogenic menopause are usually more intense than those of natural menopause due to sudden onset of symptoms, younger age, and the physical and psychological impacts such as body image concerns and sexual dysfunction[6]. Furthermore, the improved longevity of breast cancer patients and the increased use, in recent years, of aromatase inhibitors over tamoxifen, leading to profound estrogen deprivation[7,8], made it imperative to find a therapy that is effective and safe. In addition, the use HRT in breast and endometrial cancer survivors is not welcomed by most women and doctors because of the potential stimulation of residual cancer and the induction of new hormone-sensitive disease[9]. The non-hormonal alternatives which are commonly proposed to these women showed a limited success[3,10-12].

HOT FLUSHES - THE MECHANISM AND ROLE OF ESTROGEN

The entire episode of hot flushes usually lasts no more than 1-3 min. The frequency can range from 5 per year to 50 per day, with great variations among individuals or even within an individual, although 5-10 times per day is more common. They generally persist for 1 to 5 years, but in some women they can continue for as long as 44 years. There is no accepted metric for measuring severity of hot flushes[13].

Hot flushes exact aetiology is not yet understood. Although many theories were postulated to explain the pathophysiology, none of them could explain all aspects of hot flushes. Estrogen replacement was shown to ameliorate hot flushes by interacting with monoamine neurotransmitters in the brain; noradrenaline and serotonin [5-hydroxytryptamine (5-HT)][1,2].

It was hypothesized that hot flushes are triggered within the hypothalamus by α_2-adrenergic receptors on noradrenergic neurons. There is evidence to suggest increased central noradrenergic activity in women suffering from flushes, leading to disturbances in the thermoregulatory centre which is probably responsible for the occurrence of flushes[14]. It was found that yohimbine, an α_2-adrenergic antagonist, increased central noradrenaline release, provoking hot flushes, while clonidine, an α_2-adrenergic agonist, reduced central noradrenaline release, raised the sweating threshold and lowered the shivering threshold, leading to amelioration of flushes[14-16]. This theory was further supported by finding significantly elevated plasma levels of 3-methoxy 4-hydroxy phenyl glycol (MHPG), the end metabolite of brain noradrenaline in women with hot flushes[17,18].

Furthermore, it was found that 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_7$ receptors are implicated in hypothalamic control of temperature[2,19]. It was hypothesized that hot flushes are the net result of activation of estrogen withdrawal induced up regulated 5-HT$_{2A}$ receptors in the hypothalamus by mild internal or external stimuli such as high ambient temperatures, anxiety, coffee, or alcohol, resulting in a hyperthermic response[5]. Estrogen affects the function of serotonin neural system, and the blood levels of serotonin fluctuate with the circulating levels of estrogen. In spontaneous and surgically menopausal women, it was found that blood levels of serotonin were reduced by about 50% when compared to premenopausal controls and estrogen replacement restored levels to normal[20]. Further, estrogen replacement in postmenopausal women augmented serotonergic activity, increased the excretion of 5-hydroxyindoleacetic acid (5-HIAA; the main metabolite of serotonin)[21] and increased the expression of tryptophan hydroxylase, the key enzyme in serotonin biosynthesis[19]. In addition, a number of serotonergic compounds such as serotonin re-uptake inhibitors fluoxetine, venlafaxine, sertraline and paroxetine, and the serotonin disinhibition mianserin and mirtazapine were shown to reduce both the number and intensity of hot flushes[5].

FOLIC ACID: WHAT CLINICIANS NEED TO KNOW?

Background

Folic acid, a water-soluble B-Vitamin, serves as the parent for a large family of compounds having similar nutritional value to which the generic term "folates" is applied[22]. As per the definition of a vitamin, it cannot be synthesized *de novo,* and must be derived from diet or supplementation. Dietary folates is found in leafy green vegetables, legumes, beans, liver, citrus fruits and yeast[23]. The name "folate" derives from the Latin for leaf *(folia)* since leafy green vegetables do contain folate[24,25]. Multiple biochemical conversions are required for dietary folates to become tetrahydrofolates; the metabolically active and tissue-usable forms. Folates are involved - *via* donation of a methyl group - in numerous biochemical pathways including monoamine neurotransmitters synthesis, which is responsible for its effects on mood and cognition[23-25].

Pharmacokinetics

Folic acid, the synthetic molecule, is highly absorbed (85%-95%) when compared to the dietary form (50%). Folate absorption takes place in the lumen of the proximal small intestine. After assimilation by the intestinal epithelial cells, a substantial fraction of the absorbed folate is methylated and reduced, partly through the action of "methylene tetrahydrofolate reductase enzyme", to 5-methyl tetrahydrofolate, which is the main circulating form of folic acid[23]. Vitamin B$_{12}$ is involved in the methyla-

tion of homocysteine to methionine, which is needed to convert 5-methyl tetrahydrofolate to tetrahydrofolate[22]. The peak folate serum level after oral administration is reached within 30 to 60 min. The average value of folic acid in serum is 7-36 nmol/L. Tetrahydrofolate and its derivatives are distributed in all body tissues. The liver, the principal storage site, contains half of the total body stores followed by erythrocytes. The normal erythrocyte level is about 320-1300 nmol/L[25,26].

Safety

Folic acid is usually well-tolerated with no adverse effects associated with the consumption of excess folates from food in human[24,27]. Daily oral supplements of 5-10 mg synthetic folic acid appear to be well tolerated and rarely cause side effects in healthy individuals[28-30]. A few cases of allergic reactions have been reported including skin rash, swelling of the face, lips, tongue or throat, or bronchospasm[26,31,32]. Caution is necessary in administering folic acid supplements alone in megaloblastic anaemia. If the cause is vitamin B12 deficiency, the megaloblastic anaemia may be corrected , but any nuerological manifestations (*e.g.*, subacute combined degeneration of the cord) are likely to get worse[24]. Folic acid supplements should be used with cautions also in patients with epilepsy because seizures activity may be induced since it reduces the serum level of some anti-convulsants[28]. A recent meta-analysis found no increase in overall and site-specific cancer incidence in the randomized controlled trials of folic acid supplementation at doses higher than those from fortification. It included 13 trials (with 49621 participants) that compared folic acid *vs* placebo, had treatment duration of at least 1 year, and included at least 500 participants. It was found that, during an average treatment duration of 5.2 years, folic acid supplementation increased folate serum concentrations by 4-fold (573 nmol/L for the folic acid groups *vs* 135 nmol/L for the placebo groups), but had no significant effect on overall cancer incidence (1904 cancers in the folic acid groups *vs* 1809 cancers in the placebo groups, RR = 1.06, 95%CI: 0.99-1.13, $P = 0.10$). There was also no trend towards greater effect with longer treatment durations[33].

HOW FOLIC ACID COULD AFFECT BRAIN FUNCTION

Folic acid is essential for the functioning of the nervous system. It is necessary for the biosynthesis of the monoamine neurotransmitters serotonin, noradrenaline and dopamine. 5-methyltetrahydrofolate, participates in re-methylation of the amino acid metabolite homocysteine, creating methionine. The downstream metabolite of methionine; S-adenosylmethionine, is involved in numerous one-carbon methylation reactions in the body, including those that create neurotransmitters, *i.e.*, S-adenosylmethionine must be present as a methyl donor for both the serotonin and catecholamine pathways to function properly. After donation of its methyl group, S-adenosylmethionine becomes homocysteine[23,34,35]. At this point, homocysteine must either be further metabolized to become cysteine, taurine, and glutathione or re-methylated to become methionine again. Re-methylation is done *via* "methionine synthetase", which facilitates the donation of a methyl group from vitamin B12 (which gets its methyl group from 5-methyltetrahydrofolate). Therefore, some researchers believe homocysteine is simply a marker of folate and/or B12 deficiency. Without the participation of 5-methyltetrahydrofolate in this process, S-adenosylmethionine and neurotransmitter levels decrease in the cerebrospinal fluid[23,34,35].

5-methyltetrahydrofolate also appears to stabilize, enhance production of, or possibly act as a substitute for tetrahydrobiopterin (BH4), which is an essential nutrient cofactor in the biosynthesis monoamine neurotransmitters serotonin, dopamine, noradrenaline, and adrenaline[23,34,35]. It appears to be important in regenerating BH4, which is highly susceptible to oxidation. In the absence of an adequate amount of BH4, 5-methyl tetrahydrofolate may substitutes for BH4 in the "hydroxylase enzymes" involved in monoamine neurotransmitters synthesis[36,37].

Folic acid deficiency in depression and old age

Over the past four decades, degrees of folate deficiency not severe enough to produce megaloblastic anaemia, were found to be associated with psychological symptoms, particularly depressive symptoms (*e.g.*, apathy, fatigue, insomnia, irritability and concentration difficulties) and impaired cognitive functioning[38-40]. Up to 71% of individuals with severe folic acid deficiency were found to have depression[41], and a French study found a significant association between high folate intake and a lower risk of depression in middle-aged men and women[42]. Bottiglieri *et al*[34], in a study of 46 inpatients with severe depression, found that 52% of them were having high homocysteine. Further, depressed patients with increased serum homocysteine had significantly lower (1) serum, red blood cell and cerebrospinal fluid folate; (2) cerebrospinal fluid S-adenosylmethionine; and (3) the metabolites of serotonin, noradrenaline and dopamine.

Several studies reported that low blood levels of folate and vitamin B12, and high levels of homocysteine were correlated with depression especially in the elderly[34,40,41]. A recent meta-analysis of 11 studies ($n = 15315$) found a significant relationship between the risk of depression and low folate status[43,44], and it was reported that 15%-38% of adults with severe depression had borderline or low serum and red blood cell folic acid[23,45-47]. It is estimated that 20%-30% of individuals with depression have also high homocystein levels[35,43,48-50]. Investigations revealed a connection between high homocysteine levels and brain dysfunction, including cognitive function, dementia, Alzheimer's disease, and depression[23] because it has a neurotoxic effect through several mechanisms, including impaired methylation, excitotoxicity, oxidative stress and hypoxia in the central nervous system[49]. Folate deficiency, by elevating homocysteine levels, may have a

role in depression[51], and folic acid supplementation was shown to reduce elevated homocysteine levels[52].

Increased age has been observed to relate to reduced serum and cerebrospinal fluid folic acid concentrations, and with increased, homocysteine levels at the same time[43]. The results of the studies are conflicting as regards the relation between depression and serum folic acid level in elderly population with some failing to identify a relationship[51,53] and others showing an inverse relationship[54,55]. It may be argued that folic acid deficiency in individuals with depression, particularly the elderly, might be attributed to poor nutrition, medication, chronic disease, increased needs, or malabsorption; however, low folic acid levels were observed in overweight individuals with depression, and in individuals who had gained weight inadvertently[40,47].

FOLIC ACID MAY CURE HOT FLUSHES: THE CLINICAL EVIDENCE SO FAR

The scientific literatures were searched using NHS evidence website: www.evidence.nhs.uk on March 4, 2013. Then under Journals and Databases, "Healthcare Databases Advanced Search" was accessed and the following databases were searched; AMED, BNI, CINAHL, EMBASE, HEALTH BUSINESS ELITE; HMIC, MEDLINE, PsycINFO. The key words for search were: "folic acid and menopausal women" and "folic acid and hot flushes". The search result was combined using "OR" and retrieved 44 articles. Only one original article[56], an abstract[57] and a hypothesis[58] were found (n = 3). The rest of the articles have been excluded; duplicates (n = 22) or non-relevant articles (n = 19).

Gaweesh *et al*[56], in a small prospective cohort study, examined the effect of folic acid 5 mg supplementation *vs* placebo for 4 wk on the occurrence of hot flushes in 46 healthy postmenopausal Egyptian women. In the treatment group, there was significant improvement of symptoms and significant lowering in plasma levels of MHPG. There was significant negative correlation between clinical improvement in hot flushes and the plasma level of MHPG. The improvement was described as "good" on complete disappearance of hot flushes, and "moderate" when the frequency and intensity of the flushes were satisfactorily reduced. The level of improvement was subjectively decided by women based on their overall feeling as regards the number and intensity of hot flushes. In the treatment group, 9 (39.1%), 6 (26.1%) and 8 (34.8%) women had good, moderate and no improvement, respectively. The equivalent figures for the control group were 1 (5.3%), 2 (10.5%) and 16 (84.2%), respectively. The number of women who had good improvement was significantly higher in the treatment group (P = 0.01), but the difference between the two groups as regards moderate improvement did not reach statistical significance (P = 0.26). The number of women who had no improvement was significantly higher (P = 0.002) in the control group. On comparing the mean plasma levels of MHPG before and after treatment in both groups, a significant lowering in mean level was found in the treatment group (t = 6.12, mean % change = -24.1 ± 17.9, P < 0.001) when compared with the control group (t = 1.72, mean % change = -5.59 ± 16.4, P = 0.10). In the treatment group, the test of correlation [Spearman's rank correlation coefficient (r)] showed a significant negative correlation between clinical improvement in hot flushes and the plasma level of MHPG (r = -0.453, P = 0.03).

Although these results are encouraging, the study had many limitations. First, the study was underpowered with small number of participants which is not sufficient to generalize the results. Second, folic acid supplementation was given for a short duration disallowing evaluation of its benefit on the medium and long terms. Last, the bias in allocation and assessment cannot be excluded since it is not a randomized double blind controlled study.

The second study, which was published as an abstract and included two groups (n = 20 each), investigated the effect of 5 mg folic acid supplementation for 4 wk *vs* no treatment. The treatment group demonstrated an average of 57% reduction in the frequency in hot flushes by the 4th week of treatment, while no change was observed in the control group[57].

HOW MIGHT FOLIC ACID AMELIORATE HOT FLUSHES?

Hot flushes possibly occur because of the increased central noradrenergic activity leading to disturbances in the thermoregulatory centre[14,17,18], and/or activation of estrogen withdrawal induced up-regulated 5-HT$_{2A}$ receptors in the hypothalamus by mild internal or external stimuli resulting in a hyperthermic response[5]. Animal studies reported that folic acid, like estrogen, reduced noradrenaline secretion[59,60], and increased serotonin activity[59]. It was found that folic acid administered to mice produced an antidepressant-like effect mediated by an interaction with the noradrenergic receptors (α_1 and α_2) and serotonergic receptors (5-HT$_{1A}$ and 5-HT$_{2A/2C}$)[59].

It was suggested that the link between folate and noradrenaline and serotonin metabolism is probably through BH4 since there is a significant positive correlation between its CSF levels with that of 5-HIAA and red cell folate in patients with severe depression[34,61]. As previously mentioned, 5-methyltetrahydrofolate appears to stabilize, enhance production of, or possibly act as a substitute for BH4, which an essential nutrient cofactor in the biosynthesis of serotonin and noradrenaline[23,34,35]. 5-methyltetrahydrofolate causes a significant reduction in the noradrenaline secretion to only 12.9% of control release, probably by duplicating the rate limiting behaviour of a synthetic pteridine cofactor "DL,2-amino-4-hydroxy-6,7,dimethyltetrahydropteridine"[60]. Further, folate deficiency was associated with decreased serotonin activity[38], and supplementation with folic acid increased CSF levels of 5-HIAA in folate deficient patients with depression[62]. Interestingly, it was found that the regional

distribution of 5-methyltetrahydrofolate in the brain was similar to that of serotonin[63].

Slopien *et al*[64] suggested that there might be a role for folate and possible methionine metabolism involvement in the development of depression in postmenopausal women, and it was also reported that there is an association between hot flushes and high rate of depression both in postmenopausal[65-67] and perimenopausal women[68].

THE FUTURE

It is plausible to assume that folic acid supplementation objectively ameliorates hot flushes by the same mechanism as estrogen replacement, *i.e.*, by interacting with monoamine neurotransmitters in the brain; namely noradrenaline and serotonin. It lowers noradrenaline and increases serotonin activities. Nevertheless, there is a need for well designed studies: (1) To investigate the effect of folic acid supplementation on the frequency and severity of hot flushes; (2) To explore whether symptomatic postmenopausal women are deficient in folate, and which patients are most suitable for folic acid therapy. It should be borne in mind that folate levels in the normal range might still be inadequate for the purpose of methyl donation and neurotransmitter synthesis in some individuals[23]; (3) To find out the optimum dose and the proper duration of therapy. Although 5 mg folic acid supplementation is considered as the standard dose, some investigators alleged that small doses up to 2 mg administered over a long time span may be preferable because the entry of folate in the nervous system is limited by the blood brain barrier, thus rendering large quantities inefficient[41]; and (4) To study the correlation between folate levels and monoamine neurotransmitters serotonin and noradrenaline.

To resolve some of these issues, a multi-centre, double-blind, placebo-controlled randomized, phase III trial is being set up and sponsored by "University of Birmingham" and "Sandwell and West Birmingham Hospitals NHS Trust", United Kingdom to directly compare the effect of 5mg folic acid *vs* placebo in reducing the frequency and severity of hot flushes in postmenopausal women, and on the blood level of monoamine neurotransmitters serotonin and noradrenaline. If folic acid supplementation is demonstrated to be effective, this will be a turning point in the clinical practice worldwide since it represents a cheap, safe, well-tolerated alternative to the conventional HRT, particularly in breast and endometrial cancer survivors who have no options at the moment but to live with their disabling symptoms.

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TOPIC HIGHLIGHT

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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in epithelial ovarian cancer: State of the art

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Abstract

Advanced stage epithelial ovarian cancer (EOC) is difficult to treat with low overall cure rates. A new strategy combining maximal cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has been proposed to treat advanced stage EOC in the primary setting. Numerous small, heterogeneous studies have been conducted exploring outcomes in patients with predominantly advanced, recurrent or refractory disease treated with CRS + HIPEC. Although morbidity rates approaching 35% have been reported, oncologic outcomes are promising. Incorporation of HIPEC for the treatment of primary EOC has continued to gain interest. Several prospective phase 2 clinical trials were recently completed evaluating the impact of CRS + HIPEC in the primary setting. This article will briefly discuss the benefits of optimal surgical cytoreduction and the theoretical basis of intraperitoneal chemotherapy in patients with advanced stage EOC, and will then review existing literature describing oncologic outcomes in EOC patients treated with HIPEC in the primary setting.

Key words: Epithelial ovarian cancer; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Intraperitoneal chemotherapy; Survival; Toxicity

Core tip: Hyperthermic intraperitoneal chemotherapy (HIPEC), when used in combination with successful surgical cytoreduction appears to result in promising oncologic outcomes. We will eagerly await the results of the various phase 3 clinic trials, and until that time advocate the use of cytoreductive surgery + HIPEC in experienced centers under the auspices of appropriate institutional research programs.

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INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for 25% of all malignancies affecting the female genital tract, and is the most lethal gynecologic malignancy[1]. In 2012 there will be an estimated 22280 new ovarian cancer cases in the United States, with 15500 deaths[1]. Advanced stage EOC is traditionally managed with surgery, followed by platinum and taxane based combination chemotherapy[2,3].

Several factors have been identified as prognostic

for clinical outcome in patients with EOC, with extent of residual disease being investigated in numerous studies[4]. Specifically, a differential survival impact between patients with no gross residual disease *vs* optimal but visible residual disease (0.1-1.0 cm in maximal diameter) has been illustrated in patients with optimally resected stage 3 EOC[4]. These findings have been validated by other authors[5,6]. Currently, the Gynecologic Oncology Group (GOG) defines optimal residual disease as $\leqslant$ 1 cm. The reason cytoreductive surgery (CRS) is thought to be effective when combined with chemotherapy is that it removes bulky disease containing poorly oxygenated, non-proliferating cells which are either resistant or potentially resistant to chemotherapy, leaving small volume tumors, with a higher proportion of cells in the proliferative phase, that are more susceptible to chemotherapy[7].

In addition to aggressive CRS, our understanding of the distribution pattern of ovarian cancer catalyzed numerous clinical studies exploring the feasibility of intraperitoneal administration of chemotherapy. Ovarian cancer typically spreads in a diffuse intra-abdominal fashion, often limited to the peritoneal cavity, less frequently metastasizing *via* hematogenous or lymphatic routes. Despite advanced surgical techniques, microscopic tumor implants commonly remain along the peritoneal surface. Animal models suggested the ability of intraperitoneal administration of cytotoxic agents to lead to cancer cell death in lesions measuring 2-3 mm in largest diameter[8]. Therefore, successful CRS is a main pre-requisite for intraperitoneal administration of chemotherapy[9]. Furthermore, due to the presence of a peritoneal-plasma barrier, chemotherapeutic agents remain concentrated (20-1000 fold) in the peritoneal cavity for a prolonged period of time resulting in enhanced cancer cell death, with theoretically less systemic toxicity[7,10,11].

Three pivotal clinical trials were completed evaluating the impact of intraperitoneal (IP) chemotherapy on survival in patients with advanced stage ovarian cancer[12-14]. Initially, 2 randomized phase 3 intergroup trials comparing intravenous (IV) to IV + IP chemotherapy showed positive results. The GOG subsequently developed and opened protocol 172, which compared IV paclitaxel (135 mg/m^2) over 24 h with IV cisplatin (75 mg/m^2) on day 2, *vs* IV paclitaxel (135 mg/m^2) over 24 h, followed by IP cisplatin (100 mg/m^2) on day 2 and IP paclitaxel (60 mg/m^2) on day 8. A total of 6 courses were administered every 3 wk[14]. All patients had optimally resected disease with residual tumor limited to less than or equal to 1 cm in size. The median survival for the IV only and IV + IP arms were 49.5 and 66.9 mo respectively. The RR of death was 0.71 in the IP group (P = 0.0076). The authors noted that tolerability for IP chemo was a concern as grade 3 and 4 hematologic, metabolic, and gastrointestinal toxicities were significantly more common in the IP arm. Remarkably, only 86 patients (42%) of 205 allocated to the IP arm completed 6 cycles of chemotherapy, and 98 (48%) received 3 cycles or fewer of the assigned treatment.

The results of GOG 172, in combination with previous positive studies exploring intraperitoneal chemotherapy, resulted in a National Cancer Institute (NCI) clinical announcement recommending that women with optimally cytoreduced stage 3 ovarian cancer be considered for IV + IP therapy[15]. Unfortunately, adoption of the IP regimen described in protocol 172 has been limited, due to the high rate of grade 3/4 toxicities, inconvenience of in-patient administration, and poor patient tolerance.

Attempts at modification of the original regimen have been made in an effort to improve compliance and decrease toxicity. Barlin *et al*[16] investigated the oncologic outcomes associated with an outpatient IP regimen in 102 patients with optimally cytoreduced EOC. The modified regimen consisted of IV paclitaxel (135 mg/m^2) over 3 h on day 1, IP cisplatin (75 mg/m^2) on day 2, and IP paclitaxel (60 mg/m^2) on day 8, given every 21 d for 6 cycles. The median PFS and OS were 29 and 67 mo, respectively. Importantly, 80% of subjects completed 4 or more cycles of IV + IP therapy. The most frequently reported grade 3/4 toxicities included neutropenia (12%), gastrointestinal (8%) and neurologic (6%)[16]. GOG protocol 252, which completed accrual in November 2011, will help elucidate the role of intraperitoneal chemotherapy in patients with optimally resected EOC, as well as the potential role of both dose dense paclitaxel and the anti-angiogenic agent bevacizumab.

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

In an effort to obviate the toxicities encountered with repetitive cycles of intraperitoneal chemotherapy, investigators have explored the use of a single course of intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) followed by conventional intravenous chemotherapy. The concept of HIPEC is based on several important principles: (1) the direct and preferential cytotoxic effect of hyperthermia on tumor cells; (2) synergistic effects of hyperthermia when used with conventional cytotoxic agents without an associated increase in toxicity; and (3) increased drug penetration, from 3 to 5 mm, secondary to hyperthermia[17-24].

In addition, the presence of extensive adhesions in the post-operative period are hypothesized to result in both impaired drug distribution and significant toxicity/pain when traditional IP chemotherapy is given in the adjuvant setting. Utilization of intra-operative HIPEC, at the time of initial CRS, guarantees uniform distribution and systemic peritoneal coverage, potentially enhancing the anti-tumor efficacy of the drugs used.

Based on the theoretical principles described above, HIPEC was first examined in patients with peritoneal carcinomatosis due to gastrointestinal malignancies, *pseudomyxoma peritonei* and peritoneal mesothelioma[25-28]. In the surgical setting, these trails illustrated the safety and feasibility of hyperthermic intraperitoneal drug administration.

Table 1 Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy in the treatment of advanced stage primary epithelial ovarian cancer: retrospective and observational studies: Study characteristics

Ref.	*n*	Disease stage	Setting of treatment	HIPEC drug and dose	Temp. (℃)	Duration of treatment (min)	Oncologic outcome	Common grade 2-3 toxicities	Mortality rate
Tentes *et al*[8]	43	"Locally advanced" ovarian cancer	23 primary 20 recurrent	Doxorubicin 15 mg/m^2 + Cisplatin 50 mg/m^2 or Gemcitabine 1000 mg/m^2	42.5-43	60 or 90	5-yr OS: 54% In primary population 5-yr OS 82.5%	Hematologic; GI; infectious	2 deaths (sepsis)
Steller *et al*[31]	6	2-3 EOC	2 primary 4 recurrent	Carboplatin 800-1200 mg/m^2	42	90	All alive at 15 mo follow up; 5 without evidence of disease	Hematologic	No deaths
Piso *et al*[33]	19	3-4 EOC	8 primary 11 recurrent	Cisplatin 75 mg/m^2 + Mitoxantrone 15 mg/m^2	41.5	90	Median PFS 18 mo; mean OS 33 mo; 5 yr survival 15%	Hematologic; GI (anastomotic leak, fistula); bleeding; abscess	1 death (sepsis)
Rufián *et al*[35]	33	3 EOC	19 primary 14 recurrent	Paclitaxel 60 mg/m^2	41-43	60	In primary population median relapse free survival was 25 mo; median OS 38 mo	Hematologic; infectious; GI (bleeding and perforation)	No deaths
Lentz *et al*[37]	25	3 EOC	11 primary 14 recurrent	Carboplatin 400-1200 mg/m^2	Inflow < 43.5	90	Not reported	One PE; one superficial wound dehiscence	No deaths
Pavlov *et al*[39]	56	3-4 EOC	31 primary 25 recurrent	Doxorubicin 0.1 mg/kg + Cisplatin 15 mg/m^2	40	180	Median OS 38.1 mo; 5-yr OS 67%	Hematologic; GI (anastomotic leak, obstruction)	1 death (CVA)

HIPEC: Hyperthermic intraperitonealchemotherapy; Temp.: Temperature; OS: Overall survival; GI: Gastrointestinal; EOC: Epithelial ovarian cancer; PFS: Progression free survival; PE: Pulmonary embolism; CVA: Cerebral-vascular accident.

HIPEC AND OVARIAN CANCER

Observational and retrospective studies

In 1990, Cohen and Robins proposed HIPEC for the treatment of recurrent ovarian cancer[29,30]. Steller *et al*[31] studied the feasibility, toxicity and pharmacokinetics of intraperitoneal hyperthermic carboplatin administration in 6 patients at the time of primary surgical cytoreduction. Shortly thereafter, Hager *et al*[32] conducted a prospective clinical trial on 36 patients with recurrent ovarian cancer treated with CRS and HIPEC. The median OS from the first HIPEC chemotherapy treatment was 19 ± 4 mo. The 5-year OS of all patients from the start of the first HIPEC treatment was 16% ± 7%. The authors described the adverse effects as mild when compared to systemic chemotherapy.

This was followed by a study conducted by Piso *et al*[33] of 19 patients with peritoneal carcinomatosis due to primary or recurrent EOC. Surgery was followed by intraoperative HIPEC using single agent cisplatin (n = 16) or mitoxantrone (n = 3). The median progression free interval was 18 mo (range 6-36 mo), with mean overall survival time of 33 mo and a 5-year survival rate of 15%. The most common complications encountered were anastomotic leak (2 of 19) and intra-abdominal abscess formation (2 of 19)[33]. Additional studies evaluating the clinical effect of HIPEC in patients with advanced stage ovarian cancer were completed in an effort to determine the most appropriate/effective chemotherapeutic agent and the ideal hyperthermic temperature (Table 1)[8,34-39].

Ryu *et al*[34] retrospectively reviewed 117 patients with ovarian cancer, 57 who underwent CRS (conventional treatment) with HIPEC and 60 who underwent conventional treatment only. The investigators studied a HIPEC mixture consisting of carboplatin (350 mg/m^2) and interferon-α (5000000 IU/m^2). Intraperitoneal temperature was maintained at 43-44 ℃ during surgery. The overall 5-year survival rate was significantly greater in the HIPEC group *vs* control (63.4% *vs* 52.8%, respectively, P = 0.0078). This survival advantage was more pronounced amongst the subset of patients with stage 3 disease (53.8% in the HIPEC group *vs* 33.3% in the control group, P = 0.0015). In multivariate analysis, HIPEC was identified as an independent prognostic factor.

HIPEC was also studied in the recurrent setting. Zanon *et al*[40] examined the use of combined CRS and HIPEC in 30 women with recurrent EOC. Enrolled subjects underwent extensive CRS followed by intraoperative HIPEC with cisplatin (100-150 mg/m^2). In patient's cytoreduced to ⩽ 2.5 mm of residual disease, progression free survival was 17.1 mo, with an overall survival of 37.8 mo. Major post-operative morbidity occurred in 16.7% of subjects, with gastrointestinal toxicities (anastomotic leak and perforations) being the most commonly reported. One treatment related mortality, a fatal pulmonary embolism, occurred 30 d following discharge. Cotte *et al*[41] prospectively studied combination CRS + HIPEC in 81 patients with recurrent or chemotherapy resistant peritoneal carcinomatosis from ovarian cancer. Mortality and morbidity rates were 2.5% and 13.6%, respectively. With a median follow-up of 47.1 mo, the overall and disease-free median survivals were 28.4 and 19.2 mo, respectively.

HIPEC in combination with secondary cytoreduction was further investigated as consolidation therapy in patients with advanced stage EOC following surgery and systemic intravenous chemotherapy[29,42-44]. Within this

Table 2 Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy in the treatment of advanced stage primary epithelial ovarian cancer: prospective phase 2 trials

Ref.	*n*	Disease stage	Setting of treatment	HIPEC drug used and dose	Temp. (℃)	Duration of treatment (min)	OS (mo)	PFS (mo)	Common grade 2-3 toxicities	Mortality rate
Di Giorgio *et al*[47]	47	3C-4 EOC	22 primary 25 recurrent	Cisplatin 75 mg/m^2	42-43	60	30.4 (mean)	27.4 (mean)	Pleural effusions (8.5%) Infectious (8.5%) GI (10.6%) Bleeding (6.4%)	4% (PE)
Lim *et al*[48]	30	3-4 EOC	30 primary (14 of which underwent neoadjuvant treatment)	Cisplatin 75 mg/m^2	41.5	90	NR	NR	Hematologic (86.7%) GI (30%) Infectious (16.7%) Pulmonary (23.3%) CV (13.3%)	No deaths
Ansaloni *et al*[49]	26	3-4 EOC	26 primary	Cisplatin 40 mg/L perfusate + doxorubicin 15 mg/L perfusate	42.5	90	Not reached 5-yr OS 60.7%	30 (median) 5-yr PFS 15.2%	Hematologic (4%) GI (4%) Pulmonary (14.3%) Infectious (14.3%)	4% (sepsis)

Ninety-three percent with complete response to primary treatment. Seven patients with progressive disease. HIPEC: Hyperthermic intraperitonealchem otherapy; Temp.: Temperature; OS: Overall survival; PFS: Progression free survival; EOC: Epithelialovarian cancer; GI: Gastrointestinal; PE: Pulmonary embolism; NR: Not reported; CV: Cardiovascular.

cohort of patients, HIPEC (cisplatin 100 mg/m^2), when given at the time of "second-look" laparotomy, resulted in an improvement in the 5-year survival rate, although the difference did not reach statistical significance (57.9% in HIPEC group *vs* 44.8% in the control group). This was attributed to the small sample size studied (29 subjects). Notably, no HIPEC associated grade 3 or 4 toxicities were reported. An analogous study conducted by Yoshida *et al*[42] demonstrated marked median progression-free and overall survival rates in subjects treated with HIPC who had a negative second look laparotomy (82.8 and 130.3 mo, respectively).

Investigators from The NCI of Milan studied outcomes associated with CRS and HIPEC in patients with advanced, recurrent ovarian cancer previously treated with systemic cisplatin-based, taxol-based or taxol/platinum containing regimens[45]. Within the cohort of 40 patients, 5-year OS was 15%, with mean OS and PFS of 41.4 and 23.9 mo, respectively. The morbidity, toxicity and mortality rates were 5%, 15% and 0%, respectively. Dr. Helm *et al*[46] retrospectively evaluated the use of secondary CRS + HIPEC in patients with disease resected to ⩽ 5 mm. The regimens used in the study consisted of cisplatin (100 mg/m^2 in 15 patients) or mitomycin C (30-40 mg total dose in 3 patients) heated to 41-43 ℃ (105.8-109.4 degrees F) for 90 min. All patients developed grade 1 or 2 metabolic or hematologic toxicities. Grade 3 or 4 metabolic toxicity occurred in 72% and hematologic toxicity in 28%. There was one perioperative death due to pulmonary embolus. The median progression-free interval was 10 mo and median overall survival was 31 mo.

Prospective phase 2 clinical trials

The trials described above were limited by their retrospective nature, small sample size, heterogenious patient population and variation in both dose and drug used. These limitations prompted the creation and completion of larger prospective phase 2 clinical trials specifically exploring CRS + HIPEC in the up-front treatment of patients with advanced EOC (Table 2).

The first phase 2 clinical trial exploring the use of HIPEC in patients with primary advanced ovarian cancer was completed in 2007[47]. Forty-seven patients were enrolled in this open, prospective, single-center nonrandomized study; 22 underwent primary and 25 secondary CRS plus immediate HIPEC (cisplatin 75 mg/m^2) followed by systemic chemotherapy. Eighty-seven percent of the patients achieved optimal cytoreduction, whereas macroscopic residual disease (defined as lesions ⩾ 2.5 mm) was left behind in 12.7% of subjects. Major complications (gastrointestinal fistula, intra-abdominal bleeding and thrombosis) developed in 21.3% of the patients and the in-hospital mortality rate was 4.2% (2 patients with pulmonary embolism). The mean overall survival was 30.4 mo, median survival was 24 mo, and mean disease-free survival was 27.4 mo. Five-year survival was 16.7%.

This was followed by a study investigating the morbidity and feasibility of CRS + HIPEC in patients with advanced stage primary EOC. Lim *et al*[48] treated 30 patients with residual tumor measuring < 1 cm at the time of primary surgery, with intraoperative HIPEC (cisplatin 75 mg/m^2) at a temperature of 41.5 ℃ for 90 min. All the patients subsequently received adjuvant chemotherapy with combination IV platinum and taxane. Within the cohort, 28 patients (93%) experienced complete remission, and only two patients (7%) had progressive disease. The most commonly reported toxicities included nausea/vomiting, anemia, diarrhea, pleural effusions and wound infections. No deaths or morbidities requiring re-operation or intensive care unit admission were reported. The overall survival data was not yet mature given the interim nature of the evluation.

Ansaloni *et al*[49] in their open, prospective phase 2 study, included thirty-nine patients. Thirty patients (77%) had recurrent EOC and 9 (23%) had primary EOC. For HIPEC, cisplatin and paclitaxel were used for 11 patients (28%), cisplatin and doxorubicin for 26 patients (66%), paclitaxel and doxorubicin for 1 patient (3%), and doxorubicin alone for 1 patient (3%). All HIPEC were performed with open technique. The median intra-abdominal outflow temperature was 41.5 ℃. The mean peritoneal cancer index (PCI) was 11.1; according to the intraoperative tumor extent, the tumor volume was classified as low (PCI < 15) or high (PCI ≥ 15) in 27 patients (69%) and 12 patients (31%), respectively. Microscopically complete cytoreduction was achieved for 35 patients (90%), macroscopic cytoreduction was achieved for 3 patients (7%), and a gross tumor debulking was performed for 1 patient (3%). Mean hospital stay was 23.8 d. Grade Ⅰ-Ⅲ postoperative complications occurred in 7 patients (18%), and reoperations in 3 patients (8%). There was one postoperative death. Recurrence was seen in 23 patients (59%) with a mean recurrence time of 14.4 mo (60).

More recently, a multi-institutional phase 2 study was completed evaluating the impact of CRS + HIPEC on PFS and OS in 26 women with stage 3-4 EOC[50]. All enrolled subjects underwent CRS, followed by HIPEC using the closed-abdomen technique with cisplatin (40 mg/L perfusate) and doxorubicin (15 mg/L of perfusate). Patients were then treated with 6 cycles of adjuvant IV carboplatin (AUC 6) and paclitaxel (175 mg/m^2) administered every 3 wk. Macroscopically complete cytoreduction was achieved in 15 patients (57%), with minimal residual disease (≤ 2.5 mm) remaining in the other 11 (43%). After a median follow-up of 25 mo, 5-year overall survival was 60.7% and 5-year progression-free survival 15.2% (median 30 mo). Excluding operative death, all the patients underwent a median of 6 cycles of systemic chemotherapy at a median of 46 d from combined treatment (range: 29-75 d)[50]. Four patients experienced ≥ grade 3 morbidity, with one post-operative death due to sepsis.

In conclusion, the incorporation of HIPEC in the treatment of primary advanced stage ovarian cancer has shown promising results in both observational studies as well as phase 2 clinical trials. The only randomized phase 3 clinical trial exploring the impact of HIPEC on survival was conducted in patients with carcinomatosis associated with colorectal cancer, showing a significant improvement in survival amongst patients allocated to the HIPEC arm[28]. Unfortunately, patients randomized to the non-HIPEC arm of the trial did not undergo aggressive CRS, potentially impacting survival and limiting the clinical implications of the study[28].

To date, no randomized phase 3 clinical trials have been completed evaluating the impact of HIPEC on survival in patients with advanced stage ovarian, fallopian tube or primary peritoneal carcinoma. Furthermore, the use of non-randomized contemporary or historical control populations restricts the generalizability of results reported in the trials discussed above[51]. In order to address this important clinical question, 4 randomized phase 3 clinical trials are currently in various stages of design and implementation[49].

As with any new therapeutic paradigm, the benefits of HIPEC in the treatment of patients with ovarian cancer must be weighed against the side effects. Overall, HIPEC appears to be well tolerated in appropriately selected patient populations. Nonetheless, toxicity and mortality rates as high as 35% and 5%, respectively, have been reported[52]. Given the relative novelty of this approach, improvements in patient outcome and mitigation of toxicities experienced have been described by more experienced centers[53-58]. Furthermore, quality of life studies have indicated improved emotional well being and rapid return to pre-operative levels of functioning following HIPEC treatment[59].

In summary, HIPEC, when used in combination with successful surgical cytoreduction appears to result in promising oncologic outcomes. We will eagerly await the results of the various phase 3 clinic trials, and until that time advocate the use of CRS + HIPEC in experienced centers under the auspices of appropriate institutional research programs.

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TOPIC HIGHLIGHT

Federico Coccolini, MD, *Series Editor*

Cytoreductive surgery after recurrent epithelial ovarian cancer and at other timepoints

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Abstract

In this descriptive review we look at the role of surgery for advanced ovarian cancer at other timepoints apart from the initial cytoreduction for front-line therapy or interval cytoreductive surgery after neoadjuvant chemotherapy. The chief surgical problem to face after primary treatment is recurrent ovarian cancer. Of far more marginal concern are the second-look surgical procedures or the palliative efforts intended to resolve the patient's symptoms with no curative intent. The role of surgery in recurrent ovarian cancer remains poorly defined. Current data, albeit from non-randomized studies, nevertheless clearly support surgical cytoreduction in selected patients, a rarely curative expedient that invariably yields a marked survival advantage over chemotherapy alone. Despite these findings, some consider it too early to adopt secondary cytoreduction as the standard care for patients with recurrent ovarian cancer and a randomized study is needed. Two ongoing randomized trials (Arbeitsgemeinschaft Gynäkologische Onkologie-Desktop Ⅲ and Gynecologic Oncology Group 213) intend to verify the role of secondary cytoreduction for platinum-sensitive ovarian cancer compared with chemotherapy considered as standard care for these patients. We await the results of these two trials for a definitive answer to the matter.

Key words: Ovarian cancer; Cytoreductive surgery; Recurrent ovarian cancer; Secondary cytoreduction; Surgery for Platinum sensitive ovarian cancer; Surgery for Platinum resistant ovarian cancer

Core tip: The chief surgical problem to face after primary treatment is recurrent ovarian cancer. The role of surgery in recurrent ovarian cancer remains poorly defined. Current data, albeit from non-randomized studies, nevertheless clearly support surgical cytoreduction in selected patients, a rarely curative expedient that invariably yields a marked survival advantage over chemotherapy alone. Despite these findings, some consider it too early to adopt secondary cytoreduction as the standard care for patients with recurrent ovarian cancer and a randomized study is needed.

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INTRODUCTION

Recurrent disease is a challenging problem that sooner or later (within 18 mo after primary treatment) arises in about 80% of patients initially treated for advanced ovar-

ian cancer[1-3] and contributes substantially to the poor long-term outcome for this disease portending long-term survival in only 20%-30% of patients already at an advanced stage when diagnosed[4,5].

Before considering the current options for treating patients with recurrent ovarian cancer we therefore deem it useful to analyze the possible reasons explaining why the disease recurs.

The natural history of ovarian epithelial malignancies shows that tumors originating from the epithelium lining the ovarian surface, and according to the most recent cytogenic hypotheses also those arising from the epithelium covering the fallopian tubes and fimbria[6,7], spread early to the peritoneum and locoregional lymph nodes[8].

Peritoneal spread, frequently with ascites, follows a well-known anatomic course linked to peritoneal fluid dynamics leading neoplastic cells to colonize distant pelvic areas early thus making ovarian carcinoma the model for peritoneal spread from an intra-abdominal malignancy (Figure 1)[9,10].

These pathophysiological events easily explain epidemiological data showing that when the disease is first diagnosed about 75% of women already have advanced ovarian cancer [International Federation of Gynecology and Obstetrics (FIGO) Ⅲ-Ⅳ][8] with major peritoneal and lymphatic spread obviously making the whole therapeutic strategy a complex task.

Although surgery and adjuvant chemotherapy remain the mainstay of treatment for advanced ovarian cancer the optimal therapeutic goal remains hard to reach[11]. Even though the specific single therapeutic role that each of the two principle procedures (surgery and adjuvant chemotherapy) covers in integrated treatment is difficult to investigate, we underline that the outcome benefits induced by platinum and its derivatives and paclitaxel (eventually given also by the intraperitoneal route) have presumably reached a plateau that appears arduous to improve until new effective anticancer drugs become available[12].

Even though experience over years has recognized the prognostic importance of surgical cytoreduction (less residual disease = better outcome)[13], a concept underlined in a meta-analysis conducted in recent years by Bristow *et al*[14], surgery remains the most highly variable and poorly standardized therapeutic factor, depending on the various surgical schools, the individual surgeon's cancer treatment policy and aims and finally on their technical skills.

Besides, some clinical oncologists, questioning whether surgery is really curative, despite convincing clinical evidence, hypothesize that whenever surgery achieves optimal disease control biological factors come into play and exert a determinant influence on the surgical outcome[15]. Going beyond these hypotheses if we want focus on the therapeutic potential of surgery in advanced ovarian cancer we have to analyze precisely what these surgical procedures aim to achieve and most important, how they are classified.

The surgical procedure for treating ovarian cancer is defined with the term "cytoreduction", a definition that seemingly implies residual disease after surgical debulking. Indeed, published studies invariably express their surgical results in terms of residual disease, using classifications that may overlap over time but nevertheless identify as "optimal cytoreduction" surgery leaving residual disease measuring 2 to 1 cm or less. In the latest Cochrane systematic review on this topic[11] the Gynecologic Oncology Group (GOG) currently defines optimal cytoreduction as residual tumor nodules "each" measuring 1 cm or less in maximal diameter underlining, however, the ideal surgical outcome as complete cytoreduction with no visible residual disease. The same review, analyzing experience gained in the most accredited world centers or most cited studies, underlines that surgery achieves this ideal outcome in only a mean 28% of the patients treated and most published surgical results describe residual disease ranging from less than 1 cm to more than 2 cm. Equally important, published surgical reports fail to quantify the overall number of residual lesions in each patient. Yet for two patients at the same disease stage both classified as optimally cytoreduced (residual disease measuring less than 1 cm) if one patient has 10 sites of residual disease and the other, for example, has more than 100 residua, outcomes can presumably differ. Similarly, in classification systems other than those used by the GOG (completeness of cytoreduction score, by Sugarbaker[16]) the lack of a variable quantifying the overall number of residual lesions creates substantial bias in analyzing the results because the group classified as optimally cytoreduced could comprise patients with differing amounts of residual disease. This drawback, already noted previously[17] but never investigated further, merits study to decide how to analyze the results in a more meaningful manner. Hence we reasonably presume that other clinical conditions (age, stage, performance status, platinum sensitivity, body surface area and therefore pharmacological dose) being equal, in two optimally cytoreduced patients in whom the number of residual lesions differs widely adjuvant chemotherapy will yield non-overlapping results.

All these observations prompt us to suggest that recurrent disease in advanced ovarian cancer should in many patients be more correctly interpreted as residual disease given that despite adjuvant chemotherapy surgery often leaves numerically rather than diametrically important residual lesions that ultimately manifest clinically as recurrence.

SECOND-LOOK SURGERY

This term defines the surgical procedure used to confirm the response status in patients who are clinically disease-free after a front-line approach (primary cytoreduction and adjuvant chemotherapy). Second-look surgery is obviously not intended merely as a diagnostic procedure given that it envisages whenever possible resecting all clinically unrecognized disease eventually found.

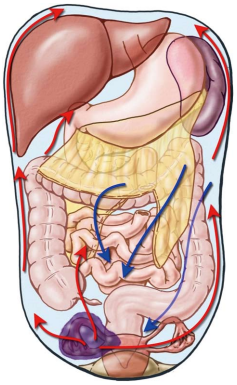

Figure 1 Peritoneal hydrodynamics.

The rationale underlying second-look surgery originally hinged on the concept that identifying residual disease foci early after front-line chemotherapy, removing them and consolidating the results with second-line chemotherapy improved survival. Positive histologic findings after second-look surgery directly reflect the initial disease stage and their percentage increases further in patients whose first operation leaves macroscopic residual disease[18]. Although second-look surgical procedures enjoyed wide use in the 1980s and 1990s their application gradually declined insofar as more than 50% of the patients identified at second-look surgery as complete responders within 12 to 24 mo thereafter went on to experience recurrent disease[19,20]. Randomized clinical trials have shown that although second-look procedures can accurately define patient responders they failed to increase survival[21]. An Italian study intended to investigate whether during a second-look procedure systematic aortic and pelvic lymphadenectomy had outcome advantages over a simple biopsy taken from clinically suspected lymph-node stations failed to show that either procedure improved outcome[22].

In synthesis, current evidence therefore suggests that second-look surgery for ovarian cancer remains a useful therapeutic option when diagnostic investigations appear contrasting and can help ascertain the patient's clinical status and eventually treat the disease but should be reserved for individual patients and has no place as a general procedure. However, it may be a valid option for patients whom are detected during second-look surgery with platinum-resistant recurrent disease. If a complete macroscopic cytoreduction can be performed, patients will benefit as otherwise no real treatment options are available, in particular if hyperthermic intraperitoneal chemotherapy (HIPEC) can be added to the concept.

SURGERY FOR PLATINUM-RESISTANT RECURRENT OVARIAN CANCER

Within 6 mo after undergoing treatment with the front-line approach (cytoreductive surgery plus primary adjuvant chemotherapy) 23% of patients with advanced ovarian cancer experience recurrent disease[23,24]. Current consensus defines these patients as platinum-resistant. Platinum-resistance is a highly complex phenomenon that can develop during the natural history of the disease after initial platinum sensitivity. Studies conducted over recent years have emphasized the role played in chemoresistance by the so-called cancerous ovarian stem cells[25]. Previous surgery and chemotherapy in platinum-resistant patients seem to provide exceedingly disappointing results with a median survival of less than 10 mo[26-29]. This concern has now stimulated research efforts thus moving basic research into pharmacologic regimens towards promising advances using biological agents alone or combined with chemotherapy agents[30-32].

From the viewpoint of the surgical approach, an extremely interesting new development seems to be the cumulative experience from two French groups who report in a large series of patients with recurrent ovarian cancer the surgical outcome after cytoreduction (peritonectomy procedures) and HIPEC and noted similar results in patients classified as platinum-sensitive and platinum-resistant[33]. These results seemingly underline the dual importance of endoperitoneal chemotherapy and concurrent hyperthermia. Endoperitoneal infusion undoubtedly has a pharmacokinetic advantage given that the "peritoneal plasma barrier" allows dose-intensity therapy and hyperthermia concurrently increases the chemotherapy agent's cytotoxic action and cell penetration perhaps overcoming problems related to platinum resistance[34,35]. If further confirmed these findings open the way to interesting future therapeutic advances, in particular because the mortality related to the procedure including HIPEC is low after absolving the learning curve although relevant morbidity is still frequent but most of it seems to be related to extended surgery. However, in HIPEC performed with oxaliplatin, postoperative bleeding after 7-10 d following surgery can be a serious complication in up to one third of all patients requiering a reoperation[36].

SURGERY FOR PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER

The 4th ovarian cancer consensus conference held in 2010 stated that surgery might be appropriate in selected patients with platinum-sensitive recurrent ovarian cancer and might be beneficial if it achieved complete resection[24]. The therapeutic value of repeating the initial surgical treatment (cytoreduction) in patients with advanced ovarian cancer who will experience tumor recurrence remains debatable. Since Berek *et al*[37] in 1983 first introduced the term "secondary cytoreduction" many papers published over the ensuing years have addressed this topic[38-44] and in recent years some investigators have even introduced the concept tertiary cytoreduction[45,46]. Secondary cytoreduction after an extended treatment-free interval (from 6 to 12 mo or more) can increase survival (though rarely leads to a definitive cure) because the cytoreductive effect sums up with an improved response

to subsequent chemotherapy[47]. But beyond single series, the potential usefulness of secondary cytoreduction after primary treatment remains controversial: most studies are retrospective, come from single centers, often enrol fewer than 100 cases, cover a long time-span and most important, are non randomized[48]. To address these doubts Bristow *et al*[47] conducted a meta-analysis investigating the prognostic importance of several variables on overall survival in 40 patient cohorts (2019 cases) undergoing secondary cytoreduction for platinum-sensitive recurrent ovarian cancer. They used simple and multiple regression analyses, with weighted correlation calculations and after controlling for all other factors, each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3.0 mo increase in median cohort survival time. The investigators concluded that among patients undergoing surgery for recurrent ovarian cancer, the proportion of patients achieving complete cytoreductive surgery is independently associated with overall post-recurrence survival time. The same study showed that other more strictly surgery-related variables such as operative time, blood loss, surgical morbidity and mortality were comparable with the data generally reported for primary cytoreduction, coming within an acceptable percentage of risk.

Yet given that outcome improves only in patients in whom surgery achieves complete cytoreduction, an inherent limitation in their meta-analysis, as Bristow *et al*[47] themselves admit, is the inability to define a correct profile for patients in whom they can achieve this aim and for whom we should reserve the surgical option. Two studies in recent years seem to answer this question by developing a risk model for predicting complete secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Desktop I study[40] evaluated three predictive factors for complete resection: good performance status (ECOG 0), complete resection at first surgery, absence of ascites and in the subsequent AGO-Desktop Ⅱ study[49] this score was validated prospectively: if all three factors are present complete resection is feasible in 76% of the patients. A second risk model was developed in 1075 patients by an International Collaborative Cohort study[50,51] that partly integrated the previous model by evaluating the progression-free interval, the Ca 125 level and the FIGO stage. From these overall data they extrapolated two categories, patients at low risk (score ≤ 4.7) in whom complete cytoreduction is possible in 53% to 83% of the cases and those at high risk (score > 4.7) in whom surgery can achieve complete cytoreduction in from 20% to 42% (Table 1).

Despite these findings, some consider it too early to adopt secondary cytoreduction as the standard care for patients with recurrent ovarian cancer and a randomized study is needed[52]. Two ongoing randomized trials (AGO-Desktop Ⅲ and GOG 213) intend to verify the role of secondary cytoreduction for platinum-sensitive ovarian cancer compared with chemotherapy considered as standard care for these patients. We await the results of these two trials for a definitive answer to the matter.

Table 1 Risk model for secondary cytoreductive surgery in patients with recurrent ovarian cancer based on the international collaborative cohort

Impact factors	Scoring					
	0	0.8	1.5	1.8	2.4	3
FIGO stage	Ⅰ / Ⅱ	Ⅲ / Ⅳ				
Residual disease at 1st surgery	0		> 0			
Progression-free interval (mo)	> 16				< 16	
ECOG performance status	0-1				2-3	
Ca 125 at recurrence (U/mL)	< 105			> 105		
Ascites at recurrence	Absent					Present

Low risk ≤ 4.7, complete resection feasible from 53% to 83%; high risk ≥ 4.7, complete resection feasible from 20% to 42%. FIGO: International Federation of Gynecology and Obstetrics; ECOG: Eastern Cooperative Oncology Group.

For patients following complete cytoreduction, HIPEC may be beneficial as suggested by a recent paper from France[33]. In the largest HIPEC series for persistent and recurrent ovarian cancer, including 246 patients, the median survival following surgical cytoreduction and HIPEC was 48.9 mo. Mortality was in this group very low with 0.37% and morbidity of 11.6%.

For platinum-sensitive recurrent disease, two other European prospective randomized trials are investigating at present the role of HIPEC. One trial is the French trial CHIPOR study: all patients get first neoadjuvant systemic chemotherapy and surgical cytoreduction. Following surgery, patients are randomized to HIPEC (cisplatinum 75 mg/m^2) *vs* no HIPEC. The other trial is the Italian trial HORSE with a similar design, however, without neoadjuvant systemic chemotherapy and the same cisplatinum dose as in the French trial[53].

In conclusion, although surgical techniques and chemotherapy regimens used to treat ovarian cancer have advanced remarkably over the past several decades, despite the best efforts the 5-year survival rate has improved by only 8% since 1975[54].

The proportion of patients with advanced ovarian cancer who relapse has remained high and fairly constant and because cure is rarely possible, key objectives are to maintain and improve quality of life and prolong survival. Patients commonly undergo multiple chemotherapy courses[55] intended to overcome the platinum resistance that follows initial platinum sensitivity, control symptoms and allow disease chronification.

The role of surgery in recurrent ovarian cancer remains poorly defined. Current data, albeit from non-randomized studies, nevertheless clearly support surgical cytoreduction in selected patients, a rarely curative expedient that invariably yields a marked survival advantage over chemotherapy alone[50,56].

Although we realize that scientific research requires level 1 evidence to conclude that one therapeutic option is better than another, randomizing a patient with recurrent ovarian cancer who is technically operable (the Desktop Ⅲ protocol requires as an inclusion criterion scores known to predict complete cytoreduction) could raise ethical doubts and probably does nothing to help patient accrual.

And finally, the latest advances from studies investigating the pathogenesis of ovarian cancer clearly show that a "blanket approach" to ovarian cancer treatment is insufficient[7]. The key future turning point for guaranteeing effective treatment depends on developing target therapies designed to exploit the molecular and genetic characteristics of individual tumor subtypes. These observations raise further doubts on the appropriateness of randomized trials enrolling patients whose tumors differ widely in biological features.

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TOPIC HIGHLIGHT

Federico Coccolini, MD, *Series Editor*

Comprehensive management of epithelial ovarian cancer with peritoneal metastases

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Abstract

Ovarian cancer has as its predominant pattern of dissemination metastases to the peritoneal surfaces and disease spread within the abdomen and pelvis that most commonly causes the patients demise. To combat peritoneal metastases, cytoreductive surgery with peritoneal and visceral resections is combined with intraperitoneal and systemic chemotherapy. Chemotherapy given in the operating room after the complete visible removal of ovarian cancer is hyperthermic intraperitoneal chemotherapy. The results of the combined treatment are determined by the extent of prior surgery, the extent of disease as established by the peritoneal cancer index, and the quality of the cytoreduction as measured by the completeness of cytoreduction score. Recent clinical information on patients with recurrent ovarian cancer suggest a median overall survival of up to 60 mo. These data are greatly improved over the one year survival observed in the past.

Key words: Peritoneal metastases; Carcinomatosis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Intraperitoneal chemotherapy; Cisplatin; Doxorubicin; Ifosfamide; Mitomycin C; Intraperitoneal port

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INTRODUCTION

Epithelial ovarian cancer (EOC) is a global healthcare problem. It affects over 200000 women and causes 125000 deaths annually[1]. Within the United States, EOC is the ninth most common female cancer (21000 cases annually) and the fifth most common cause of cancer death (14600) in women[2]. Improved strategies for EOC are needed because currently less than 50% of women with EOC will survive 5 years[3,4]. In the general population the lifetime risk of ovarian cancer is 1 in 70 but there are women with much higher risk especially those with germ line mutations of BRCA1 and BRCA2 tumor suppressor genes and certain mismatch repair genes[5].

SURGICAL MANAGEMENT OF OVARIAN CANCER

The surgical intervention in EOC with peritoneal metasta-

ses may occur with initial treatment (frontline), at interval debulking surgery following neoadjuvant chemotherapy or with recurrence. The major treatment modalities are cytoreductive surgery (CRS), perioperative chemotherapy including hyperthermic intraperitoneal chemotherapy (HIPEC), and long-term combined intravenous and intraperitoneal chemotherapy. Second look surgery may be indicated in selected patients. It has been established that improved outcome is associated with small-volume residual disease following CRS. With current thinking a highest goal of treatment must be CRS to remove all visible evidence of disease[6,7]. Or if that is not possible, surgery should leave the least amount of residual disease[8,9]. In the past, CRS that left residual cancerous lesions up to 2 cm in greatest dimension was considered "optimal". However, the precise definition of optimal cytoreduction has been open to wide differences of opinion which have changed considerably over time. It is now accepted that leaving no visible disease should always be considered optimal CRS at all time-points for EOC surgery except for palliation[10-12].

Several divergent types of surgical procedures are necessary to achieve complete cytoreduction because EOC is often widespread within the abdominal and pelvic cavity. In the past, disease involving upper abdominal structures such as the undersurface of the diaphragm, liver surface or parenchyma, porta hepatis, pancreas, and spleen were considered obstacles to the achievement of optimal CRS. It has been shown that the resection of tumor from these sites does improve survival whether this is achieved by the gynecologic oncologists or surgical oncologists[13]. The actual sites of intra-abdominal disease not amenable to safe resection at a particular institution vary according to surgical expertise and practice. Some of the sites most likely to result in an incomplete resection include parenchymal liver metastases, extensive disease in the porta hepatis, retroperitoneal adenopathy behind and superior to the pancreas and extensive disease involving proximal small bowel and small bowel mesentery.

PATIENT SELECTION FOR A COMPREHENSIVE TREATMENT PLAN

Successful initiation of an optimal surgical outcome requires a knowledgeable selection of patients, a strong commitment from the surgical team, and institutional support. The initial selection of patients is based on two well defined criteria: First, the ability of the patient to survive an extensive surgical procedure with acceptable morbidity and mortality and second, no evidence of intraoperative findings that would result in a futile surgical effort. Patients of advanced age, poor performance status, malnourished or with medical conditions that would decrease the likelihood of postoperative survival should be excluded. Also, patients with systemic metastases, multiple sites of bowel obstruction, common bile duct obstruction or ureteral obstruction should rarely be considered for complete CRS.

Complete CRS requires dedication from a surgeon

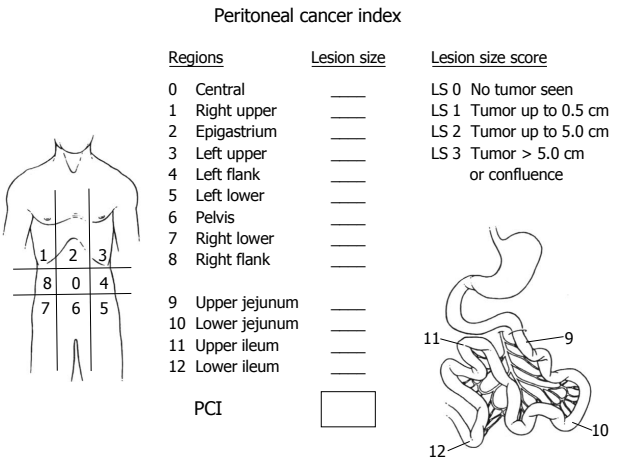

Figure 1 The peritoneal cancer index uses the distribution of cancer implants throughout the abdomen and pelvis combined with a lesion size of these nodules in order to quantitate the disease upon abdominal exploration. PCI: Peritoneal cancer index.

who must have broad surgical knowledge, unusual technical skills and the stamina to endure long procedures. Realizing that these interventions are extensive and thereby costly, institutional backing is important. An effort to educate other physicians involved in this treatment, as well as nurses and ancillary personnel, should be undertaken. The steep learning curve that characterizes this treatment strategy makes it essential to design a careful plan and to regularly critically evaluate all adverse events.

QUANTITATIVE PROGNOSTIC INDICATORS

The three assessments helpful for patient selection in order to treat patients most likely to benefit are the prior surgical score (PSS), the peritoneal cancer index (PCI) and the completeness of cytoreduction score (CC). These scores are determined from 13 abdominopelvic regions. Two transverse planes and two sagittal planes are used to divide the abdomen into 9 abdominopelvic regions (0-8). The upper transverse plane is located at the lowest aspect of the costal margin. Regions 9 and 10 define the upper and lower portions of the jejunum, and regions 11 and 12 define the upper and lower portions of the ileum[14].

Surgical trauma promotes the implantation and progression of cancer nodules on peritoneal surfaces[15]. Prior surgeries may modify the natural history of ovarian cancer by inducing cancer growth at crucial anatomic sites located deep to the peritoneal layer[16]. Patients with no prior abdominopelvic surgery or biopsy only receive a PSS of 0, those with up to one abdominopelvic region dissected receive a PSS of 1, those with two to five abdominopelvic regions receive a PSS of 2 and those with six or more regions dissected receive a PSS of 3.

The PCI is a quantitative prognostic indicator determined after abdominal exploration and complete separation of intestinal adhesions (Figure 1). This index adds a lesion size parameter to the abdominopelvic regions so

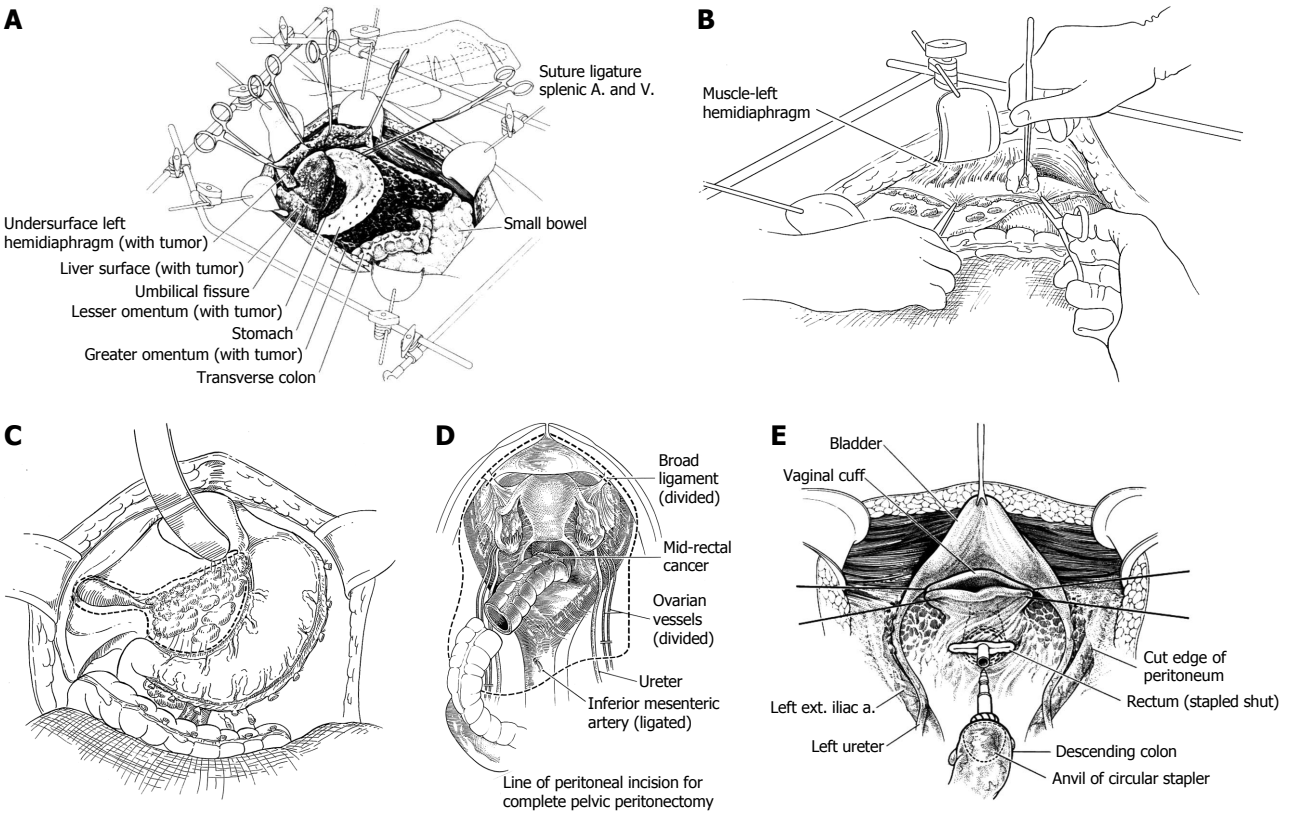

Figure 2 Peritonectomy procedures. A: A fixed retractor is used to provide exposure of the entire abdomen so that peritonectomy procedures on the anterior abdominal wall, beneath the hemidiaphragms, and within the pelvis can proceed in an efficient manner; B: Left upper quadrant peritonectomy; C: Cholecystectomy, lesser omentectomy and peritonectomy of the omental bursa; D: Rectosigmoid colon resection and complete pelvic peritonectomy; E: Reconstruction after rectosigmoid colon resection and complete pelvic peritonectomy. The vagina is closed prior to the hyperthermic intraperitoneal chemotherapy. The low stapled colorectal anastomosis is performed after the chemotherapy lavage is complete (all from Sugarbaker[19]).

that a numerical score estimating the extent of carcinomatosis is available. The PCI is an accurate prognostic indicator for ovarian cancer[17].

CC is a quantitative prognostic indicator determined once the surgical resection has been completed. A patient receives a CC-0 score when no visible peritoneal carcinomatosis remains after cytoreduction, CC-1 is recorded when tumor nodules persist after cytoreduction but they measure less than 0.25 cm, CC-2 when remaining tumor measures between 0.25 to 2.5 cm. When tumor nodules are greater than 2.5 cm or there is confluence of unresectable tumor, a CC-3 score is given to the patient. Many prior studies in ovarian cancer have shown that the extent of disease remaining after cytoreduction is directly related to the survival[7-17].

PERITONECTOMY AND VISCERAL RESECTIONS USED TO ACHIEVE COMPLETE CYTOREDUCTION IN SELECTED PATIENTS

The goal of CRS is to reduce the tumor burden within the abdomen and pelvis to its absolute minimal volume. The best result is a patient who is visibly free of disease at the close of the procedure. The surgery combines a series of peritonectomy procedures and visceral resections. The peritonectomy procedures include anterior parietal peritonectomy, stripping of right and left hemidiaphragm, pelvic peritonectomy, and omental bursa peritonectomy. Visceral resections include hysterectomy and oophorectomy, greater and lesser omentectomy, splenectomy, right colectomy and rectosigmoid colectomy.

Construction of the surgical field to provide simultaneous exposure of the abdomen and pelvis

A fixed retractor that provides a rigid frame around the whole abdomen (Thompson Surgical Instruments, Traverse City, Michigan) is positioned so that continuous retraction of all parts of the abdominal incision occurs (Figure 2A). The retraction system must be securely anchored to the operating table to provide for continuous unencumbered visualization of a large operative field. An incision starting above the xiphisternal junction and continuing down to the pubis through the midline is constructed. An ellipse is created around the umbilicus to allow for the peritoneal plane to be clearly exposed throughout the extent of the abdominal incision. The fascia is divided through the linea alba from xiphoid bone to pubic bone. If there has been prior midline abdominal incision, it is widely excised. Routinely, the xiphoid is completely resected at the xiphisternal junction as part of the specimen. With the fascia divided the parietal peritoneum remains intact.

Parietal peritoneal stripping from the anterior abdominal wall

A single entry into the peritoneal cavity in the middle portion of the incision (peritoneal window) allows the surgeon to digitally and visibly assess the parietal peritoneum and the small bowel surfaces. If cancer nodules are palpated on the parietal peritoneum larger than those involving the small bowel and its mesentery, a decision for a complete dissection is made. Except for the small defect in the peritoneum required for this peritoneal exploration, the remainder of the peritoneum is kept intact to facilitate the peritonectomy.

Stripping the visceral peritoneum from the surface of the bladder

After dissecting generously the peritoneum on both sides of the bladder, the apex of the bladder (preferably the urachus) is localized and placed on strong traction using a Babcock clamp. The peritoneum with the underlying fatty tissues are stripped away from the muscular surface of the bladder. Broad traction on the entire anterior parietal peritoneal surface and frequent room temperature saline irrigation reveals the point for tissue transection that is precisely located between the bladder musculature and its adherent fatty tissue. This dissection is continued inferiorly down to the cervix.

Parietal peritoneal dissection to the paracolic sulcus and beyond

The self-retaining retraction system is steadily advanced more deeply into the abdominal cavity. Firm broad traction on the peritoneum at the point of dissection facilitates accurate progress. The peritoneum strips readily from the undersurface of the hemidiaphragm. The dissection connects the right and left subphrenic peritonectomy superiorly and the complete pelvic peritonectomy inferiorly. As the dissection proceeds beyond the peritoneum overlying the paracolic sulcus (line of Toldt) the dissection becomes more rapid because of the loose connections of the peritoneum to the underlying fatty tissue at this anatomic site.

When the anterior parietal peritonectomy has been completed, removal of this large peritoneal layer eradicates cancer implants from the posterior aspect of the anterior abdominal wall. Complete exploration of the abdomen and pelvis proceeds.

Peritoneal stripping from beneath the left hemidiaphragm

To begin peritonectomy of the left upper quadrant, the peritoneum is progressively stripped off the posterior rectus sheath (Figure 2B). Broad traction must be exerted on the tumor specimen throughout the left upper quadrant. Strong traction combined with ball-tip electrosurgical dissection allows separation of the peritoneum with tumor from all normal tissue in the left upper quadrant including the diaphragm muscle, the left adrenal gland, and the superior aspect of perirenal fat. The splenic flexure of the colon is divided from the peritoneum of the left abdominal gutter and moved medially.

Greater omentectomy and splenectomy with completion of the left subphrenic peritonectomy

To free the mid-abdomen of tumor, the greater omentectomy-splenectomy is performed. The greater omentectomy is elevated and then separated from the transverse colon using electrosurgery. The omental tissue on the anterior aspect of the transverse mesocolon is also resected. The gastroepiploic vessels on the greater curvature of the stomach are ligated and divided. Also, the short gastric vessels are transected. This freely exposes the splenic artery and vein at the tail of the pancreas. These vessels are ligated in continuity and proximally suture ligated taking care not to traumatize pancreas parenchyma. This allows the greater curvature of the stomach to be reflected to the right from the pylorus to the gastroesophageal junction.

Peritoneal stripping from beneath the right hemidiaphragm

Peritoneum is stripped away from the right posterior rectus sheath to begin the peritonectomy in the right upper quadrant of the abdomen. Strong traction on the peritoneum infiltrated by tumor is used to elevate the rolled muscular edge of the hemidiaphragm into the operative field. Again, ball-tipped electrosurgery on pure cut is used to dissect at the interface of tumor and normal tissue. Coagulation current is used to divide the blood vessels as they are encountered and before they bleed.

Cholecystectomy and peritoneal stripping of the hepatoduodenal ligament

The gallbladder is removed in a routine fashion from its fundus toward the cystic artery and cystic duct (Figure 2C). Blunt dissection of the cystic artery and cystic duct away from the common duct and right hepatic artery distinguishes these structures from the surrounding tumor and fatty tissue. These structures are ligated and divided.

To strip the peritoneum from the anterior aspect of the hepatoduodenal ligament, its peritoneal reflection to the liver surface is divided. Special care is taken not to injure the left hepatic artery, which is usually the most superficial of the portal structures. The peritoneum, often layered by tumor nodules, is firmly grasped using a Russian forceps and peeled away from the common bile duct and hepatic artery. The underside of the hepatoduodenal ligament must be visualized and peritoneum stripped if tumor is present.

Resection of the hepatogastric ligament and lesser omentum

The left lateral segment of the liver is retracted left to right to expose the hepatogastric ligament and lesser omentum in its entirety. A circumferential release of this ligament from the fissure between the left lateral portion of the liver and segment 1 occurs first. The arcade of right gastric artery to left gastric artery along the lesser curvature of the stomach must be skeletonized. After electrosurgically dividing the peritoneum on the lesser curvature of the stomach, digital dissection with extreme pressure from the surgeon's thumb and index finger separates lesser omental

fat and tumor from the vascular arcade. As much of the anterior vagus nerve is spared as is possible with patience and persistence. The tumor and fatty tissue surrounding the right and left gastric arteries are split away from the vascular arcade. In this manner the specimen is centralized over the major branches of the left gastric artery. With strong traction on the specimen, the lesser omentum is released from the left gastric artery and vein.

Stripping of the peritoneum from the omental bursa

With the left lateral segment of the liver retracted to the right, further exposure of the peritoneal floor of the omental bursa is achieved through elevation of the left side of the caudate lobe of the liver. The peritoneal reflection between caudate and vena cava is electrosurgically divided. Also, the peritoneal reflection towards the left hepatic vein is divided. Then, blunt stripping of the peritoneum covering the crus of the right hemidiaphragm is completed. This peritoneal stripping continues over the lymph nodes along the common hepatic artery and up into the tissues of the lesser omentum. Care is taken to avoid the origin and branches of the left gastric artery. Care is also taken to eliminate tumor nodules from the shelf created by the caudate lobe beneath the posterior aspect of the hepatoduodenal ligament.

Resection of rectosigmoid colon, uterus, ovaries and cul-de-sac of Douglas

To being the rectosigmoid colon resection a linear stapler is used to divide the sigmoid colon just above the limits of the pelvic peritoneal metastases; this is usually at the junction of sigmoid and descending colon. The vascular supply of the distal portion of the bowel is traced back to its origin on the aorta. The inferior mesenteric artery and vein are ligated, suture-ligated, and divided. This allows one to pack all the viscera, including the proximal descending colon into the upper abdomen.

Ball-tipped electrosurgery is used to dissect at the limits of the pelvic peritonectomy (Figure 2D). The surgeon works in a centripetal fashion. Extra-peritoneal ligation of the uterine arteries is performed just above the ureter and close to the base of the bladder. In women, the bladder is moved gently off the cervix and the vagina is entered. The vaginal cuff anterior and posterior to the cervix is transected using ball-tipped electrosurgery, and the rectovaginal septum is entered. Ball-tipped electrosurgery is used to divide the perirectal fat beneath the peritoneal reflection. This ensures that all tumors that occupy the peritoneum within the cul-de-sac are removed intact with the specimen. The anterior rectal musculature is skeletonized using ball-tipped electrosurgery. Preservation of the lower half of the rectum will allow for a larger stool reservoir and diminish frequent bowel movements. A stapler is used to close off the rectal stump and the rectum is sharply divided above the stapler.

Secure vaginal closure and colorectal anastomosis

Additional sutures are placed to close the apex of the vagina (Figure 2E). These sutures are left long so that they may be used to elevate the vaginal cuff and clearly expose the stump of the rectum.

Systematic pelvic and aortic lymphadenectomy

Once peritonectomy and visceral resections and after para-rectal and para-vesical spaces have been observed, systematic pelvic and aortic lymphadenectomy are performed.

Pelvic lymphadenectomy dissection begins at the origin of the external iliac vessels and continues caudally around them along the medial border of the psoas muscle. The aponeurotic fascia is kept intact and the branches of the genito-femoral nerve are carefully spared to limit the risk of postoperative neurological sequelae. The dissection proceeds through the areolar plane between the adventitia of the artery and the lymphatic tissue. The lower limit of the external iliac lymphadenectomy is represented by the deep inferior epigastric vessels. Lymph nodes along the external iliac vessels are removed *en bloc* with those adjacent to the common iliac vessels. The psoas fascia, superficially, and the fascia covering the internal obturator and levator ani muscles, deeply, constitute the lateral boundaries of lymphadenectomy, while the medial margin is represented by an ideal plane between the umbilical artery, anteriorly, and the rectum, posteriorly. After obturator nerve identification, lymphadenectomy of the obturator fossa is performed with the mobilization of the superficial obturator nodes which are removed *en bloc* with the perilymphatic fatty tissue around the internal iliac vessels at the origin of the internal pudendal vessels. Lymphadenectomy is completed by removing deep obturator and gluteal nodes.

Aortic lymphadenectomy begins at the aortic bifurcation up to the renal vessels. After having exteriorized the transverse colon and the small bowel, the superficial intercavo-aortic, precaval, and preaortic nodal groups are removed. Lymph nodes located lateral to the vena cava (*i.e.*, paracaval nodal group) are separated from it and removed *en bloc*. Removal of the lymph nodes lateral to the aorta is carried out up to the level of the left renal vein, after entering the plane between the Toldt's and Gerota's fasciae, mobilizing the descending colon from the renal capsule, the psoas muscle, and the ovarian pedicle and displacing the ureter laterally. Lastly, lymph nodes behind the vena cava (*i.e.*, retrocaval nodal group) and the lumbar vessels (*i.e.*, deep intercavo-aortic nodal group) are removed if enlarged, by dissecting from the pre-vertebral fascia after displacing the vena cava and the aorta laterally and medially (Figure 3).

RATIONALE FOR HIPEC AND EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

After the completion of cytoreduction when no visible cancer remains, it is invariably true that invisible to the naked eye, an immense number of cancer cells will remain within the peritoneal cavity. Tumor manipulation, transected lymphatic ducts leaking tumor cells throughout

Table 1 Intraoperative bidirectional chemotherapy orders

Add cisplatin (50 mg/m^2) _____ mg to 2 L of 1.5% dextrose peritoneal dialysis solution
Add doxorubicin (15 mg/m^2) _____ mg to same 2 L of 1.5% dextrose peritoneal dialysis solution
Add ifosfamide (1300 mg/m^2) _____ mg to 1 L normal saline
Begin continuous *iv* infusion over 90 min simultaneous with *ip* chemotherapy
Add mesna disulfide (260 mg/m^2) _____ mg in 100 mL 0.9% sodium chloride to be given *iv* as a bolus 15 min prior to ifosfamide infusion
Add mesna disulfide (260 mg/m^2) _____ mg in 100 mL 0.9% sodium chloride to be given *iv* as a bolus 4 h after ifosfamide infusion
Add mesna disulfide (260 mg/m^2) _____ mg in 100 mL 0.9% sodium chloride to be given *iv* as a bolus 8 h after ifosfamide infusion
Send all the above to operating room No. _____ at _____ o'clock on _____ (date) for a 90-min treatment

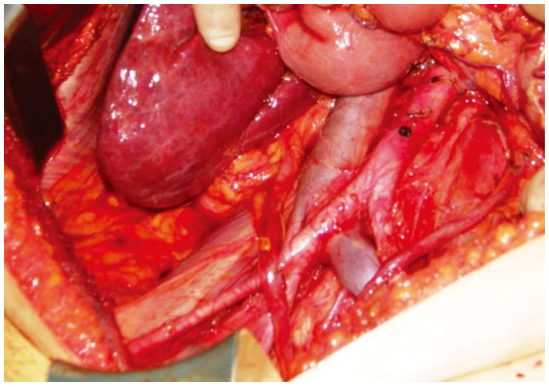

Figure 3 Retroperitoneal space after pelvic and periaortic lymphadenectomy (from archives of Frigerio L).

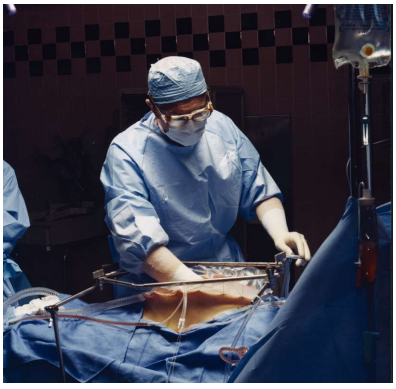

Figure 4 Hyperthermic intraperitoneal chemotherapy proceeds by constructing a reservoir from the abdominal space. The skin edges are elevated on a self-retaining retractor and a plastic sheet covers the open abdomen. A cruciate incision in this plastic sheet allows free access of the surgeon's double-gloved hand. Uniform distribution of heat and chemotherapy is maintained throughout the 90 min of the Hyperthermic intraperitoneal chemotherapy treatment.

the procedure, and small tumor nodules remaining on the abdominal and pelvic surfaces of organs not amenable to peritonectomy procedures, namely small bowel, make necessary the implementation of some method that will eradicate residual tumor cells. Another well known site for persistent disease is the suture lines that are an ideal site for cancer cell implants. Tumor cell entrapment occurs on these raw surfaces with fibrin accumulating and tissues compressed together by stitches or staples. Suture lines are at high risk for recurrence if constructed before the HIPEC.

Technique for heated intraoperative intraperitoneal chemotherapy

An abdominopelvic reservoir is constructed by tenting up the skin edges on a fixed retractor that allows hand distribution of the chemotherapy agent and total containment. The gloved hand guarantees that the perfusate reaches all surfaces within the peritoneal cavity, such as the space between the bowel loops, the space behind the liver, and the pelvic cavity (Figure 4).

In order to keep the temperature at a constant 42 ℃, a hyperthermia pump forces the solution through a heat exchanger. Then it proceeds into the abdominopelvic cavity through an inflow catheter. The hyperthermic chemotherapy fluid is drained from the abdomen through four closed drains going back to the heat exchanger, and closing the circuit. The inflow catheter and the closed suction drains are secured watertight with purse-string sutures on the skin of the abdomen to avoid leaks and spillage. The chemotherapy solution circulates for 90 min at 42 ℃.

After the 90 min of HIPEC with manual distribution, the surgeon may assume that fibrin and tissue debris and the microscopic residual disease they contain have been eradicated. At this time, all the anastomosis and any additional reconstruction can occur. Closed-suction drains and an inflow catheter are properly positioned for subsequent early postoperative intraperitoneal chemotherapy with paclitaxel. Standardized orders for bidirectional intraperitoneal chemotherapy are given in Table 1. Cisplatin and doxorubicin are given by intraperitoneal administration and ifosfamide by intravenous continuous infusion (55-56).

Technique for early perioperative intraperitoneal chemotherapy

In the first five postoperative days the patient receives normothermic intraperitoneal paclitaxel (20-40 mg/m^2 per day), with the goal of consolidating the intraperitoneal chemotherapy treatments. The extremely favorable area under the curve ratio and the remarkable drug penetration of up to 80 cell layers deserve mention. Standardized orders for early postoperative intraperitoneal chemotherapy with paclitaxel are given in Table 2.

RESULTS OF COMPREHENSIVE TREATMENT IN ADVANCED PRIMARY AND RECURRENT OVARIAN CANCER

In patients who have failed the standard treatments of primary ovarian cancer the survival is short with an estimated

Table 2 Early postoperative intraperitoneal chemotherapy orders

Paclitaxel _____ mg (20-40 mg/m^2 × _____ m^2) (maximum dose: 80 mg) in_____mL 6% Hespan® (Braun B, Irvine, CA) *via* the Tenckhoff catheter or IP port daily
Start date: _____ Stop date: _____ (For daily doses > 500 mL total volume, pharmacy will split dose equally into two bags)
Instill as rapidly as possible *via* the Tenckhoff catheter or *ip* port
Dwell for 23 h
Drain from Jackson-Pratt drains for one hour prior to the next instillation
Continue to drain the abdominal cavity by Jackson-Pratt drains after the last dose of *ip* chemotherapy
During the initial 6 h after chemotherapy instillation, patient's bed should be kept flat
The patient should be on the right side during instillation
Turn ½ hour post instillation onto the left side and continue to change sides at ½ hour intervals for 6 h
Monitor with a pulse oximeter during the first 6 h of each intraperitoneal chemotherapy

Table 3 Clinical information from recent reports on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with peritoneal metastases from ovarian cancer

Ref.	*n*	Median follow-up (mo)	Median disease-free survival (mo)	Median overall survival (mo)	Overall 5-year survival (mo)	Median length of hospital stay (d)	Mortality (%)	Morbidity Grade 3 (%)	Morbidity Grade 4 (%)
Bereder *et al*[20]	246	NR	13	49	35	17	0.4	12	
Pavlov *et al*[21]	56	60	26	38	NR	14	2	0	2
Fagotti *et al*[22]	25	18	10	NR	NR	13	0	8	8
Guardiola *et al*[23]	47	23	14	NR	NR	18	0	NR	13
Di Giorgio *et al*[24]	47	NR	20	24	17	22[1]	4	9	13
Bae *et al*[25]	67	NR	NR	NR	66	NR	0	0	0
Cotte *et al*[26]	81	47	19	28	NR	17[2]	3	5	2

[1]Two-year survival results; [2]Refers to results expressed as mean. NR: Not reported.

median survival of 9 mo. The median survival of 28 patients with advanced primary and recurrent EOC who had an attempt at complete cytoreduction combined with perioperative chemotherapy at the Washington Cancer Institute was 45.8 mo[16]. Further analysis by Look *et al*[16] of the clinical features that affected survival showed that extent of prior surgery and completeness of cytoreduction were independent factors significantly affecting survival. Those patients with extensive prior surgery, that is with three or more abdominopelvic regions subjected to surgical dissection, were less likely to receive a complete cytoreduction and their survival was significantly shorter. Patients with a low PSS who had less than three abdominopelvic regions previously dissected had a median survival of 6.5 years, compared to 1.5 years for those patients with a higher PSS ($P < 0.001$). Patients with an adequate cytoreduction had a median survival of 55.9 mo; suboptimal cytoreduction showed an 8 mo survival ($P = 0.037$).

Tentes and colleagues reported on the PCI as a quantitative prognostic indicator in 60 women with ovarian cancer[17]. Those patients with a PCI lower than 10 had a median survival of 80 mo and a 5-year survival of 65%, while those patients with a PCI greater than 10 had a median survival of 38 mo and a 5-year survival rate of 29% ($P = 0.0253$).

Recently, Bijelic *et al*[18] published a systematic review analyzing 14 studies that reported on cytoreduction and HIPEC. Ten studies reported a positive impact of CRS and HIPEC on survival and in 4, survival was not analyzed. Morbidity ranged from 5% to 36% and the median mortality was 3%.

Recent results of treatment

This comprehensive management plan has been reported in approximately 35 manuscripts over the last two decades. As experience in patient selection and refinements in surgical technology have occurred, a gradual improvement in survival benefits and a decrease in morbidity and mortality have occurred. Clinical information from 7 recent reports are presented in Table 3.

In conclusion, this highly specialized treatment needs to be performed by qualified surgeons who are knowledgeable about peritonectomy procedures. Accepting the fact that there might be a selection bias, the results with this comprehensive treatment are encouraging. Multi-institutional studies are in progress to further validate the benefits of complete CRS in patients with ovarian cancer. The strong rationale, the initial favorable results by competent groups, and the demonstrated safety justify the current use of complete CRS.

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TOPIC HIGHLIGHT

Federico Coccolini, MD, *Series Editor*

Cytoreductive surgery in primary advanced epithelial ovarian cancer

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Abstract

Epithelial ovarian cancer is one of the most common malignancy and one of the principal causes of death among gynaecological neoplasm. The majority of patients (about 70%) present with an advanced International Federation of Gynaecology and Obstetrics stage disease. The current standard treatment for these patients consists of complete cytoreduction and combined systemic chemotherapy (CT). An increasing proportion of patients undergoing complete cytoreduction to no gross residual disease (RD) is associated with progressively longer overall survival. As a counterpart, some authors hypothesized the improving in survival could be due more to a less diffused initial disease than to an increase in surgical cytoreduction rate. Moreover the biology of the tumor plays an important role in survival benefit of surgery. It's still undefined how the intrinsic features of the tumor make intra-abdominal implants easier to remove. Adjuvant and hyperthermic intraperitoneal CT could play a decisive role in the coming years as the completeness of macroscopic disease removal increases with advances in surgical techniques and technology. The introduction of neo-adjuvant CT moreover will play a decisive role in the next years Anyway cytoreduction with no macroscopic residual of disease should always be attempted. However the definition of RD is not universal. A unique and definitive definition is needed.

Key words: Ovarian cancer; Cytoreduction; Complete; Hyperthermic intraperitoneal chemotherapy

Core tip: The present paper reviews the efficacy of complete cytoreductive surgery in the treatment of primary advanced epithelial ovarian cancer. Outlining the importance for standard criteria in defining the completeness of cytoreduction. Moreover the biology of the tumor plays an important role in survival benefit of surgery. It's still undefined how the intrinsic features of the tumor make intra-abdominal implants easier to remove. Adjuvant and hyperthermic intraperitoneal chemotherapy could play a decisive role in the coming years as the completeness of macroscopic disease removal increases with advances in surgical techniques and technology.

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INTRODUCTION

Approximately 225500 women worldwide are diagnosed

each year with ovarian cancer. About 140200 women die every year for this disease[1]. In the United States, ovarian cancer remains the leading cause of death among women diagnosed with gynaecological cancer[2]. The strongest predictor of mortality has been demonstrated to be the International Federation of Gynaecology and Obstetrics stage. Unfortunately the majority of patients have an advanced-stage of disease at the time of diagnosis. This is strongly linked with the poor prognosis of the disease[3,4]. Moreover most of the patients with advanced-stage disease will experience relapse. Even with a good response to primary treatment, only 20%-25% of women can be expected to be long-term survivors[5]. Survival rates are strongly influenced by the adjuvant chemotherapy (CT) regimen. However, primary cytoreductive surgery (CRS) to minimize the amount of residual disease (RD) is equally important. The fist description of a survival advantage associated with an ovarian tumor debulking procedure was published by Meigs in 1934[6]. A few decades after, the necessity of initial CRS in treatment of epithelial ovarian cancer (EOC) gained traction with the report by Griffiths[7]. Hoskins *et al*[8,9] reported two studies of the Gynaecologic Oncology Group (GOG) (protocols 52 and 97), that illustrated the key points of CRS for advanced-stage EOC: (1) the inverse relation between the maximal diameter of RD and overall survival (OS); (2) the maximal diameter of RD above which CRS has no appreciable effect on survival; and (3) introduced the concept of multi-factoriality of survival determinants. During the last 20 years, the improvements in surgical capability have facilitated the achievement of maximal cytoreduction in an increasingly higher percentage of patients with as consequence related decrease of the average of RD maximal diameters[9-20]. Similar advances in CT agents and regional delivery regimens have magnified the potential survival advantage associated with a maximal surgical effort[7].

PRIMARY CRS

Treatment of advanced EOC has advanced in last 10 years. The innovation of the last three decades in the surgical management of peritoneal cancer diffusion introduced the possibility to treat patients that were long considered untreatable. Peritoneal carcinomatosis had been considered as a metastatic inoperable grade of cancer, before the Sugarbaker era. Actually, the universally accepted treatment diagram for advanced EOC considers as key points the maximal CRS and the adjuvant CT also for grossly peritoneal diffused disease. Grade ⅢC and Ⅳ are no longer considered as "lost". Many studies have demonstrated that a progressively more aggressive surgical effort is associated with improvements in disease-free and OS rates. It has been demonstrated the necessity to perform aggressive surgery in dedicated centres with high volume surgeons. High volume surgeons have, in fact, demonstrated to have an in-hospital mortality lower up to 69% than low volume surgeons[21]. The concept of "population-based cytoreduction", introduced in a meta-analysis in 2002, stimulated reflection about the necessity to aggressively treat each single case of advanced EOC to gain in survival for the whole considered population[22]. The more the surgeon became radical and increased his/her surgical volume the more he/she prolongs the disease-free and OS and reduces the in-hospital mortality. As a counterpart, some authors hypothesized the improving in survival could be due more to a less diffused initial disease than to an increase in surgical cytoreduction rate[23-25]. Moreover the biology of the tumor plays an important role in survival benefit of surgery. It's still undefined how the intrinsic features of the tumor make intra-abdominal implants easier to remove[26]. In general, upper abdominal tumor implants are suggestive of an aggressive tumor biology[6]. Covens and Berman criticized the role of CRS in advanced EOC. They proposed that both survival and surgical resectability are mostly determined by tumor biology instead of the operative effort by the surgeon[24,27]. The retrospective review of data from the Scottish Randomized Trial in Ovarian Cancer revealed in a population of 889 patients with disease stage ranging from IC to IV that the benefit of optimal debulking surgery seems to depend from the extent of disease before surgery[25]. The trial stratified patients into four pre-operative prognostic group depending on the staging. Survival was then analysed on the basis of the extent of CRS by stratification into three groups: No gross RD, RD $\leqslant$ 2 cm, RD $\geqslant$ 2 cm. Patients in the first two groups with a less extensive pre-operative disease benefited from CRS to RD $\leqslant$ 2 cm. Patients in the other two groups did not increase the survival with a CRS to RD $\leqslant$ 2 cm. Authors proposed to consider the tumor biology as determinant in survival and that CRS could not completely supply to the poor prognosis given by the intrinsic aggressiveness of some species of cell-clones.

The staging procedure could be performed by laparoscopy or *via* a vertical incision. An open staging procedure is the most trustworthy in order to assess the extent of disease and to evaluate the possibility to proceed with a complete cytoreductive procedure. All intra-abdominal surfaces and organs should be palpated, including the diaphragm, liver, spleen, gall bladder, small and large intestine, and mesentery. It's important to carefully evaluate the retroperitoneum for bulky adenopathy. Samples of the diffused cancer should be obtained, usually from involved omentum or adnexa. In the absence of gross extra-ovarian disease, multiple peritoneal biopsies should be obtained, along with a pelvic and para-aortic lymphadenectomy. In patients with early-stage ovarian cancer during the CRS phase, systematic lymphadenectomy should be part of the complete staging procedure. Maggioni *et al*[28] demonstrated as nearly 25% of patients with apparent early-stage ovarian cancer who undergo lymphadenectomy are upstaged to stage ⅢC due to the presence of node metastases. Some authors consider the role and benefit of systematic lymphadenectomy as unclear in patients with advanced-stage EOC. Panici *et al*[29]

randomized 427 patients with stage Ⅲ/Ⅳ EOC to either systemic lymphadenectomy or resection of bulky nodes. The 5-year OS rate was of 48.5% and 47%, respectively with no statistical significance differences. However they reported a longer progression-free survival in the systemic lymphadenectomy group (31.2%), than in the no-lymphadenectomy group (21.6%). Parazzini *et al*[30] analysing 456 women with advanced stage Ⅲ/Ⅳ ovarian cancer, demonstrated no correlation between nodal status and survival. Moreover in advanced EOC nodal status was not a prognostic factor for patients undergone to optimal cytoreduction.

Complete cytoreduction is reached when no visible tumor remains after the surgical procedure. Confusion exists in defining the results of the surgical intervention in terms of RD. The term "optimal" cytoreduction has been variably defined during the years in the different studies ranging from 0 to 2 cm in RD diameter. The GOG defined optimal the remaining of residual nodules of 1 cm or less[31]. Alternatively as optimal has been given the definition of no RD[31-35]. No residual tumor has also been described as complete cytoreduction[10,34]. A survey among members of the society of Gynaecologic Oncologists has been conducted. Results from this study demonstrated the heterogeneity of believing. About 12% of respondents defined no RD as optimal cytoreduction and 60.8% used the threshold of 1 cm to define the same concept[36]. Actually however the most largely adopted is the GOG classification which defines as optimal the RD of ≤ 1 cm.

Starting from this classification a number of prospective and retrospective studies have been conducted to investigate the feasibility of and the impact on survival of CRS in advanced EOC.

Generally CRS for EOC can be divided into simple and radical surgical procedures. Simple CRS consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, limited excision of pelvic/para-aortic lymph nodes, peritoneal excision, and sometimes segmental bowel resection. These procedures can be performed in the majority of patients with low risk of complications. To achieve optimal cytoreduction, surgery for advanced EOC frequently requires the addition of radical procedures: radical oophorectomy, rectosigmoid colectomy, multiple bowel resections, diaphragm peritonectomy or resection, liver resection, porta hepatis surgery, splenectomy, distal pancreatectomy, gastric resection, extensive nodal debulking, and intrathoracic surgery, These procedure could accomplish an higher rate of complications[7,37-68].

Since the first reports about the feasibility and the efficacy of optimal CRS in advanced EOC many authors have published about the topic. Many of them, however, reported case series in which patients have not homogeneously undergone CT or presented data without survival analysis focusing on the impact of RD. The more recent reports reach a major homogeneity from the chemotherapeutic point of view and have evaluated more extensively the impact and the extension of CRS and the RD.

Up to now, 15 studies have been published. The majority of them report cases treated with the standard systemic treatment of combined platinum-taxanes CT and CRS. Only one analyzed cases treated also with intraperitoneal CT[69]. Published studies divide patients into different classes of cytoreduction. The most utilized is the three level divisions: RD 0, 0-1, > 1 cm. In few studies a subgroup division is adopted. Some authors preferred to divide patients either into RD 0, 0-0.5, 0.6-1, 1-2 and > 2 cm or into RD 0, 0-1, 1-2, > 2 cm. Lastly, one paper divides patients into RD 0, 0-1, 1-5 and > 5 cm (Table 1).

This division demonstrated as no univocal evaluation of RD has been still adopted. Eisenkop *et al*[12] in 2003 reported a retrospective series of 408 patients with ⅢC stage EOC treated with either cisplatin/ciclophosfamide or paclitaxel/carboplatin CT and CRS. They reported an OS in the RD 0 group of 76.2 mo decreasing to 28.6 in the RD > 1. In the same year, Ozols *et al*[70] published a prospective analysis of 792 stage Ⅲ patients with a paclitaxel+cis-/carboplatin CT regimen divided into RD 0 and RD 0-1 which demonstrated an OS for the first group > 60 mo. OS reduced to 44 mo in the second group. In 2006 three papers have been published reporting stage Ⅲ-ⅢC patients. Two retrospective studies from Chi *et al*[13] and Aletti *et al*[14] reported both series of patients treated with either cisplatin/ciclophosphamide or paclitaxel/cisplatin CT added to CRS. Chi *et al*[13] divided patients into subgroups which distributed the RD into subcentimeters families reporting an OS of 106 mo for the RD 0 group progressively decreasing to 34 mo for the RD > 2 cm. Aletti reported an OS > 84 mo for the RD 0 and of 16 mo for RD > 2 cm. The last 2006 publication is the prospective report from Armstrong *et al*[69]. They reported a series of 415 women treated with cisplatin/paclitaxel CT administered either intraperitoneally or intravenously. For the two CT route (intraperitoneal and intravenous) groups they reported similar OS for RD 0 cm and RD 0-1 cm (78/75 mo and 127/135 mo respectively). Winter *et al*[15] and Wimberger *et al*[71] published another two retrospective reports. The first one reported about 861 patients with ⅡB-Ⅳ stage EOC which undergone paclitaxel/cisplatin or ciclophosphamide/cisplatin CT and CRS, with OS for RD 0 group of > 84 mo. The second one analyzed a series of 1895 stage Ⅳ women with carbo-/cisplatin + paclitaxel CT with OS ranging from 71.9 to 35 mo for RD 0 cm and RD > 1 cm groups respectively. Salani *et al*[72] also reported their retrospective series of 125 stage Ⅲ-Ⅳ patients tretated with cis-/carboplatin+palcitaxel CT with an OS ranging from 46.4 to 12 mo in RD 0 cm and RD > 1 cm respectively. The 2008 report by Winter *et al*[15] collected 360 women with stage Ⅳ EOC treated with carbo-/cisplatin+paclitaxel CT and CRS. They divided patients into groups ranging from RD 0 cm to RD > 5 cm. The OS ranges from 64.1 to 20.4 mo in the first and in the last group respectively. du Bois *et al*[17] and Bookman *et al*[73] published the two largest series of 3123 and 4312 patients respectively. du Bois *et al*[17] collected retrospectively patients with stage ⅡB-Ⅳ EOC who underwent carbo-/cisplatin+paclitaxel

Table 1 Cahracteristics of the included studies

Ref.	*n*	Disease stage (FIGO)	Age (yr)	Residual disease (cm)	*n* (%)	Overall survival (mo)	Associated cht	Route
Eisenkop *et al*[12]	408	ⅢC	63	0	351 (86)	76.2	PC, TP	*iv*
				0-1	41 (10)	32.2		
				> 1	16 (4)	28.6		
Chi *et al*[13]	465	ⅢC	60	0	67 (15)	106	NA	*iv*
				0-0.5	70 (15)	66		
				0.6-1	99 (21)	48		
				1-2	53 (11)	33		
				> 2	176 (38)	34		
Aletti *et al*[14]	194	ⅢC	64	0	46 (24)	> 84	PC, TP	*iv*
				0-1	85 (44)	34		
				1-2	22 (11)	25		
				> 2	41 (21)	16		
Winter *et al*[15]	1895	Ⅲ	57	0	437 (23)	71.9	TP, TC	*iv*
				0-1	791 (42)	42.4		
				> 1	667 (35)	35		
Winter *et al*[16]	360	Ⅳ	59	0	29 (8)	64.1	TP, TC	*iv*
				0-1	78 (21)	28.7		
				1-5	164 (46)	29.8		
				> 5	89 (25)	20.4		
du Bois *et al*[17]	814 (26)	ⅡB-ⅢB	59	0	1046 (34)	99.1	TP, TC, TC-TOP, TCE	*iv*
	1779 (57)	ⅢC		0-1	975 (31)	36.2		
	530 (17)	Ⅳ		> 1	1105 (35)	29.6		
Peiretti *et al*[18]	199 (76)	ⅢC	58	0	115 (44)	> 61.3	NA	NA
	60 (24)	Ⅳ		0-0.5	50 (19)	61.3		
				0.6-1	33 (13)	42.4		
				1-2	18 (7)	35.3		
				2	43 (17)	42.6		
Wimberger *et al*[19]	213 (28)	ⅡB-ⅢB	NA	0	227 (30)	> 84	PC, TP	*iv*
	548 (72)	ⅢC-Ⅳ		> 1	247 (32)	37		
					287 (38)	31		
Armstrong *et al*[69]	415	Ⅲ	56	0 (*ip* cht)	78 (38)	NA	TP	*iv*, *ip*
				0-1 (*ip*)	127 (72)	53		
				0 (*iv* cht)	75 (36)	78		
				0-1 (*iv*)	135 (64)	39		
Ozols *et al*[70]	792	Ⅲ	56	0	281 (35)	> 60	TP, TC	*iv*
				0-1	511 (65)	44		
Wimberger *et al*[71]	573	Ⅳ	59	0	70 (12)	54.6	TP, TC	*iv*
				0-1	168 (29)	25.8		
				> 1	334 (58)	23.9		
Salani *et al*[72]	97 (78)	Ⅲ	63	0	39 (31)	46.5	PC, TP	*iv*
	28 (22)	Ⅳ		> 1	53 (42)	28.3-37.8		
					23 (18)	12		
Bookman *et al*[73]	3681 (85)	Ⅲ	59	0	1044 (24)	68	TC	*iv*
	631 (15)	Ⅳ		0-1	1949 (45)	40		
				> 1	1319 (31)	33		
Chang *et al*[74]	189 (93.1)	ⅢC	54	0	63 (31)	86	TP, TC	*iv*
	14 (6.9)	Ⅳ		0-1	77 (37.9)	46		
				> 1	63 (31)	37		

PC: Platinum-cyclophosphamide; TP: Paclitaxel-cisplatin; TC: Paclitaxel-carboplatin; TC-TOP: TC-topotecan; TCE: TC-epirubicine; cht: Chemoterapy; NA: Not declared/assessed; FIGO: The International Federation of Gynecology and Obstetrics.

CT for stage ⅡB-ⅢB and carboplatin/paclitaxel and topotecan or epirubicin for more advanced stages. He reported an OS of 99.1 mo for RD 0 group decreasing to 29.6 mo for RD > 1 cm. Bookman *et al*[73] reported 4312 women with stage Ⅲ-Ⅳ disease undergone to carboplatin/paclitaxel and topotecan or epirubicine CT regimen with an OS of 68 mo for RD 0 cm and 33 mo for RD > 1 cm.

In 2010 three retrospective papers were published mixing stage ⅢB-Ⅳ patients. Peiretti *et al*[18] described 259 patients without publishing the intravenous CT regimen he reported an OS of > 61.3 mo for RD 0 and 41.6 for RD > 2 group. Interesting data in this paper regards the peculiar distribution of the OS among the RD groups. The authors divided patients into RD 0, RD 0.1-0.5 cm, RD 0.6-1 cm, RD 1-2 cm and RD > 2 cm. RD 0 cm and RD 0.1-0.5 cm have the same OS, RD 0-1 cm and RD > 2 cm patients have similar OS contrastingly with

the OS of RD 1-2 cm group who have a 10 mo shorter OS. These data contrast with all the other studies where the OS progressively declined with the increasing of the amount of RD. Kommoss *et al*[20] described 287 without the intravenous CT regimen with ⅢB-Ⅳ stage disease. RD 0 cm group reached an OS of 68.8 mo and the RD > 1 cm of 18.2 mo. In 2010, Wimberger *et al*[19] published another retrospective trial of 573 women with stage Ⅳ disease treated with carbo-/cisplatin and paclitaxel intravenous CT with an OS of 54.6 mo for RD 0 cm and 23.9 mo for RD > 1 cm group. The last paper about the effect of CRS in advanced EOC has been published in 2012 by Chang *et al*[74]. This retrospective description of 224 cases of stage ⅢC-Ⅳ patients with adjuvant platinum-paclitaxel CT with an OS of 86 mo in RD 0 cm and of 37 in RD > 1 cm group.

All the described papers demonstrated that CRS plays a pivotal role in advanced EOC treatment. The necessity of adjuvant CT has already been demonstrated and the necessity to reach a progressively more radical surgical cytoreduction has not been contradicted in the last 30 years. Surgical effort must be absolute. The extent of cytoreduction should be extended as much as is possible. The majority of reported studies adjust data for many differently combined factors such as: ASA, performance status, ascites, histology, tumor grade, RD, operative time, diaphragm or mesentery involvement, disease site in general. Even after these adjustments, data demonstrated always the same: as more the CRS is radical as more the OS is longer. The only exception to this rule derived from the study by Peiretti *et al*[18] in which OS rate doesn't linearly correlate to the RD group. The correspondence between the increasing of RD and the diminishing of OS seen in all the published literature in Peiretti's paper found a partial confirm.

The existing literature shows as the percentage of RD 0 procedures is absolutely different between the different centers and it doesn't apparently depend from the number of the treated patients. The number of enrolled patients in the published studies in fact could, in our opinion, be considered as a proxy of the surgical activity of the centers. In fact all the studies but three are retrospective and the evaluated periods of time are all comparable. The reported series have been all described slightly different CT regimens. Except for the Armstrong *et al*[69] study all the patients received intravenous CT. Observing the percentage of RD 0 reaching it seems to not be related to the CT regimen. The same could be observed for OS. Lastly, since the first publication about the discussed topic (2003) and the last (2012), there have not been major changes in the outcome of the treatment of advanced EOC by CRS and CT. As stated before, this suggests the presence of other factors from which depend the survival outcomes. Recent studies demonstrated the possibility to apply to ovarian cancer different drugs respect to the standard platinum based CT as bevacizumab[75]. However it has to be validated on the long course. Lastly different studies have investigated the possibility to apply weekly platinum/taxanes based CT regimens[76].

One topic that has not been largely investigated by the different authors is the quality of life (QoL) in the treated patients. It is a neglected area that should be more considered as a substantial part of the treatment of these women. Maximizing the surgical effort to eradicate the disease necessarily conduces to more aggressive procedures with the possibility to increase the morbidity. The evaluation of the impact of such a kind of procedures on the QoL of patients will necessarily lead to exaltation of the benefits of the neo-adjuvant therapies which could potentially reduce the disease load and consequently the surgical aggressiveness. Moreover the evaluation of the QoL must be pivotal in treating patients with advanced EOC in situations where the 5-year survival rate and so on the complete heal is not so relevant as the disease free survival and the quality of the gained surviving period. Introduction of neo-adjuvant CT regimen and the progressively more diffused use of hyperthermic intraperitoneal CT will play a decisive role in the next years in reaching a progressively more frequent removal of all macroscopic RD. They will also contribute to discern those factors other than CRS aggressiveness which strongly influence the survival outcomes.

CONCLUSION

Authors are used to report differently the results of CRS procedures, univocal definition of CRS results is needed. In order to increase the OS complete cytoreduction (RD 0 cm) should be always attempted and the primary aim of CRS should be no macroscopic RD.

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TOPIC HIGHLIGHT

Federico Coccolini, MD, *Series Editor*

Criticalities in randomized controlled trials on HIPEC for ovarian cancer

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Abstract

Since the 1990s, many oncological surgery groups around the world started to apply hyperthermic intraperitoneal chemotherapy (HIPEC) to the different peritoneal spread cancers. The rationale of the application of HIPEC after surgery is to complete the cytoreductive procedure. This combined treatment has now been successfully applied to many different intra-abdominal neoplasms. However, the treatment of peritoneal surface malignancies and the administration of HIPEC still lack high graded evidence data, especially in ovarian cancer. Experimental data exists about every step of the treatment of peritoneal spread ovarian cancer but unfortunately they have not yet been translated into phase Ⅲ clinical randomized trials. Moreover, treatment protocols differ between different centers. A systematic review of published randomized trial protocols was performed. HIPEC techniques are miscellaneous and not yet standardized. Well structured phase Ⅲ randomized trials among specialized centers are needed to investigate the efficacy of this therapeutic approach, as well as technical details that may contribute to the standardization of the procedure and limit morbidity and mortality. In particular, new criteria are mandatory to uniformly stage the disease, to objectively evaluate the extension of cytoreduction and consequently the residual disease, to decide the best method of performing hyperthermia and to perfuse drugs. Moreover, pharmacokinetic and pharmacodynamic studies are urgently needed to assess the best type and dose of anticancer drugs.

Key words: Randomized trial; Ovarian cancer; Hyperthermic intra-peritoneal chemotherapy; Hyperthermia

Core tip: Hyperthermic intra-peritoneal chemotherapy techniques are miscellaneous and not yet standardized. Well structured phase Ⅲ randomized trials among specialized centers are necessary to investigate the efficacy of this therapeutic approach, as well as technical details that may contribute to the standardization of the procedure and limit morbidity and mortality.

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INTRODUCTION

Treatment of peritoneal surface malignancies presents peculiar challenges to specialized teams who face them daily. The peritoneal spread of cancer, more than other forms of diffuse neoplastic disease, brings suffering to

patients directly linked to the loco-regional progression. These symptoms are often strongly disabling. Innovative therapies are developed day by day and applied to these cohorts of patients to control and/or palliate these symptoms that are often only due to the loco-regional cancer diffusion without systemic disease. In the 1980s, Sugarbaker *et al*[1] from the Washington Cancer Institute started to consider peritoneal carcinomatosis from intra-abdominal neoplasms as a loco-regional disease. They promoted a loco-regional treatment combining cytoreductive surgery (CRS) with intra-peritoneal (IP) administration of chemotherapy (CT). Adding hyperthermia to IP, CT was also investigated by Spratt *et al*[2] and has been successively performed and studied by many researchers and clinicians. Since the 1990s, many oncological surgery groups around the world started to apply hyperthermic intra-peritoneal chemotherapy (HIPEC) to the different peritoneal spread cancers[3]. The rationale of the application of HIPEC after CRS is to complete the cytoreduction by reaching all the microscopic cancer residuals which the surgeon cannot see and consequently remove. The combined treatment of CRS and HIPEC has now been successfully applied to many different intra-abdominal neoplasms[4-6]. Unfortunately, the peritoneal surface malignancies and the administration of HIPEC have always been based more on common sense than on high graded evidence data. Experimental data exists about every step of the treatment of IP cancers (CT, IP CT, CRS and HIPEC) but unfortunately they have not been translated into phase Ⅲ clinical randomized controlled trials (RCT) able to give high-impact results to demonstrate the real impact of HIPEC on the clinical course of IP cancers, especially of advanced epithelial ovarian cancer (EOC)[7].

RESEARCH STRATEGY

A thorough literature search of MEDLINE, EMBASE, COCHRANE, ClinicalTrial.gov, WHO International Clinical Trials Registry Platform and the EU Clinical Trials Register electronic databases was performed by 2 independent reviewers (FC and DC) to identify relevant studies. Bibliography evaluation of all selected study and recent reviews was performed to identify all additional studies. The search was not limited to any time duration. Only papers written in English were considered. To enable assimilation of all relevant published research, all search terms were expanded and all sub-categories were included. The exact syntax of search terms included ovarian neoplasms as well as randomized trial and other mesh terms.

SELECTION CRITERIA

Inclusion into the current systematic review was based on the following criteria for all retrieved studies: randomized trials evaluating the use of HIPEC in ovarian cancer. The purpose is to analyse discrepancies between the different protocols by studying the same disease in terms of inclusion/exclusion criteria, duration and kind of therapy, follow-up and primary and secondary outcomes.

IDENTIFIED STUDIES

A search of the databases using the above search terms led to identification of a total of 7 papers, five published protocols and 2 proposed studies. The complete manuscripts of all 5 published protocols were independently assessed and included in the review.

DATA EXTRACTION

Information from the studies was extracted by 2 researchers (FC and DC) using the data extraction form. Disagreements about data analysis were solved by discussion with a third author (ML).

Seven RCTs evaluating the effectiveness of HIPEC in EOC at different time points of EOC evolution have been proposed; five are already on course (Table 1)[8-11] and two have been only proposed[12].

The first is a South Korean study (NCT01091636)[9]. It is a phase Ⅱ trial evaluating the efficacy of HIPEC in the treatment of either primary or recurrent ovarian cancer. All patients in this trial will be scheduled to undergo CRS. After surgery, if the residual disease is less than 1 cm in the recurrent disease group, patients will always receive HIPEC. In the primary disease group, patients are randomized to receive HIPEC or not. Primary endpoint is progression free survival; secondary end points are overall survival and quality of life. The sample size is 168 patients and the completion date will be December 2013. HIPEC will be performed at a mean temperature of 41.5 ℃ for 90 min with platinum at a dose of 75 mg/m^2. This study enrols participants only by invitation.

The second is a study from the Netherlands (NCT00426257)[9]. It is a phase Ⅲ trial evaluating the efficacy of HIPEC after secondary debulking surgery. The scheduled 280 patients will be randomized to receive secondary debulking surgery with or without HIPEC. The two criteria indicated as indication for secondary debulking are the impossibility of performing primary debulking for tumor extension or the patient's general condition or a primary debulking procedure with a residual disease of more than 1 cm. In both cases, patients will undergo chemotherapy before the surgical procedure. Primary outcome is recurrent free survival; secondary outcomes are toxicity, morbidity, quality of life, tumor response and overall survival. The finishing date will be March 2013. HIPEC will be performed with platinum at a dose of 100 mg/m^2.

The last published protocol evaluating HIPEC in primary advanced EOC (NCT01628380)[8] is the CHORINE study. This is an Italian multicentric trial which has the peculiar characteristic of evaluating the role of HIPEC after neo-adjuvant chemotherapy. This phase Ⅲ trial is scheduled to recruit 94 patients to be randomized into two arms. The randomization will be done after

Table 1 Studies included in the review

Protocol no. (Name)	Country	Time point	Sample size	Randomization	Treatments	Primary outcome	Secondary outcome
NCT01091636	South Korea	Primary, recurrent OC	168	After surgery residual disease < 1 cm	CRS ± HIPEC with platinum 75 mg/m^2 at 41.5 ℃ for 90 min	Progression free survival	Overall survival, quality of life
NCT00426257	The Netherlands	Secondary debulking surgery	280	ND	CRS ± HIPEC with platinum 100 mg/m^2	Recurrence free survival	Toxicity, morbidity, quality of life, tumor response and overall survival
NCT01628380 (CHORINE study)	Italy	Primary advanced OC after NACT	94	After surgery residual disease < 2.5 mm	CRS ± HIPEC with platinum 100 mg/m^2 + taxol 175 mg/m^2, at 42 ℃ for 90 min, open or closed technique	Disease free survival	Morbidity, mortality, time to chemotherapy beginning after surgery, overall survival, 1, 3, 5-yr disease free survival and 1, 3, 5-yr overall survival
NCT01376752 (CHIPOR study)	France	Recurrent OC	444	After surgery residual disease < 2.5 mm	CRS ± HIPEC platinum 75 mg/m^2	Overall survival	Relapse free survival
NCT01539785 (HORSE study)	Italy	Recurrent OC	158	ND	CRS ± HIPEC platinum 75 mg/m^2) at 41.5 ℃ for 60 min, closed technique	Progression free interval	Overall survival, morbidity and mortality

OC: Ovarian cancer; NACT: Neoadjuvant chemotherapy; HIPEC: Hyperthermic intraperitoneal chemotherapy; CRS: Cytoreductive surgery; ND: Not declared.

CRS. Only patients with an optimal completeness of cytoreduction with a residual disease of a maximum of 2.5 mm will be randomized. The primary outcome will be the disease free survival and the secondary ones will be morbidity, mortality, time to chemotherapy beginning after surgery, overall survival, 1, 3, 5-year disease free survival and 1, 3, 5-year overall survival. Platinum (100 mg/m^2) plus taxol (175 mg/m^2) will be administered with either an open or closed technique at a temperature of 42 ℃ for 90 min for HIPEC. The scheduled finishing date will be June 2014.

Two randomized trials evaluate the efficacy in recurrent EOC. The first is the CHIPOR study (NCT01376752)[10]. This multicentric phase Ⅲ trial from France aims to study the effect of HIPEC on complete cytoreduced patients (CC-0 or CC-1 with a residual of max 0.25 cm). The randomization will be done after cytoreduction. If CC-0 or CC-1 criteria are reached, patients will undergo HIPEC with platinum at 75 mg/m^2. Primary outcome is overall survival and the secondary outcome is relapse free survival. The scheduled number of patients is 444 and the scheduled finishing date is April 2018.

The last registered trial is the HORSE study (NCT01539785)[11]. This Italian multicentric phase Ⅲ trial randomizes patients into two arms and CRS will be compared to CRS + HIPEC. The CRS + HIPEC arm patients will be treated with platinum (75 mg/m^2) at 41.5 ℃ for 60 min with a closed technique. Primary outcome is progression free interval and the secondary outcomes are overall survival, morbidity and mortality. The scheduled number of patients to be enrolled is 158 and the scheduled finishing date is February 2015.

Lastly, two proposed trials have to be mentioned. These two proposals have been published in a letter by Chua *et al*[11]. The authors proposed two trials to investigate the HIPEC procedure in primary and advanced ovarian cancer, dividing patients into two arms for each study and treating them with either CRS plus HIPEC (platinum 100 mg/m^2) or CRS alone. In their opinion, the CRS effort should be maximal and its aim is the absence of macroscopic residual disease.

As already stressed by other authors[12-14], the main difficulty to reach clinically relevant results in the treatment of EOC with HIPEC is strongly determined by the impossibility of obtaining a sufficient number of patients in a single center. In fact, in many centers, patients with peritoneal carcinomatosis are still considered as terminal and so are often not referred to the specialized surgical oncology groups to be correctly evaluated. Many clinicians are sceptical about the use of such an aggressive regimen of CRS plus HIPEC because of the potential increase in morbidity and mortality in a category of weak patients. Also, patients challenge the accrual for RCT because their referral to peritoneal surface malignancies specialized centers is mainly driven by the will to undergo CRS and HIPEC. They seldom accept to be randomized to receive HIPEC treatment or not. Lastly, the single institution is an obstacle that strongly limits the possibility of participating in a multicenter RCT. Each center in fact utilizes different procedures, surgeons operate in a different way and consider the completeness of cytoreduction differently at any time point[15,16], and anesthesiologists or surgeons adopt different pre- and post-operative care systems.

RCTs about HIPEC are poorly or not sponsored by pharmaceutical companies which prefer to promote trials where chemotherapy is administered systemically with new targeted agents[17]. Moreover, the different studies are mainly retro- or prospective phase Ⅰ and Ⅱ; insuffi-

cient randomized phase Ⅲ trials exist. Standard treatment has to be inserted into these kinds of trials with an arm to compare, which allows discerning the real impact of HIPEC without a confounding bias. On the other hand, however, the possibility of concluding a multicentric randomized trial crashes against the different habits or institutional lacking, which increases the difficulty of getting homogeneous proceedings in the different centers. To all these factors has to be added the lack of scientifically defined indications about the chemotherapy regimens. Intraperitoneal chemotherapy in fact is often administered at a "common sense dose". Each center adopts a different dosage determined either by the patient characteristics or the habits or personal belief of the operators. No definitive studies exist about the drug dosages to be used intraperitoneally. No studies have in fact evaluated the optimal dose in relationship to the efficacy, tissue penetration and cancer penetration in big samples of population because the necessary sample size would be huge. However, we are studying the efficacy of HIPEC without knowing how its administration is done. From the surgical point of view, in fact, technical improvement has nearly reached its maximum. We certainly need to know if and how HIPEC allows gain in DFS or OS. However, we still do not know if and how we can gain improvement with chemotherapy with the commonly used drugs.

Another issue to be clarified is the duration of perfusion. No definitive pharmacokinetic and pharmacodynamic studies have clarified the right time, right doses or the administration interval for the different drugs. Some authors perfuse for 60 min; others for 90 min. Some administer all drugs at the beginning; other fractionate the doses into 2, 3 or more administrations, in consideration of the kinetics of the molecules.

Some authors utilize the open technique; others the closed one. Experimental studies demonstrated the different drug distribution in the different techniques. However, no definitive data and consequently indication have been published.

Complications of the procedure are reported using many different reporting scales. Each scale differentiates complications in its own manner and no conclusive data could be obtained[4]. Some authors classified complications and adverse events by using the Bozzetti classification[18]. Others authors have used different classification systems, such as the Clavien one or its two proposed modifications from Feldman or Elias[15]. Others have used the National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE)[18]. These scales are not specifically designed to assess and report CRS + HIPEC complications. The 2006 peritoneal surface malignancies workshop (Milan, Italy) established the CTCAE as the standard system to report CRS+HIPEC complications. However, no univocal classification has been adopted yet. For this reason, no comparison between the different reports could be done.

In the majority of studies dedicated to therapeutic strategy in ovarian cancer, no information is reported regarding peritoneal disease extent as the FIGO classification is used. Stage Ⅲc includes patients with localized disease and patients with extensive peritoneal carcinomatosis. When classification of the disease distribution is reported, two main grading systems are used. The Gilly classification partially considers dimension or diffusion but gives an incomplete idea of the surgical field before CRS[19]. The peritoneal cancer index (PCI) by Sugarbaker and Jacquet precisely described dimension or distribution of the disease[20]. This allows uniform data and results. Moreover, PCI was demonstrated to have prognostic value[21,22].

The classification of the completeness of cytoreduction is still controversial. Different scoring systems are used; mainly the Lyon[23] and the Sugarbaker classification[17]. The increase in DFS benefit with the increasing of the completeness of cytoreduction toward no residual disease[4,24,25] is demonstrated. The scientific community is modifying its opinion by agreeing on the meaning of complete cytoreduction as no macroscopic residual disease. However, there is no univocal opinion and consequently the surgical goal still has to be reached in this field.

CONCLUSION

HIPEC techniques are miscellaneous and not yet standardized. Well structured phase Ⅲ randomized trials among specialized centers are necessary to investigate the efficacy of this therapeutic approach, as well as technical details that may contribute to the standardization of the procedure and limit morbidity and mortality. In particular, new criteria are mandatory to uniformly stage the disease, to objectively evaluate the extension of cytoreduction and consequently the residual disease, to decide the best method to perform hyperthermia and to perfuse drugs. Moreover pharmacokinetic and pharmacodynamic studies are urgently needed to assess the best type and dose of anticancer drugs.

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TOPIC HIGHLIGHT

Federico Coccolini, MD, *Series Editor*

Anesthetic management of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedures

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Abstract

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedure are performed with increasing frequency to treat patients with diffused peritoneal carcinomatosis. These procedures have showed to increase life expectancy in what was previously considered a "terminal condition". Anyway patients face major and life threatening derangements of their hemodynamic, respiratory and metabolic physiologic balance during the surgery and in the immediate postoperative period. Despite the need of an advanced organ monitoring and support all these derangements seem to be mild and short-lived when timely addressed, at least in the majority of patients. Intensive care physicians are involved in providing surveillance and organ support till the patient is effectively weaned after the operation. Moreover, the anesthesiologist as perioperative physician is involved in pain control, metabolic and nutritional support of this cohort of patients. This task can be challenging considering that part of the patients are already on a long list of pain control medication after previous surgery or chemotherapy. A malnourished state is common too and it is secondary to difficult feeding, wasting syndrome from the tumor and massive ascites. The last issue the anesthesiologists need to be aware of is the impact over the quality of life (QoL) of this procedure. The patient's underlying pathology is unlikely to be definitively cured so no treatment is an acceptable choice. The possibility to withhold the treatments must be part of the consultation process like the discussion about the QoL in the immediate, as well as in the long-term, after the operation. Careful monitoring and treatment of every aspect that can impact the QoL must be taken and the efforts to be poured into an effective preservation of the QoL must be doubled when compared with a patient scheduled for major abdominal surgery.

Key words: Peritoneal carcinomatosis; Anesthesia; Hyperthermic intraperitoneal chemotherapy; Morbidity; Mortality

Core tip: The strenght of this review is to be part of an editorial project that addresses all the aspects of hyperthermic intraperitoneal chemotherapy and cytoreductive surgery procedure. As last article of this special number it gives a comprehensive overview of the anestesiologic issues and an in-depth view of the perio-

perative problems and how they affect life and quality of of the patients that undergone this type of surgery. Moreover for every topic preoperative, intraoperative and postoperative considerations are provided in order to give a clear guide to the physician that approchese these patients.

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INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are extensive, life and quality of life (QoL) threatening procedure. All the available studies covered an extremely selected population of patients usually young (less than 70 years old), without relevant comorbidity [mainly American Standards Association (ASA) 1 or 2] and with a near to normal performance status scale (Karnofsky performance status > 80%)[1-5]. Despite this highly selected population, morbidity and mortality are as high as 65%[1] and 12%[6], respectively. Patients face major hemodynamic, respiratory and metabolic derangements during the procedure that need to be timely addressed; moreover anesthesiologists, as perioperative physicians, are committed to providing surveillance and organ/metabolic support in the first period after the procedure itself.

We will provide an overview of the challenges the anesthesiologist has to face; for every issue we will provide preoperative, intraoperative and postoperative considerations, when appropriate.

RESPIRATORY STATUS

These patients could be pre-operatively hypoxic because of ascites, pleural effusion and atelectasis. During the HIPEC phase of the procedure there is an increase in airway pressure and a reduction in functional residual capacity. As the abdominal cavity is filled-up with the chemotherapeutic agent we observe an elevation of the diaphragm and an increase in the intra-abdominal pressure (IAP)[7,8]. An increased $PaCO_2$ and a decrease in the A-a gradient and arterial pH is the hallmark of the gas exchanges deterioration. All these changes are short-lived after the HIPEC phase is terminated apart from the pH reduction, due to a persistence of the metabolic acidosis[9].

Preoperative consideration

Standard evaluation with Chest X-ray and careful medical history record is probably enough. However, pulmonary function test should be considered if a history of increased bronchial reactivity is reported. Moreover due to the high incidence of hydrothorax preoperative pleural effusion evacuation and Continuous Positive Airway Pressure (CPAP) periods should be considered in order to optimize pulmonary reserve before surgery.

Intraoperative considerations

An impaired tissue oxygenation and an increase in peak airway pressures up to 30 mmHg are reported during the HIPEC phase secondary to the cranial shift of the diaphragm[4]. A lung protective strategy consisting of low tidal volume, positive end expiratory pressure and recurrent recruitment maneuvers should be considered as the respiratory derangements are similar to those observed during long laparoscopic procedures and should be treated accordingly[10]. Whenever a previous history suggestive of severe reduction of Functional Residual Capacity is reported an open abdomen technique, as the coliseum one, should be employed for its smoother impact on hemodynamic and respiratory systems[11].

Postoperative considerations

The vast majority of patients can be extubated in the operating room at the end of surgery. Anyway, beside patients still on mechanical ventilation at the end of the procedure all the patients should be monitored postoperatively for respiratory complications. Postoperative CPAP can be extremely useful to speed up the recovery as reported by Arakelian *et al*[12] and should be discussed pre-operatively with the patients and planned for the first postoperative period.

HEMODYNAMIC BALANCE

CRS and HIPEC phase of the procedure show different hemodynamic features. During the CRS we face an extreme surface exposure, often severe bleeding, massive ascites evacuation, as in the case of ovarian tumors, and extensive tumor and peritoneal resection. Keeping normovolemia can be difficult and fluid turnover exceeding the well-established 6-8 mL/kg per hour for major abdominal surgery[13] is often reported. About 12 mL/kg per hour is the most frequent fluid requirement observed during this procedure to keep an adequate end-organ perfusion as detected by urinary output or appropriate advanced hemodynamic monitoring[3,4,14,15]. HIPEC phase is characterized by two conflicting features. If hyperthermia induces a hyperdynamic state the increased IAP, when the abdominal cavity is filled up with chemotherapeutic agent, creates a hypovolemic state due to the reduction of the venous return. A plain description of the hemodynamic parameters during the HIPEC phase is: an increase in heart rate[3,15], mean central venous pressure (CVP), pulmonary artery pressure, wedge pressure[7,15], intrathoracic blood volume index[14] and cardiac index[11,15,16]; on the contrary mean arterial pressure and systemic vascular resistance showed a trend, if not a statistically significant, reduction over the baseline[9,14]. An increase in end tidal CO_2[3] and an increase

in oxygen extraction and consumption rate are the signs of the hypermetabolic state that is due to the hyperthermia[17]. All these changes are constantly reported to be short-lived after the completion of the HIPEC phase and the vast majority of patients, if not all, were weaned off from hemodynamic support at discharge from the operating room, if ever supported with an amine infusion. Moreover the hemodynamic derangements can be reduced if: an open abdomen technique is employed and the core temperature is kept as close to normal as possible. Esquivel *et al*[11] reported only a statistically significant increase in cardiac output during the HIPEC phase when the "Coliseum Technique" was used while the increase in heart rate, mean CVP and the decrease in systemic vascular and mean arterial pressure were not a statistically, and clinically, significant trend. The earliest report from Shime *et al*[17] in 1994 on the effect of the hyperthermia on the hemodynamic balance showed remarkable changes with a reduction in mean arterial pressure and systemic vascular resistance from 93.8 to 75.5 mmHg and from 2214 to 1239 dynes × s/min^{5} × m^{2}, respectively, and an increase in cardiac index and wedge pressure from 3.4 to 4.6 mL/min per square meter and from 7.5 to 9.6 mmHg, respectively. Those changes were paired with a core temperature that approached 40 ℃ at the end of the perfusion whereas in more recent studies the core temperature never outreached 38 ℃[3,9]. This proportionally direct effect of temperature over the hyperdynamic state of the patient is well known. Several studies conducted during the procedures of whole-body hyperthermia showed how when the core temperature gets warmer the hyperdynamic state gets worst[18].

Preoperative considerations

No study specifically targets the cohort of patients with heart failure. To this day, in the large RCTs published patients with an uncontrolled cardiac disease were excluded as no patient with ASA higher than 3 was considered eligible[3,12]. A thorough cardiac evaluation (echocardiogram, stress test if there's suspected reduced coronary reserve) can be a prudent approach if a history of previous heart failure or reduced physical activity is reported. In this case the patients should be referred to the cardiologist for evaluation and risk stratification. Beside this we consider it sensible to refer every patients to a cardiologist if he/she had a possible cardiotoxicity from previous chemotherapy and/or he/she developed a fast malnourishment state. Indication for HIPEC should be questioned whenever an uncontrolled cardiac disease is detected and eventually the patients should be considered for palliative care only.

Intraoperative considerations

All the hemodynamic changes are constantly reported to be short lived after surgery. Despite this, major fluid shift and amine support are constantly reported too. All the available case series used at least as hemodynamic monitor: hourly urinary output, CVP and an invasive arterial line[3,9] whereas others used invasive, or advanced, monitoring such as pulmonary artery catheter[7,15,17], continuous esophageal echo-Doppler monitoring[8,11,16] or transthoracic thermodilution technique[14] (Picco; Pulsion Medical System, Munich, Germany). In our institution invasive monitoring is usually considered mandatory just for patients with a known reduced cardiac performance. Anyway some minimally invasive devices as Vigileo/flo-Trac, Pulsion Picco, trans-esophageal echocardiography can be extremely helpful in guiding transfusion and fluid turn-over therapy. Several authors[11,16,19] argued that CVP is unreliable due to the increased IAP and table tilting during the HIPEC phase. Moreover the urinary output can be reduced secondary to toxicity of chemotherapeutic agent or to the increased IAP itself. In this scenario the possibility to evaluate in a real time manner dynamic parameters of cardiac preload and fluid responsiveness is of utmost importance in order to reduce the risk "flood or dry" the patient and to ensure an appropriate end-organ perfusion. Beside fluid therapy amine support is an open issue during the procedure. No standardized protocol to face cardiac failure is reported and the amine used is related to the local policies of the different institutions. Low doses dopamine were employed by Cafiero *et al*[16] and by Miao *et al*[9] to prevent renal dysfunction as a "renal dose" of dopamine is reported to increase renal perfusion during laparoscopic procedures[20]. Anyway dopamine seems to have little effect, if at all, because none of the studies where it was not employed showed an increased rate of renal failure.

Postoperative considerations

Hemodynamic unbalances are usually short lived. Anyway Cooksley *et al*[8] reported that a 26% of the patients were still on vasopressor at the end of the procedure and at the arrival in intensive care unit (ICU), even if no patients developed renal failure or had a difficult weaning from hemodynamic support. Moreover fluid requirement can be difficult to anticipate as massive fluid loss through the drainages, up to 4 L a day[4], are reported. Careful fluid turn-over substitution and timely weaning from vasopressor support advocate for an intensive, or at least intermediate, care to deliver adequate post-operative surveillance so to prevent renal dysfunction and decreased end-organ perfusion.

PAIN CONTROL

The elective pain control modality in the vast majority of the centers is thoracic epidural[3,4,8,9,14,17,19]. Massive surface scarring is enough to justify the high level of pain reported and the longer use of advanced and invasive modality of pain control. For example, the cohort of patients from Schmidt *et al*[3] had a median of 7 d of continuous infusion of local anesthetic and opioids *via* the epidural route, which is much longer than the usual 3/4 d after major abdominal surgery.

Preoperative considerations

It is important to notice that the patients scheduled

for CRS and HIPEC procedure had a long, and often troubled, medical history. Some of them are already on a long list of analgesic medications and some others show features of chronic and neuropathic pain after the chemotherapy. No study specifically addresses this issue as chronic pain facilities are extremely heterogeneous around the world and the patients themselves undergo surgery with a different diagnosis of disease and had more or less invasive procedures and different chemotherapeutic regimen. However a consult with the palliative care/chronic pain physician can be useful in order to plan a follow-up of the patients when they're discharged from the hospital. Thoracic epidural is probably the best option to control pain perioperatively. It is associated with a shorter mechanical ventilation period, from 10 to 3 h[3], and a better patient satisfaction[21]. Anyway these patients seem to be efficiently and safely managed perioperatively even with high level of intravenous opioids. A percentage of patients ranging from 38%[3] and 21%[9] had no epidural catheter and they did not show a significant increase in perioperative complications, if we exclude a longer period on mechanical ventilation and ICU admission. Coagulation unbalances are common in these patients as they develop massive ascites or have a long-standing history of bleeding or malnourishment. However, it does not seem to affect the safety of the placement of a thoracic epidural catheter as no epidural hematoma is reported[22]. Risk benefit ratio is probably in favor of thoracic epidural considering the difficulty to control pain and wean from mechanical ventilation that these patients have.

Intraoperative considerations

A continuous infusion of local anesthetic and/or opioids through the epidural route is felt unsafe by several authors[9,23-25] because of its high potential to worsen hypotensive episodes due to its synergic effect with hyperthermia in reducing the systemic vascular resistances and because of the sympathetic blockade epidural analgesia produces. Anyway Schmidt *et al*[3] found no detrimental effect using epidural analgesia during the procedure. We can speculate whether there's any potential advantage in using epidural analgesia in the prevention of the development of chronic postoperative pain in a similar manner to its use during thoracic surgery[26]. Beside this there's an increasing amount of data that suggest how the use of epidural analgesia may improve patients survival rate by decreasing the incidence of tumor relapse or at least elongating the time to relapse of the tumor. de Oliveira *et al*[27] found a significantly longer time to cancer recurrence in the patients that had thoracic epidural working during the procedure of CRS, but not HIPEC, (73 mo *vs* 38 mo in the control group) in a cohort of patients affected by ovarian cancer. On the contrary, time for cancer recurrence was not different between the patients that never had thoracic epidural or had it just as postoperative pain relief technique. This possible positive effect can be secondary to the increased function of nartural killer cells when the surgical stress response is reduced[28,29] and high level of intravenous opioids is avoided[30].

Postoperative considerations

Postoperatively all the usual precautions and the usual surveillance should be taken. In case of the development of chronic pain the patients should be referred to a palliative care center or to a chronic pain clinic.

COAGULATION CONSIDERATIONS

Coagulation abnormalities are always reported in this cohort of patients. They are defined as an abnormal elongation of prothrombin time - international normalised ratio (INR), activated partial thromboplastin time (aPTT) and/or pathological reduction of platelets count over the baseline[3,4,8,9]. This dysfunction is reported to peak around 24/48 h post-surgery[3,8], with a restoration of a normal coagulation profile in 72 h[3], even if baseline values are reached in almost 5 d[9]. Schmidt *et al*[3] reported that Fresh Frozen Plasma (FFP) and packed red blood cells (PRBC) were transfused in 50% of the patients intra-operatively and 28% post-operatively. Coagulation abnormality is, probably, multifactorial in its genesis. The two sides of the problems seem to be a dilutional dysfunction[31] secondary to massive fluid shift and bleeding and an impairment of coagulation factors profiles due to massive ascites[32] and malnourishment.

Preoperative considerations

Standard coagulation evaluation (INR, aPTT, platelets count, list of antithrombotic drugs) is enough and no author advocates for more expensive tests. The fear of intraoperative bleeding should not prevent us from considering the high thrombotic risk that some patients may have. Some of them are women, in their fifties, with an ovarian cancer, that are going to keep for 8-10 h a gynecological position on the operating table. All of these are well known prothrombotic risk factors. Special care is required by patients with massive ascites. Ascitic fluid is rich in proteins with a varying concentration of 0.5-4.2 g/100 mL of proteins. Of this amount 50%-70% is albumin, 30%-45% are globulins and 0.3%-4.5% is fibrinogen. The evacuation of up to 2-3 L of this fluid changes something more than the oncotic pressure of the patient. Vorgias *et al*[32] calculated the theoretical substitution requirement of patients optimally debulked from ovarian cancer and found out that infusions for up to 3 d of 2 units of FFP and human albumin were required.

Intraoperative considerations

Coagulation during CRS and HIPEC procedure means to deal in a short period of time with: dilution coagulopathy due to large amount of crystalloids and/or colloids infusion; transfusion coagulopathy due to PRBC transfusion to keep an adequate oxygen delivery, in the scenario of massive bleeding; and long-standing coagulation abnormalities due to dysproteinemia secondary to malnourishment and ascites evacuation. This scenario complicates the understanding of normal coagulation tests such as INR, aPTT and platelet counts. Thromboelastography (TEG) gives the possibility of a thorough evaluation of

the coagulation profile and it is probably more useful in this type of surgery than in others. Even if no paper specifically addresses this question TEG-guided transfusion of blood products may substantially reduce bleeding and eventually blood-products requirements similarly to what happens in other major surgeries[33].

Postoperative considerations

The coagulation profile takes at least 5 d[9] to get back to baseline values so surveillance and timely transfusion is needed. Renal status, electrolyte balance, glycemic and temperature control: renal dysfunction, electrolyte disorder and hyperglycemia are frequently observed[3,7,9,34]. They are related to the fluids infused, end-organ perfusion achieved and quality and quantity of perfusate used to deliver the chemotherapeutic agent in the abdominal cavity. Temperature control is of utmost importance as it is directly related to the gravity of deregulation in the hemodynamic and coagulation balance.

RENAL STATUS, TEMPERATURE AND METABOLISM

Standard evaluation: If ureteral stents are positioned preoperatively to be used as landmark during CRS phase it should be advisable to check for their bilateral patency.

Intraoperative considerations

Calcium, potassium, sodium are routinely checked. Minor electrolyte such as magnesium should be tested too as their unbalance is reported[9]. The use of furosemide to enhance urine output to clear as much chemotherapeutic agent as possible is frequently reported[9,14,16]. Forced diuresis by the use of high dose loop-diuretics is still considered "standard of care" during chemotherapy with compound derived from platinum. Despite this "standard practice" there is no definitive evidence of renal protection by the use of high dose of loop-diuretics, as stated by the Special Interest Group on Cancer Care of the European Society of Clinical Pharmacology[35]. They recommended a "brisk diuresis" during the platinum compound infusion and in the immediate days after by a prolonged saline infusion. In our case series of CRS and HIPEC we had three renal insufficiencies in 70 cases during the last year, two of them were obstructive, none of them required dialysis (unpublished data). This small incidence of renal impairment was probably related to the invasive monitoring of euvolemia during the procedure despite a diuretic use (20 mg of furosemide before HIPEC induction). In our opinion diuretics use has still a place in the "standard of care" of these patients as hypovolemia can be easily detected and corrected if invasive monitoring is ensued and there is no clear evidence "against" the use of loop-diretics. Drug clearance is mainly linked to renal blood flow and not to plain urine output. the prolonged use of diuretics can be misleading as we can face a good urinary output in the presence of an unnoticed end-organ perfusion decrease therefore euvolemia must be pursued with any effort. De Somer *et al*[34] reported hyperglycemia and hyponatremia when a perfusate of 5% dextrose was used as a carrier for oxplatin. This paper points out the need for the anesthesiologist to know the composition of the perfusate and to prevent possible electrolyte unbalances due to the abdominal perfusion itself. Even if the peritoneal surface is reduced the exposed area is still enough to give a statistically, and clinically, relevant impact over the electrolytes and fluid balance. Temperature control devices and strategies need to match the different requirements during the CRS and HIPEC phase of the procedure. During the cytoreduction when the abdominal cavity is open there is an intense warm loss and hypothermia must be prevented using all the warming devices available (*i.e.*, forced air warming, warmed infusions, arm blankets). On the contrary patients must be cooled down during the HIPEC phase when the warm infusate is delivered into the abdominal cavity. Cold fluids, ice packs, cooling mattress[14,16,17] have been used to cool the patients during the HIPEC procedure. Sometimes those devices were used to lower the core temperature before the abdominal cavity filling[7,9].

Postoperative consideration

None of these disturbances is reported to be long lasting after the completion of the procedure so just standard care is needed.

QoL

CRS and HIPEC represent a radical treatment in a patient that has little possibility, if any, to be definitively cured. Data from the literature suggest that patients that understand their "terminal state" are likely not to wish to submit themselves to extensive, life and QoL threatening procedures[36]. In this scenario no treatment, obviously excluding palliative and supportive care, is an acceptable choice and a careful counseling between physician and patient is mandatory. Anyway patients that are referred to a center that performs CRS and HIPEC are usually aware that the procedure will gain time for them, or at least for the majority of them. Moreover McQuellon *et al*[37] eported that no patient in the cohort of long-term survivor regretted having undergone the procedure. Although perioperative mortality and morbidity can be high[1,6], median survival improves significantly and for colorectal cancer a survival rate of 30% at 5-year is reported[38,39]. The quality of the life gained with this procedure has been evaluated in several papers[37,40-44]. Regardless of the cohort of patients analyzed, or the scores used to describe the QoL, all the papers reported - after a drop in quality and physical functioning in the first few months following the procedure - a steady increase that reached baseline[4,5,42] or overshot it as in the case of patients with ovarian cancer and massive ascites[39]. McQuellon *et al*[37] published the only report on long-term survivors after HIPEC and CRS. They showed as 87% of the patients that survived longer than 3 years rated their health as good or excellent and none of them regretted having undergone the procedure. To interpret data from QoL studies on HIPEC patients mean to deal with at least three main problems. The first one is the non

standardized use of score across the studies as already reported by Piso *et al*[43]. Secondarily it is extremely complicated to interpret data from QoL studies as, especially in a cohort of patients with a terminal disease, factors as adaptation to disease, response shift, dispositional optimism can deeply change some of the scoring and maybe have little effect over the life of the patients[41,45]. The typical effect is that little improvement in QoL may be not significant at a population level but, at the patient level, it can be important enough to enter or not a rehabilitation or supportive care program. Thirdly a significant proportion of the patients do not reply to the follow-up since some of them die or their conditions are so deteriorated that they cannot reply to the questionnaires. McQuellon *et al*[40] evaluated the QoL data of patients starting with a cohort of 64 patients at baseline but only 23 patients replied to the 1-year follow-up questionnaire. Another study[42] evaluated 96 patients at baseline but only 24 were able to complete the 1-year follow-up, similarly Schmidt *et al*[4], with a baseline cohort of 67 patients and a 25 patients at the time of the follow-up. Even though it is possible to consider and weigh during the analysis the effect of missing data and of the non-random distribution of the results we need to focus keep in mind that probably the data just reflect the best possible outcome of this surgery and that a real "average effect" it does not exist.

POSTOPERATIVE CARE

The procedure is long and complex and even though the physiological derangements are predominately short-lived these patients deserve an intense postoperative monitoring. Postoperative respiratory support is not always necessary even if CPAP periods can be useful to get back to baseline respiratory function levels[12]. Cooksley *et al*[8] reported to have extubated all the patients in the OR before discharging them to the Critical Care Unit, whereas Miao *et al*[9] extubated 62% before PACU admission. Interestingly Schmidt *et al*[3] observed how the presence of a working epidural analgesia was significantly associated with a reduction in the mechanical ventilation period (3.1 h *vs* 10.3 h, respectively) and in an higher proportion of patients extubated in the operating room (41% *vs* 14%, respectively). From an hemodynamic point of view these patients are rarely on amine support but suffer from high volume of fluids loss from the drains, up to 4 L a day[3], secondary to the huge wounded surface. Even if the postoperative period is less troubled than the surgery one these patients needs to be monitored for a while and all the derangements eventually corrected in a timely manner. No study specifically addresses the right place to be discharged after the OR or the right period of critical care monitoring. Anyway we agree with the statement by Cooksley *et al*[8], that a shorter hospital length of stay is probably due to admission, and prolonged observation period, in a critical care unit.

NUTRITIONAL SUPPORT

No author addressed the specific topics of the nutritional and metabolic support in the patients undergoing CRS and HIPEC. This category of patient is known to have a poor nutritional baseline as malnutrition prevalence is reported to be as high as 67%[46] in ovarian cancer patients and 54%[47] and 83%[48] in colorectal and gastric cancer, respectively. Moreover the debulking phase of the surgery involves massive resections that are likely to cause a deep catabolic and pro-inflammatory state. All malnourished patients should have a nutritional consultation before surgery and should start a nutritional support to reach a better metabolic profile[49] before surgery. Although little is known about the effect on small bowel physiology of the hyperthermic intrabdominal chemotherapy, it is advisable that these patients should be treated according to the guidelines about perioperative nutritional support after major surgery[50]. So nutritional states must be assessed preoperatively and enteral feeding started as soon as possible after the resolution of mechanical bowel obstruction. Positioning a nasojejunal catheter can be a valuable option to start early enteral feeding as already reported in this group of patients[8]. This area of research is of increasing interest due to the fact that starvation, or better malnourishment, has been identified as a major determinant of surgery success and QoL recovery.

CONCLUSION

CRS and HIEPC are complex procedures. High morbidity and mortality rates are reported, nonetheless it has showed its power to gain life in a relevant part of the patients and its safety in high volume centers. Respiratory and hemodynamic derangements were the first ones to be extensively evaluated. Morbidity related to these two systems failure is decreasing since pathophysiology of hyperthermia is better understood and better temperature, hemodynamic and respiratory control is achieved through new devices or technique. The research agenda of this procedure is an open challenge and the issue to be addressed in the next future are how to increase QoL of the patients through a better understanding of the coagulation derangement, and issues concerning pain patterns, nutritional support and social rehabilitation.

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TOPIC HIGHLIGHT

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Natural history of epithelial ovarian cancer and its relation to surgical and medical treatment

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Abstract

Epithelial ovarian cancer (EOC) represents approximately 90% of primary malignant ovarian tumors, the sixth most common cancer in women and the second most common gynecologic cancer. Approximately 80%-85% of all ovarian carcinomas in Western society are serous and up to 95% of patients are in advanced stages (FIGO stage Ⅲ-Ⅳ) at diagnosis. Treatment of ovarian cancer is mainly based on three key approaches: surgical removal of neoplasia; chemotherapy to kill cancer cells; direct chemotherapy on peritoneal surfaces. The application of hyperthermic chemotherapy to the peritoneal cavity (HIPEC) after radical surgery may also be an attractive option. We analyzed the natural history of EOC in the literature and identified various time-points where sensitivity to chemotherapy, freedom from disease and overall survival are different. We propose eight time-points in EOC history with homogeneous oncological findings. The effectiveness of HIPEC in EOC treatment should be evaluated based on these eight time-points and we believe that retrospective and prospective studies of HIPEC should be evaluated according to these time-points.

Key words: Ovarian cancer; Hyperthermic intraperitoneal chemotherapy; Chemo-sensitivity; Time-points; Survival

Core tip: The standard treatment for advanced ovarian cancer consists in complete cytoreductive surgery and intravenous combination chemotherapy with a platinum compound and a taxane. Although response rates to initial therapy are high, many patients will recur and die of peritoneal carcinomatosis. The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to the standard therapy aims at increasing survival by reducing peritoneal recurrence. In this review we discuss the time points where HIPEC can be proposed.

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INTRODUCTION

Epithelial ovarian cancer (EOC) represents approximately 90% of primary malignant ovarian tumors, the sixth most common cancer in women and the second most common gynecologic cancer[1]. At diagnosis, the majority of patients (70%) are in advanced stage of the disease (FIGO ⅡB-Ⅳ) with rapid and asymptomatic widespread cancer cells in the pelvic structure and peritoneal cavity[2]. Disease stage at presentation is the most important prognostic factor determining outcome; 70%-80% of women at stage I survive for five years compared to only 15% of those at stage Ⅳ[3].

Recent advances in pathology and genetics have shown that EOC is a heterogeneous disease with various

risk factors, genetic abnormalities and oncological pathways that partly determine biological behavior, response to chemotherapy, and prognosis[4]. A dualistic model places the major histological types into two groups: types I and Ⅱ. Type I cancers (mucinous, endometrioid, clear cell carcinomas and low-grade serous carcinomas) demonstrate a relatively insidious clinical course with generally better prognosis. These develop in a stepwise fashion from well-established precursor lesions, such as borderline tumors and endometriosis[5,6]. Type I are relatively genetically stable and typically display a variety of somatic mutations in genes including *K-ras*, *BRAF*, *PTEN*, *CTNNB1* but very rarely TP53. In contrast, Type Ⅱ cancers (high-grade serous carcinomas, high-grade transitional carcinomas, malignant mixed mesodermal tumors and undifferentiated carcinomas) are extremely aggressive neoplasms with remarkable early sensitivity to platinum-based chemotherapy but are frequently diagnosed at advanced stages. They are chromosomally highly unstable and harbour TP53 mutations in more than 95% of cases[7,8]. Approximately 80%-85% of all ovarian carcinomas in Western society are serous. Up to 95% of patients with FIGO stage Ⅲ-Ⅳ disease have serous carcinomas whereas FIGO stage I serous carcinomas are uncommon[9,10].

Like other cancers, EOC can spread through lymphatic and blood vessels to nodes and parenchyma of distant organs (liver, lung and brain). However, a distinctive feature of these tumors is their ability to spread from the ovary to the abdominal cavity, forming nodules of variable size on the surface of the parietal and visceral peritoneum, including the omentum. The coalescence of nodules forms plaque or masses in the abdominal-pelvic cavity. Blockage of diaphragmatic lymphatics prevents outflow of proteinaceous fluid from the peritoneal cavity, causing the accumulation of ascites in advanced disease. Tumor dissemination from the peritoneal cavity to the pleural cavity occurs through the diaphragmatic peritoneum and leads to pleural effusion[11,12].

TREATMENT OF PRIMARY ADVANCED OVARIAN CANCER

The main treatment of advanced disease consists of surgical removal of all visible nodules in the abdominal cavity followed by intravenous chemotherapy (platinum-based drugs with or without taxanes). The combined effect of surgery and chemotherapy is often the complete eradication of cancer cells.

Treatment of ovarian cancer is mainly based on three key areas: surgical removal of neoplasia; chemotherapy to kill cancer cells; application of chemotherapy directly on peritoneal surfaces.

In advanced disease (FIGO stage ⅡB-ⅢC) the surgical removal of neoplasia with optimal cytoreduction (nodules ≤ 1 cm left) is recommended. An additional survival advantage of complete cytoreduction (no visible residual disease) has been recently reported[12]. Several studies have shown that specialized gynecological oncologist surgeons are more likely to perform optimal surgery than general surgeons[13]. The frequent presence of multiple neoplastic implants on peritoneal surfaces together with pelvic and upper abdominal organs implies that surgeons must be prepared to remove organs beyond the pelvis, such as peritoneal surfaces of colic gutters, diaphragmatic domes, and to carry out surgical procedures on the colon, bowel, liver, gallbladder, stomach, and spleen. This implies multidisciplinary surgical effort and the possibility of higher postoperative morbidity. This idea has not been accepted by the majority of gynecologic oncologists due to the lack of scientific data. If initial maximal cytoreduction is not carried out, interval debulking surgery (IDS) should be considered in patients responding to chemotherapy or with stable disease. IDS should ideally be carried out after three cycles of chemotherapy then followed by three further chemotherapy cycles[14].

Chemotherapeutic efficacy for ovarian carcinoma showed a dramatic shift after the introduction of platinum compounds and since 1996 the combination of platinum plus paclitaxel has been the standard treatment. The current rationale of six cycles of treatment as standard is based on three randomized trials which analyzed the impact of chemotherapy duration (*i.e.*, number of cycles) on OS. None of these studies demonstrated a difference in median survival time, but longer durations were associated with increased toxicity, especially neuropathy[15]. Other chemotherapy regimens, such as gemcitabine and liposomal doxorubicin in association with carboplatin-paclitaxels were compared to carboplatin-plaxitel alone in the Phase Ⅲ Gynecologic Cancer Intergroup (GCIG) trials (GOG 0182-ICON 5). These showed no statistically significant superiority or clinically useful benefit associated with the three drugs compared to the controls. Currently carboplatin-paclitaxel remains the treatment of choice even though angiogenesis inhibitors in combination with the standard treatment have been approved by the US Food and Drug Administration[16]. The main issue with EOC is the chemo sensitivity of cancer cells. Data shows that only 50% of patients have a complete clinical response to standard Ⅳ chemotherapy and that 30% of them have microscopic metastasis at surgical exploration. Most advanced stage patients who achieve clinical remission after completion of initial treatment develop recurrent disease and drug resistance, and their cure rate is less than 30%. These factors are major limitations in the treatment of patients with EOC. In order to overcome these limitations, different treatments such as secondary cytoreduction, second line chemotherapy drugs, high dose chemotherapy, intra-peritoneal (IP) chemotherapy, radiotherapy, immunotherapy and hormone therapy should be considered. To date, none of these approaches, apart from IP chemotherapy, has been found to have a significant impact on survival[17].

IP chemotherapy refers to the administration of cytotoxic agents directly to the peritoneal cavity. The rationale is that a higher concentration of cytotoxic drugs and longer duration of exposure can be achieved while re-

Table 1 Time-points of optimal cytoreduction and survival result of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy of 1021 patients with carcinomatosis from ovarian cancer

Ref.	Patients (*n*)	Time-point of optimal cytoreduction	Median disease free survival (mo)	Overall 3-yr survival (%)	Overall 5-yr survival (%)
Ansaloni *et al*[21]	39	1, 2, 3, 4, 5	42[1]	NR	NR
Deraco *et al*[28]	56	4, 5	NR	NR	23
Pomel *et al*[30]	31	2, 3	27	67[2]	NR
Bereder *et al*[31]	246	2, 4, 5	13	60	35
Pavlov *et al*[32]	56	1, 4, 5	26	NR	NR
Fagotti *et al*[33]	25	4, 5	10	NR	NR
Guardiola *et al*[34]	47	2	14	63[2]	NR
Di Giorgio *et al*[35]	47	1, 4, 5	20	NR	17
Bae *et al*[36]	67	2, 3	NR	NR	66
Cotte *et al*[37]	81	5	19	NR	NR
Helm *et al*[38]	18	5	10	NR	NR
Rufián *et al*[39]	33	1, 4	NR	46	37
Raspagliesi *et al*[40]	40	3, 5	11	NR	15
Reichman *et al*[41]	13	1, 4	15	55	NR
Gori *et al*[42]	29	3	57[1]	NR	NR
Look *et al*[43]	28	1, 5	17	NR	NR
Ryu *et al*[44]	57	2, 3	26	NR	54
Piso *et al*[45]	19	1, 4, 5	18	NR	15
Zanon *et al*[46]	30	2	17	35	12
Chatzigeorgiou *et al*[47]	20	5	21	NR	NR
de Bree *et al*[48]	19	4, 5	26	63	42
Cavaliere *et al*[49]	20	NR	NR	50[2]	NR

[1]Results expressed as mean; [2]Two-year survival result. NR: Not reported.

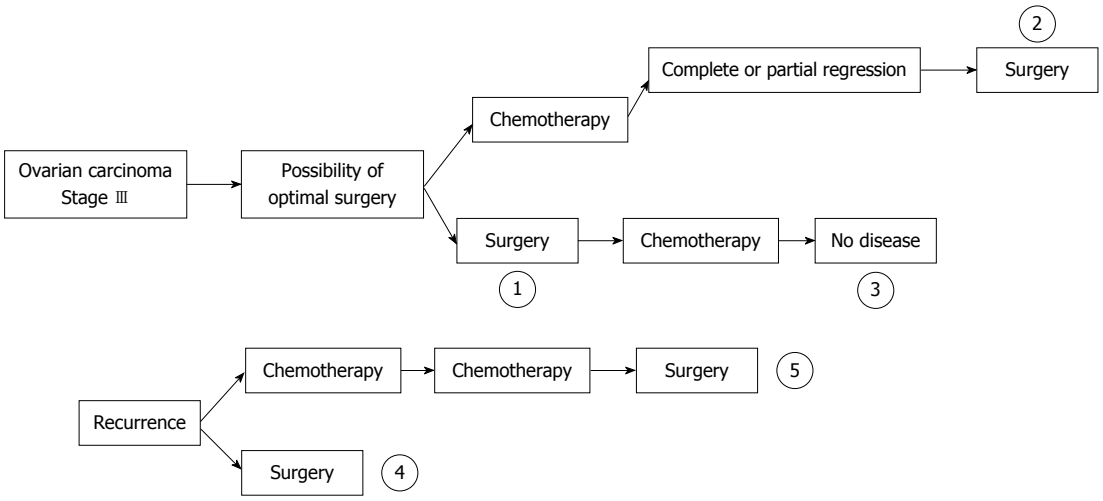

Figure 1 Epithelial ovarian cancer natural history: Time-points where intra-peritoneal hyperthermia chemotherapy can be proposed.

ducing the toxicity normally associated with intravenous therapy[18-20]. In fact, IP administered cytotoxic drugs can directly target tumor masses confined to the abdominal cavity, thus bypassing the poor vascularization of small volume disease and thereby increasing peri- and intra-tumoral drug concentration. Cisplatin can penetrate small volume tumors to a maximum depth of 1-3 mm and may therefore only benefit those patients with microscopic residual disease. By using large intra-peritoneal doses, the tumor surface can be exposed to high concentrations of cisplatin with only a small amount of drug leaking into the circulation. By this means, the amount of cisplatin reaching the tumor through capillaries is doubled when compared to the maximum tolerated dose delivered intravenously. Several studies have documented the advantages of IP compared to IV chemotherapy[20]. Post-operative adhesions after cytoreductive surgery can limit the access of the active drug to tumor areas and other complications, such as infections due to the IP catheter, may occur. Intra-operative administration of IP chemotherapy has been designed to overcome such obstacles. Intra-peritoneal hyperthermia chemotherapy (HIPEC) is a new treatment method based on increasing the sensitivity of cancer cells to the direct cytotoxic effect of chemotherapeutic agents at high temperature and increasing the concentration of chemotherapeutic agents that penetrate

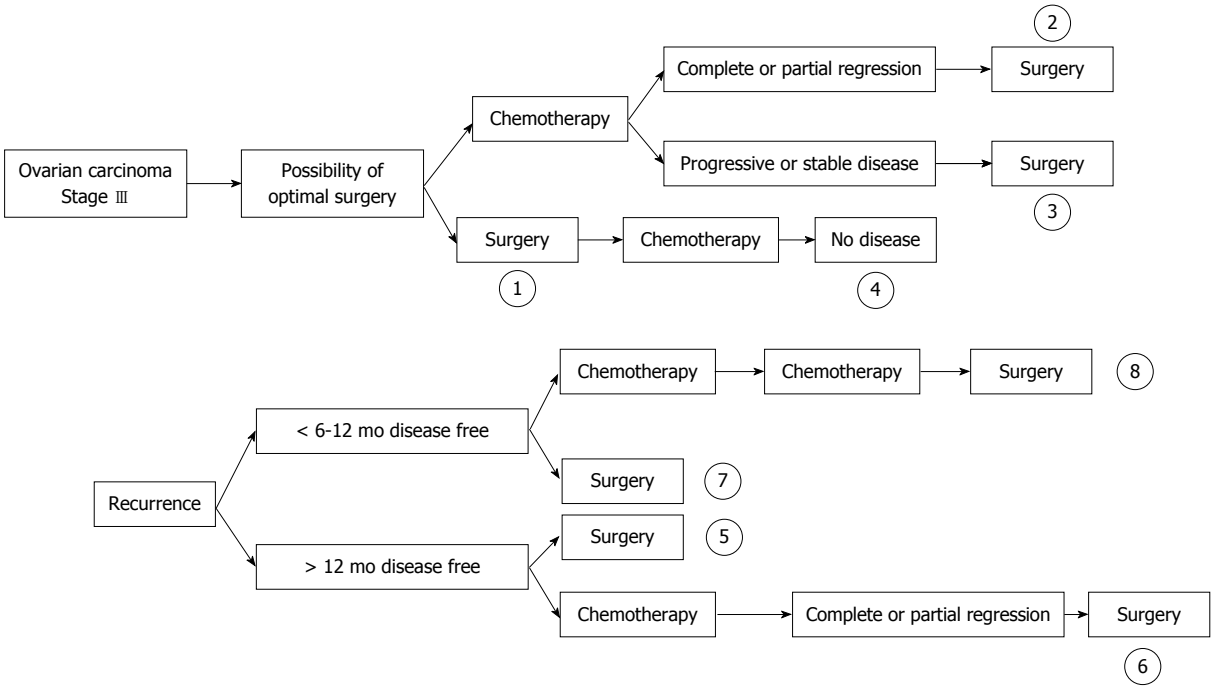

Figure 2 Epithelial ovarian cancer natural history: Time-points where intra-peritoneal hyperthermia chemotherapy can be proposed and where chemo-sensitivity and chemo-insensitivity were evaluated.

cancer tissues[21-23].

TREATMENT OF RECURRENCE

Approximately 70% of patients with advanced cancer who experience clinical remission after initial surgery and chemotherapy will develop recurrent disease[24].

In general, patients who progress during treatment with platinum are considered to have "platinum-refractory" disease and patients who show recurrence < 6 mo after completion of first-line platinum chemotherapy are considered to have "platinum resistant" disease. These patients are candidates for salvage therapy with second line chemotherapy. Patients who relapse after an interval of > 6-12 mo are defined as "platinum-sensitive" and are candidates for chemotherapy and/or surgery. The concept of chemo-sensivity is based on clinical data; re-subjecting the patient to the previous chemotherapy regimen obtains about a 20% response, but drug administration is the only method by which to verify cell response. Because of the late onset of relapse, platinum-sensitive patients should in reality be regarded as including both chemo-sensitive and chemo-insensitive patients[25].

Appropriate treatment of recurrence (chemotherapy/surgery), which may be based on time and nature of relapse and the role of surgery, remains a field of discussion and controversy.

In general, surgical resection may be considered in platinum-sensitive patients. Resectable disease, good performance status and complete secondary cytoreduction are one of the best predictors of survival in these patients[26-28].

In ovarian platinum-sensitive recurrence, surgical cytoreduction offers the following potential benefits: (1) cytoreduction of tumor volume offers patients a greater chance of response to chemotherapy; and (2) the elimination of potentially chemo-resistant cells. However, surgical cytoreduction is generally not undertaken without also scheduling postoperative chemotherapy since surgery alone rarely offers a cure.

ADVANCED EOC NATURAL HISTORY TIME-POINTS

We analyzed literature using the search terms "ovarian cancer" and "HIPEC treatment". EOC naturally presents various time-points where surgery, chemotherapy or HIPEC can be identified with homogenous chemo-sensitivity, response to therapy, and survival. Chua *et al*[27] proposed five time-points: (1) time of primary treatment; (2) time of IDS; (3) time of consolidation therapy after complete pathological response following initial therapy; (4) time of first recurrence; or (5) time of salvage therapy (Figure 1). The results of the most important paper are shown in Table 1[28-49].

Given that chemo-sensitivity is an important issue for the prognosis and the homogeneity of these patients, we considered eight time-points upon which a clinical trial could be based: (1) time of primary treatment where optimal cytoreduction is achieved (group with chemo-sensitive and chemo-insensitive tumors); (2) time of IDS after neo-adjuvant chemotherapy with partial or complete response (chemo-sensitive group); (3) time of IDS after neo-adjuvant chemotherapy with stable disease (chemo-insensitive group); (4) time of consolidation therapy after complete pathological response following initial therapy (chemo-sensitive group); (5) time of first recurrence when disease relapses more than 12 mo after treatment (chemo-sensitive/chemo-insensitive group); (6) time of first recurrence when disease relapses more than 12 mo

after treatment and a course of chemotherapy obtains complete response (chemo-sensitive group); (7) time of first recurrence when disease relapses less than 12 mo after treatment (chemo-insensitive group); and (8) time of salvage therapy after various chemotherapy lines (chemo-insensitive group) (Figure 2). Correct analysis of past and future clinical trials should take account of these time-points in patient evaluation.

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TOPIC HIGHLIGHT

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Pharmacology of cancer chemotherapy drugs for hyperthermic intraperitoneal peroperative chemotherapy in epithelial ovarian cancer

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Abstract

The peritoneal parietal and visceral surfaces of the abdomen and pelvis are an important anatomic site for the dissemination of epithelial ovarian cancer (EOC). The transcoelomic spread of cancer cells gives rise to peritoneal carcinomatosis (PC) which, without special treatments, is a fatal manifestation of EOC. In order to control PC cytoreductive surgery to remove macroscopic disease is combined with perioperative intraperitoneal (IP) and perioperative intravenous chemotherapy to eradicate microscopic residual disease. Chemotherapy agents are selected to be administered by the IP or intravenous route based on their pharmacologic properties. A peritoneal-plasma barrier which retards the clearance of high molecular weight chemotherapy from the peritoneal cavity results in a large exposure of small cancer nodules on abdominal and pelvic surfaces. Tissue penetration is facilitated by moderate hyperthermia (41-42 ℃) of the IP chemotherapy solution. Timing of the chemotherapy as a planned part of the surgical procedure to maximize exposure of all peritoneal surfaces is crucial to success.

Key words: Intraperitoneal chemotherapy; Epithelial ovarian cancer; Ifosfamide; Cisplatin; Carboplatin; Taxanes; Pharmacokinetics; Pharmacodynamics

Core tip: Intraperitoneal (IP) chemotherapy is an important adjuvant treatment strategy in patients with advanced epithelial ovarian cancer. Although the clinical benefits have been demonstrated both in phase Ⅱ and Ⅲ trials, the pharmacologic rationale for this treatment strategy needs to be clarified. This manuscript reviews the pharmacokinetic and pharmacodynamic rationale of IP chemotherapy and analyzes the available data.

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INTRODUCTION

Epithelial ovarian cancer (EOC) is the second most common gynecologic malignancy. Worldwide in 2008, approximately 225000 women were diagnosed with EOC and 140000 died from their disease[1]. Seventy-five percent of these patients present with advanced disease outside of the pelvis at the time of diagnosis[2]. Besides the lymphatic and hematogenous routes of dissemination, transcoelomic spread of tumor cells is an acknowledged phenomenon

ultimately giving rise to peritoneal carcinomatosis (PC). In most patients, this intraperitoneal (IP) spread occurs before surgery as a direct consequence of full-thickness invasion of the involved organ by tumor and subsequently exfoliation of tumor cells in the peritoneal cavity. Alternatively, IP spread may be the result of surgical trauma that causes release of tumor cells from transected lymph and blood vessels and manipulation of the primary tumor. The combination of optimal cytoreductive surgery (CRS) and effective platinum-based chemotherapy has resulted in significant survival benefit for these women. Nevertheless five year survival for patients with International Federation of Gynecologists and Obstetrics stage ⅢC EOC only reaches 32.5%[3]. In an attempt to improve clinical results in EOC patients the IP route of chemotherapy administration has been explored both as an alternative and as an addition to systemic chemotherapy. This topic highlight manuscript aims to review the pharmacokinetic and pharmacodynamic data currently available regarding the IP delivery of cancer chemotherapy agents in patients with PC of ovarian origin. Pubmed was questioned with the search terms; EOC, peritoneal metastases, PC, IP chemotherapy, CRS, pharmacology, pharmacokinetics, pharmacodynamics. No exclusion criteria were used. Relevant English language articles were reviewed both in abstract and full text.

PERITONEAL PLASMA BARRIER

The rationale of administering chemotherapeutic drugs into the peritoneal cavity is based on the relative transport barrier which is formed by the tissue surrounding the peritoneal space. The peritoneum is a complex three-dimensional organ covering the abdomino-pelvic organs and the abdominal wall. It contains a large potential space. The most elaborate description of the ultra structure of the peritoneum in man goes back to 1941 by Baron[4]. The peritoneum consists of a monolayer of mesothelial cells supported by a basement membrane and five layers of connective tissue which account for a total thickness of 90 μm. The connective tissue layers include interstitial cells and a matrix of collagen, hyaluron, and proteoglycans. The cellular component consists of pericytes, parenchymal cells and blood capillaries. The complex is often referred to as the peritoneal membrane. This description is a working model derived from research regarding the peritoneum as a dialysis membrane.

The accepted function of the peritoneum is twofold. First, it reduces friction between intraabdominal organs and the abdominal wall by producing a lubricant solution made of glycosaminoglycans and phospholipids[5]. Secondly, it is of major importance together with lymphoid aggregates dispersed on the visceral and parietal peritoneum in the host defense against intraabdominal infections. A third suggested function of the peritoneum in malignancy may be its role as a first line of defense against PC[6]. Any disruption in the peritoneal lining facilitates the adhesion-invasion cascade of tumor cells, resulting in the development of peritoneal tumor nodules on the abdominal or pelvic surface[6,7].

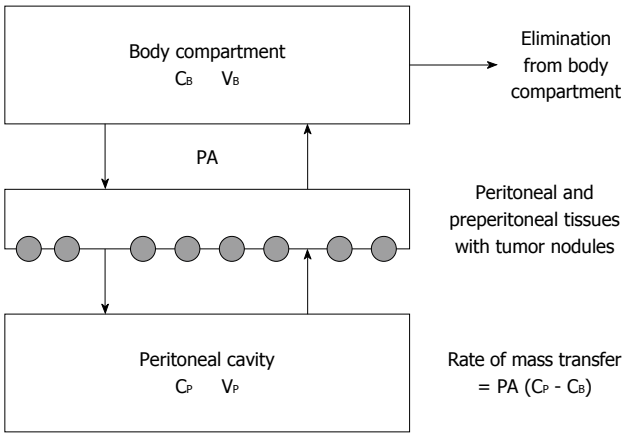

Figure 1 Three-compartment model of peritoneal transport in which transfer of a drug from the peritoneal cavity to the blood occurs across the peritoneal membrane and preperitoneal tissues. In these tissues the peritoneal surface cancer nodules are located. The permeability-area product (PA) governs this transfer and can be calculated by measuring the rate of drug disappearance from the cavity and dividing by the overall concentration difference between the peritoneal cavity and the blood (B). C_B: The free drug concentration in the blood (or plasma); V_B: Volume of distribution of the drug in the body; C_P: The free drug concentration in the peritoneal fluid; V_P: Volume of the peritoneal cavity. Modified from Dedrick *et al*[16].

Contrary to intuitive thinking the elimination of the mesothelial lining as performed during peritonectomy procedures does not significantly alter the pharmacokinetic properties of the peritoneum in the transport of chemotherapeutic agents from the peritoneal cavity to the plasma compartment. Flessner *et al*[8] demonstrated in a rodent model that neither removal of the stagnant fluid layer on the mesothelium nor removal of the mesothelial lining influenced the mass transfer coefficient over the barrier. Indirect evidence supporting this hypothesis in humans can be derived from the fact that the extent of the peritonectomy in PC patients does little to alter the IP chemotherapy pharmacokinetics of Mitomycin C or 5-fluorouracil[9,10]. Newer data suggest that major resections of visceral peritoneum increase the clearance of doxorubicin and mitomycin from peritoneal space[11,12]. Basic research rather demonstrates that not only the mesothelial lining but also the blood capillary wall and the surrounding interstitial matrix are the principal barrier for clearance of molecules from the abdominopelvic space[13].

Most basic research concerning the pharmacokinetic properties of the peritoneum is derived from the peritoneal dialysis literature[14]. A simplified mathematical diffusion model considers the plasma to be a single compartment separated by an effective membrane from another single compartment, the peritoneal cavity (Figure 1). This results in the following equation: Rate of mass transfer = permeability area (PA) [concentration in peritoneal cavity (C_P) - concentration in the blood (C_B)].

Although this offers a simple conceptional model of transport and states the importance of the effective exposure area, it only offers quantitative predictability once PA is empirically determined for each drug. It also does not offer insight into the actual tissue penetration at the level

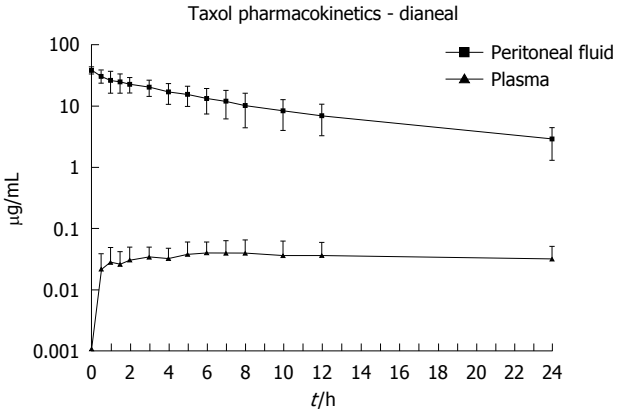

Figure 2 Pharmacokinetic study of concentration versus time for intraperitoneal paclitaxel. The chemotherapy agent at 30 mg/m^2 was instilled directly into the peritoneal cavity as rapidly as possible in a 1.5% dextrose peritoneal dialysis solution. The concentration of paclitaxel was determined in peritoneal fluid and in plasma for 24 h[51].

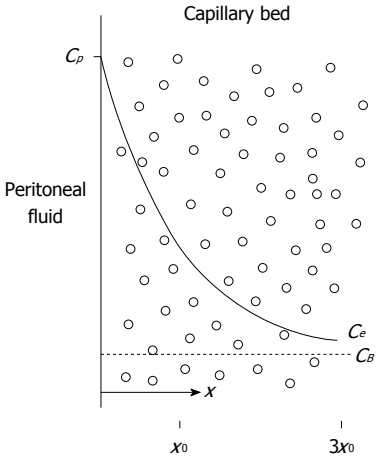

Figure 3 Conceptual diagram of tissue adjacent to the peritoneal cavity. Solid line shows the exponential decrease in the free tissue interstitial concentration, C_e, as the drug diffuses down the concentration gradient and is removed by loss to the blood perfusing the tissue. Also shown are the characteristic diffusion length, x_0, at which the concentration difference between the tissue and the blood has decreased to 37% of its maximum value, and $3x_0$, at which the difference has decreased to 5% of its maximum value. C_P: The free drug concentration in the peritoneal fluid; C_B: The free drug concentration in the blood (or plasma). Modified from Dedrick *et al*[16].

of the peritoneal membrane. Neither does it predict penetration of chemotherapy into the tumor nodules which is the single most important factor determining response to cancer treatment.

PHARMACOKINETIC RATIONALE OF PERI-OPERATIVE IP CANCER CHEMOTHERAPY

Pharmacokinetics explores what the body does to the cancer chemotherapy drug and pharmacodynamics explores what the drug does to the body. The IP route of delivering chemotherapy is logistically less convenient and technologically more challenging than conventional intravenous chemotherapy. This explains why the pharmacokinetic rationale of IP chemotherapy needs to be clarified to justify this route of cancer chemotherapy administration. IP administration of chemotherapeutic agents gives high response rates in PC patients because the peritoneal plasma barrier provides dose-intensive therapy. Based on peritoneal dialysis research, Dedrick *et al*[15] concluded that the peritoneal permeability of a number of hydrophilic anticancer drugs may be considerably less than the plasma clearance of that same drug. This results in a significantly higher concentration in the peritoneal cavity as compared to the plasma after IP administration. This concentration difference offers the opportunity of exposing the residual tumor cells after CRS to high doses of chemotherapeutic agents with reduced systemic concentrations and lower systemic toxicity. This advantage is expressed by the area under the curve (AUC) ratios of IP *vs* plasma exposure[14,15]. The marked increase in exposure of peritoneal surfaces to chemotherapy solution as compared to plasma is illustrated in Figure 2. The chemotherapy agent, paclitaxel has a high molecular weight (853.9 kDa) and is hydrophilic compound; consequently it is slow to cross the peritoneal cavity to plasma barrier. The AUC ratio is approximately 1000[12].

An important consideration is that high IP concentration or AUC IP/intravenous does not automatically confer a greater efficacy. Even with greatly elevated IP cancer chemotherapy concentrations, there may be limited penetration of the chemotherapeutic agent into the peritoneal tumor target. The ideal drug for IP chemotherapy has a high peritoneal tissue concentration as a result of direct IP administration and a high penetration into the cancer nodule[12]. This should occur along with slow diffusion through the capillary endothelium deep in the subperitoneal space of the cancer chemotherapy solution. Low systemic concentrations and reduced systemic toxicity are maintained by rapid metabolism and excretion of drug within the body compartment.

PHARMACODYNAMICS OF IP CHEMOTHERAPY

The efficacy of IP cancer chemotherapy protocols is governed by both non-pharmacokinetic variables (tumor nodule size, density, vascularity, interstitial fluid pressure, binding, temperature) and pharmacokinetic variables. As such, the simplified two-compartment model described above may not provide an adequate theoretical model for penetration of the intraoperatively administered (either intravenous or IP) chemotherapy into the peritoneal wall and into the tumor nodules. Dedrick *et al*[16,17] proposed a mathematical model seen in Figure 3 addressing the tissue penetration of low-molecular weight molecules. The drug diffuses from its peritoneal concentration, C_P, to its blood concentration, C_B, along an exponential concentration gradient over the peritoneum and preperitoneal tissues. The extracellular "deep" concentration, C_e, can then calculated according to the formula: $C_e = C_B + (C_P - C_B) \exp[- (k/D)^{1/2}x]$.

Table 1 Pharmacokinetic and pharmacodynamic variables of perioperative cancer chemotherapy

Pharmacokinetic variables	Pharmacodynamic variables
Dose	Tumor nodule size
Volume	Density
Duration	Vascularity
Carrier solution	Interstitial fluid pressure
Pressure	Binding
Molecular weight	Temperature

In this formula (k/min) is the rate constant for removal of the active drug from the tissue. Movement through the tissue is characterized by the diffusivity, D (cm^2/min) and x is the distance from the serosal surface (cm). This model implies that there is an exponential concentration decrease of the drug from abdominopelvic cavity across the membrane to the plasma compartment. Consequently, the depth of penetration of an effective chemotherapy concentration is very limited and is in the order of 1-2 mm[18,19]. Ozols *et al*[20] confirmed adriamycin penetrating only 4-6 cell layers of tumor on the diaphragm in a rodent model of ovarian cancer. In all likelihood there is a variable penetration for each drug and type of tumor. This has important consequences for implementing perioperative chemotherapy in PC patients. Over the past 40 years; the designation of "optimal" CRS in EOC has evolved greatly from no residual disease > 1 cm to no gross residual disease[21]. Since the landmark study by Hoskins *et al*[22], there is a growing body of evidence supporting that patients with no gross residual disease have an important survival benefit[23-25]. In the Gynecologic Oncology Group trial patients with 0.1-1.0 cm and > 1.0 cm residual disease had an increased risk of recurrence (HR = 1.96, 95%CI: 1.70-2.26; and HR = 2.36, 95%CI: 2.04-2.73, respectively) and death (HR = 2.11, 95%CI: 1.78-2.49; $P < 0.001$; and HR = 2.47, 95%CI: 2.09-2.92, respectively) when compared to patients with no macroscopic residual disease[22]. In 3216 patients with EOC, du Bois *et al*[25] in a pooled analysis of three randomized controlled trials, after multivariate analysis demonstrated a statistically significant overall and progression-free survival benefit when complete resection was compared to patients with residual small (1-10 mm) tumor burden after surgery ($P < 0.001$).

Although the techniques of performing CRS in EOC have become more and more standardized, unfortunately the same cannot be said of the intraoperative and postoperative IP cancer chemotherapy regimens used in clinical practice today.

Table 1 summarizes all pharmacokinetic and pharmacodynamic variables involved in these various perioperative cancer chemotherapy protocols. One could state that the PK variables influence the amount of drug showing up at the level of the tumor nodule and that the PD variables subsequently determine what goes on inside the tumor nodule. As such the tumor nodule should be considered the most appropriate endpoint in the pharmacologic exploration regarding these treatment strategies. A much needed standardization of the IP cancer chemotherapy regimens should be based on both pharmacologic investigation at this level of the tumor nodule and further phase Ⅱ and Ⅲ clinical trials.

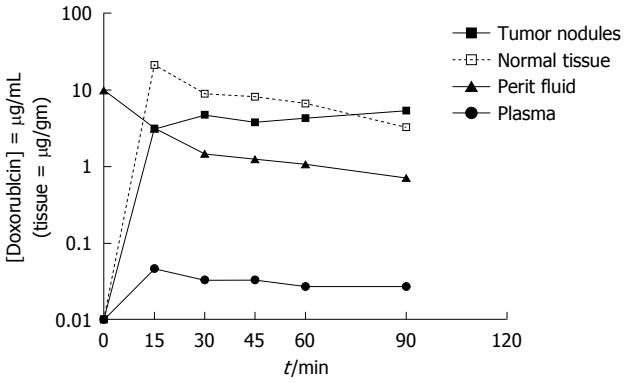

Figure 4 Doxorubicin levels in tumor nodules, normal adjacent tissues, peritoneal fluid and plasma during hyperthermic intraperitoneal perioperative chemotherapy over 90 min with 15 mg/m² doxorubicin intraperitoneal administration. Modified from Van der Speeten *et al*[32].

CYTOTOXIC DRUGS UNDER INVESTIGATION FOR IP ADMINSTRATION IN EOC

The number of reported variations in IP chemotherapy treatment protocols for EOC is extensive. All these variations reflect attempts to improve diffusivity D, decrease the rate constant K, permeability P or effective membrane area A.

Doxorubicin

Doxorubicin ($C_{27}H_{29}NO_{11}$) or hydroxyldaunorubicin (adriamycin) is an anthracycline antibiotic. Historically it has been categorized as a DNA-intercalating drug but experimental work suggests that interaction of doxorubicin with the cell surface membrane rather than its intracellular uptake is an essential first step for doxorubicin cytotoxity[26,27]. Because of its wide *in vitro* and *in vivo* activity against a broad range of malignancies, its slow clearance from the peritoneal compartment due to the high molecular weight of the hydrochloride salt (579.99 kDa), its favorable AUC ratio of IP to intravenous concentration times of 230, and the absence of risk for dose-limiting cardiotoxicity when used intraperitoneally; doxorubicin was considered a potential beneficial agent for perioperative IP delivery in EOC. This was supported by both experimental and clinical pharmacokinetic data[20,28-32]. Figure 4 shows the pharmacologic profile of intraperitoneally administered doxorubicin[32]. The consistent finding of doxorubicin sequestration in tumor nodules raises questions about the possible underlying mechanism. Simple diffusion, forces as proposed by Dedrick and Flessner are not enough to explain the phenomenon. In the absence of experimental data supporting active transport of cancer chemotherapy drugs over membranes the authors postulate active binding to the cell membrane as

a possible mechanism. The sequestration phenomenon of doxorubicin in tumor nodules is a constant one in its presence regardless the underlying pathology or subtype. A consequence is that the cancer chemotherapy levels measured in the tumor nodules may be more important than considered in the past.

Cisplatin

Cisplatin (cis-diamminedichloroplatinum-Ⅲ, CDDP) causes apoptotic cell death by formation of DNA adducts[33]. It has been well studied in the setting of adjuvant normothermic postoperative IP chemotherapy of residual small volume ovarian cancer after CRS. Three randomized trials showed a significant survival benefit[34-36]. In the setting of CRS and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC), cisplatin has been used for intracavitary therapy of ovarian cancer in several phase Ⅱ studies[37,38]. Currently three randomized phase Ⅲ studies are recruiting patients to determine the role of CRS + HIPEC in primary and recurrent EOC. Schem *et al*[39] showed an excellent *in vitro* and *in vivo* thermal augmentation of cisplatin. The penetration of cisplatin into tumor nodules was studied by several groups. Los *et al*[40] for the first time described intratumoral distribution of cisplatin after IP administration and suggested that the advantage over IP *vs* IV administration was maximal in the first 1.5 mm. van de Vaart *et al*[41] investigated the cisplatin induced DNA adduct formation and could measure this 3-5 mm into the tumor tissue. Esquis *et al*[42] in an experimental model reported an enhanced cisplatin penetration when cisplatin was administered with increased pressure.

Carboplatin

Carboplatin [(1,1-cyclobutanedicarboxylato)platinum(II)] is a higher molecular weight platinum compound than cisplatin. Its main advantage is its decreased renal toxicity. As such it is currently explored in normothermic IP chemotherapy protocols in patients with advanced ovarian cancer[43,44]. Czejka *et al*[45] in a clinical study with normothermic carboplatin reported a relative bioavailability (calculated as AUC-values) which was at least 6 times higher in the IP fluid than in the serum for 48 h. Los *et al*[19] compared carboplatin and cisplatin after IP administration in a rat model of PC. Their data demonstrate that despite a clear pharmacokinetic advantage of IP carboplatin over cisplatin; its capacity to penetrate into peritoneal cancer nodules and tumor cells is far lower than that of cisplatin. These data limit have limited clinical its application in the past. In contrast, a more recent direct comparison reveals a comparable or better drug penetration of IP carboplatin when compared to IP cisplatin given at equitoxic doses[46]. This has recently revived clinical interest in its IP application.

Taxanes

Paclitaxel and docetaxel are taxanes considered for IP chemotherapy. The taxanes stabilize the microtubule against depolymerization; thereby disrupting normal microtubule dynamics[47]. They exert cytotoxic activity against a broad range of tumors. Due to their high molecular weight these molecules have a remarkable high AUC ratio of respectively 853 and 861[48]. This translates itself into a clear pharmacokinetic advantage for IP administration[49]. The data regarding possible thermal augmentation of taxanes are conflicting[50-53]. Taxanes have been used in a neoadjuvant IP setting as well as intraoperatively and postoperatively. Their cell-cycle specific mechanism of action makes them a particular good candidate for repetitive application such as in normothermic adjuvant postoperative IP chemotherapy[34,35]. Novel formulations of taxanes aiming at an increased bioavailability are under investigation for IP administration during HIPEC[54].

ROLE OF HYPERTHERMIA

Adding hyperthermia to IP chemotherapy may increase tumor response to cancer chemotherapy through several mechanisms. First, heat alone has a direct anti-tumor effect. Mild hyperthermia above 41 ℃ induces selective cytotoxicity of malignant cells by several mechanisms: impaired DNA repair, protein denaturation and, inhibition of oxidative metabolism in the microenvironment of malignant cells. This leads to increased acidity, lysosomal activation and, increased apoptotic cell death[55-57]. In this setting, thermal tolerance can be induced by up regulation of heat shock proteins, which may limit the importance of a direct anti-tumor effect of heat[58]. Second, applying mild hyperthermia augments the cytotoxic effects of some chemotherapeutic agents. Synergy between heat and cancer chemotherapy drugs may arise from multiple events such as heat damage to ABC transporters (drug accumulation), intra-cellular drug detoxification pathways and, to repair mechanisms of drug-induced DNA adducts[59]. Such augmented effects are postulated for doxorubicin, platinum complexes, mitomycin C, melphalan, docetaxel, irinotecan and, gemcitabine[28,59-64]. Third, hyperthermia may increase the penetration depth of the cancer chemotherapy solution into tissues and tumor nodules. Jacquet *et al*[28] report tissue penetration of doxorubicin is enhanced when the cancer chemotherapy solution is administered intraperitoneally at 43 ℃. In addition, hyperthermia does not affect the pharmacokinetic advantages of IP doxorubicin with low plasma and distant tissue levels.

The elevated interstitial fluid pressure in tumor nodules, compared to normal tissue, is an acknowledged phenomenon[65]. Furthermore, in experimental tumors with a single nodule, interstitial fluid pressure is relatively uniform in the nodule and drops precipitously in the periphery at the tumor-normal tissue interface[66]. Furthermore, Leunig e*t al*[67] report a thermal dose-dependent decrease in interstitial fluid pressure in experimental solid tumors in an animal model after hyperthermia. All this experimental data however could not establish a direct effect of hyperthermia on survival. Klaver *et al*[68] in a rat model of PSM for first time separated the intraoperative IP chemo-

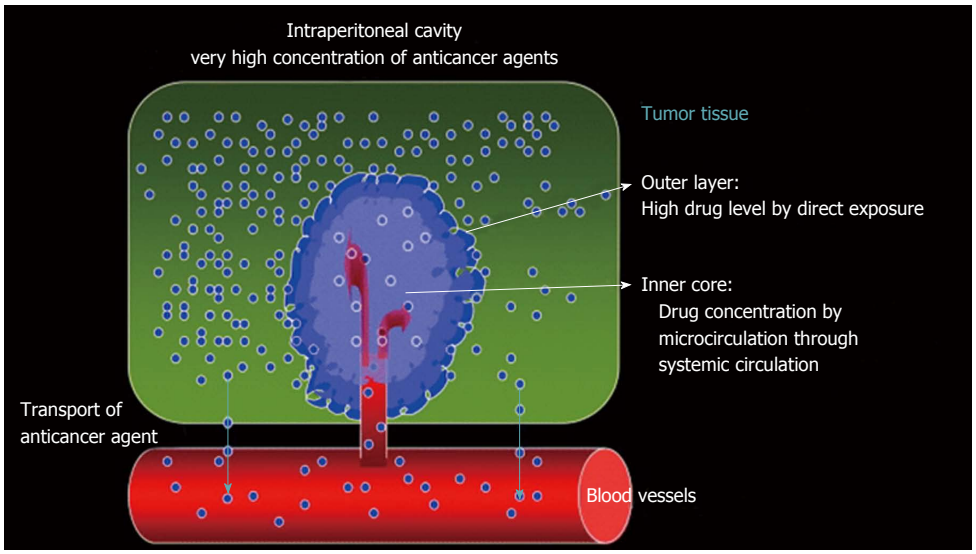

Figure 5 Pharmacologic concept of bidirectional intravenous and intraperitoneal chemotherapy. Modified from Fujiwara *et al*[69].

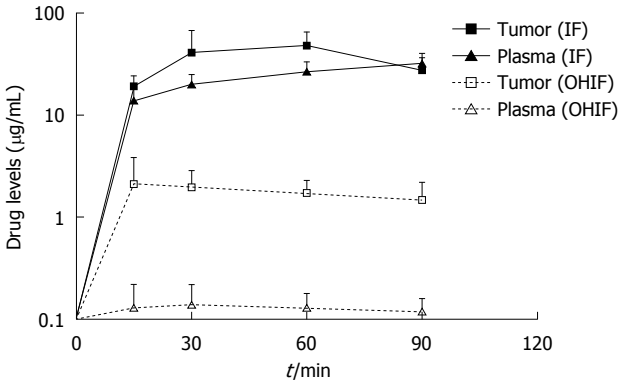

Figure 6 Comparison of ifosfamide and 4-hydroxyifosfamide concentrations in tumor nodules and in plasma during bidirectional intraoperative chemotherapy. OHIF: 4-OH-ifosfamide.

therapy from the IP hyperthermia. They demonstrated that the survival of the PC rats after CRS was highly dependent on the presence of the chemotherapeutic agent in the perfusate but not on the hyperthermia. No similar human data are available at this point in time.

BIDIRECTIONAL INTRAOPERATIVE CHEMOTHERAPY: RATIONALE AND PHARMACOLOGIC DATA

The Dedrick-model for peritoneal transport predicts transport by diffusion from the peritoneal compartment through a peritoneal and preperitoneal tissue layer to the plasma and, vice versa[15]. Figure 5 demonstrated that through combining intraoperative intravenous and intraoperative IP cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer containing the cancer nodules[69]. Chemotherapy from both the IP and intravenous compartments converges on the tissues at the interface of peritoneal space and peritoneal surface where the tumor nodules reside. Elias *et al*[70] first reported the clinical use of intraoperative intravenous 5-fluorouracil and leucovorin in conjunction with oxaliplatin-based hyperthermic IP perioperative chemotherapy in patients with PC of colorectal origin. More recently our group reported a similar effort in ovarian cancer with intravenous intraoperative ifosfamide[71]. The treatment strategy that has been employed in our studies is very similar to that published by Zylberberg *et al*[72] for ovarian cancer. His study showed excellent clinical results when systemic ifosfamide infusion was combined with IP cisplatin. We modified his ifosfamide regimen using an infusion over 90 min in the operating room. We demonstrated consistent high levels of ifosfamide and its active metabolite 4-OH-ifosfamide throughout and after the 90-min infusion in the peritoneal tumor nodules without increasing its systemic toxicity (Figure 6). This created a pharmacologically advantageous situation where a normothermic administered IV drug became subject to the effect of the local hyperthermia in the peritoneal fluid and tumor nodule. Timing of intravenous chemotherapy (intraoperative *vs* postoperative) is not pharmacokinetically neutral and as such emerges as a new pharmacokinetic variable.

TIMING OF IP CANCER CHEMOTHERAPY IN RELATION TO TIMING OF CRS

In the clinical application of IP chemotherapy in EOC patients, intervention can occur at four points in the timeline.

Induction IP and/or intravenous chemotherapy

Induction IP and/or intravenous Chemotherapy is suggested as an option for reducing dissemination to the extra-abdominal space, testing the tumor biology and, for reducing the extent of small PC nodules and, theoreti-

cally this approach, called neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy[73]. Radiological and clinical responses with NIPS have been reported by several groups[74-76]. However, although NIPS may reduce the tumor load to be addressed by CRS, it has several disadvantages. Adhesions from prior surgical interventions may interfere with adequate IP drug distribution and, as complete responses are unusual, further cytoreduction-chemotherapy is necessary if the approach is to be curative. NIPS is reported to add to morbidity and mortality of further surgical treatment and, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible to assess[77].

Early postoperative intraperitoneal chemotherapy

Early postoperative intraperitoneal chemotherapy (EPIC) has some conceptual advantages. It is administered after CRS at the time of minimal residual tumor burden and, IP treatments initiated before wound healing occurs can minimize non-uniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits. The proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell-cycle specific drugs such as the taxanes. Most EPIC regimens are administered postoperatively (day 1 to day 4/5) through both an inflow catheter and outflow drains inserted at the time of CRS and, can be applied with or without HIPEC[78].

Long-term combined IP and systemic chemotherapy

Several phase Ⅲ trials demonstrated that intravenous plus IP chemotherapy improves survival in patients with optimally debulked stage Ⅲ ovarian cancer, compared to intravenous chemotherapy alone[34-36,69]. Some of these studies report a significant number of catheter-related problems and inability of the patient to complete the intended number of chemotherapy cycles This approach may alsobe used as "chemotherapeutic bridging" between incomplete initial surgery and definitive cytoreduction or second look surgery. This type of chemotherapy is an adjuvant and not a perioperative use of chemotherapy.

HIPEC

HIPEC has been explored in more than 40 studies in EOC. Unfortunately, most of these trials are small in number (< 50 patients) and have broad entry criteria[79]. Four randomized trials (NCT00426257, NCT01376752, NCT01539785 and NCT01091636) are currently exploring the role of HIPEC in the treatment of EOC. Failure analysis for CRS in EOC patients indicates recurrent cancer occurs most frequently within the abdominal and pelvic cavity. Although systemic metastases occur, treatment failures rarely occur in liver, lungs or, other systemic sites. In order to optimize the treatment of patients with PC, the greatest benefit will probably result from a combination of the four treatment strategies.

CONTROVERSIES AND FUTURE DIRECTIONS

Despite a growing evidence supporting the role of IP chemotherapy in the treatment of EOC, important controversies and questions remain to be answered. As the initial trials with IP chemotherapy in EOC were combined intravenous-IP chemotherapy regimens, some authors designate the observed effect to being the result of the dose density of the regimen, rather than the effect of the IP chemotherapy. Also, the current weekly schedules of intravenous taxanes as in JGOG 3016, MITO 7, GOG 0262 and ICON 8 have further raised the bar[80,81]. These improvements in systemic chemotherapy however do not annihilate the pharmacologic and clinical data supporting the superiority of a combined intravenous-IP approach. High grade EOC is characterized by an important overexpression of vascular endothelial growth factor (VEGF). As a logical consequence VEGF inhibitors as bevacuzimab are under investigation, both by the intravenous and IP route[82-84].

CONCLUSION

The administration of perioperative IP chemotherapy in EOC patients with PC should be governed by pharmacologic principles. Patients who have minimal residual disease as a result of optimal CRS are candidates for perioperative chemotherapy by the IP and intravenous route. Hyperthermia of the IP chemotherapy solution might increase the cytotoxicity of the drug within the peritoneal cavity. Heating of the peritoneal and preperitoneal tissues will maximize the systemic chemotherapy effects on carcinomatosis, a phenomenon known as heat targeting. IP chemotherapy has become an important part of EOC treatment and should become a standard modality for prevention and treatment of a wide variety of cancers that involve the peritoneal surfaces.

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TOPIC HIGHLIGHT

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Neoadjuvant chemotherapy and cytoreductive surgery in epithelial ovarian cancer

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Abstract

Ovarian cancer is one of the leading causes of death among gynecological cancers. This is because the majority of patients present with advanced stage disease. Primary debulking surgery (PDS) followed by adjuvant chemotherapy is still a mainstay of treatment. An optimal surgery, which is currently defined by leaving no gross residual tumor, is the goal of PDS. The extent of disease as well as the operative setting, including the surgeon's skill, influences the likelihood of successful debulking. With extensive disease and a poor chance of optimal surgery or high morbidity anticipated, neoadjuvant chemotherapy (NACT) prior to primary surgery is an option. Secondary surgery after induction chemotherapy is termed interval debulking surgery (IDS). Delayed PDS or IDS is offered to patients who show some clinical response and are without progressive disease. NACT or IDS has become more established in clinical practice and there are numerous publications regarding its advantages and disadvantages. However, data on survival are limited and inconsistent. Only one large randomized trial could demonstrate that NACT was not inferior to PDS while the few randomized trials on IDS had inconsistent results. Without a definite benefit of NACT prior to surgery over PDS, one must carefully weigh the chances of safe and successful PDS against the morbidity and risks of suboptimal surgery. Appropriate selection of a patient to undergo PDS followed by chemotherapy or, preferably, to have NACT prior to surgery is very important. Some clinical characteristics from physical examination, serum tumor markers and/or findings from imaging studies may be predictive of resectability. However, no specific features have been consistently identified in the literature. This article will address the clinical data on prediction of surgical outcomes, the role of NACT, and the role of IDS.

Key words: Advanced stage ovarian cancer; Neoadjuvant chemotherapy; Interval debulking surgery

Core tip: Neoadjuvant chemotherapy (NACT) is an option when the primary surgery is expected to be impossible or suboptimal, or when high morbidity is anticipated. Delayed primary surgery or interval debulking surgery (IDS) is performed in patients who show some clinical response to neoadjuvant or induction chemotherapy. Preoperative clinical data to predict surgical outcomes and selection criteria for primary surgery followed by adjuvant chemotherapy or for NACT followed by IDS will be discussed in this chapter.

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INTRODUCTION

Because of the lack of effective screening procedures to detect early stage ovarian cancer, the majority of patients present with advanced disease (stage Ⅲ-Ⅳ), resulting in a poor overall survival. The current standard management of patients with advanced ovarian cancer (AOC) is "debulking or cytoreductive surgery" followed by platinum-based chemotherapy. The aim of primary debulking surgery (PDS) is to remove as much cancer as possible, since the amount of residual tumor is one of the most important prognostic factors for survival[1,2]. When the cytoreduction is successful, the term "optimal debulking surgery" is applied. The definition of optimal debulking surgery has changed over the past 30 years from a residual tumor sized not more than 1-2 cm to no macroscopic disease[2-4]. However, it is not always possible to debulk tumors in the pelvis and upper abdomen optimally, especially when they have invaded the neighboring viscera. To achieve the goal of no residual disease and improve disease specific survival, "ultra" radical surgical techniques have been developed[5]. However, data on quality of life are not available and the documentation of adverse events is incomplete. Furthermore, many other factors must be considered, such as the patient's status or medical contraindications, morbidity-related treatment, and the reluctance or expertise of some surgeons/centers to practice such an aggressive procedure[4,6-10].

When PDS is not possible or is predicted to be unsuccessful, or where morbidity might be excessively high, chemotherapy prior to PDS is an option; so called "neoadjuvant chemotherapy" (NACT)[10]. The chemotherapy is given after the diagnosis of ovarian cancer, preferably by tissue biopsy. On the other hand, when PDS is incomplete and there is a bulky residual tumor, "induction chemotherapy" is usually given for 2-3 cycles to reduce tumor size. Secondary surgery or so called "interval debulking surgery" (IDS) is considered before continuing more cycles of chemotherapy when there is no evidence of progressive diseases[11].

PREDICTION OF OPTIMAL SURGICAL OUTCOME

The achievement of optimal surgery varies according to the extent of the disease itself and the ability of the surgical team to perform the operation. These factors must be taken into consideration in estimating whether the PDS will be possible and successful. The evaluation should be as accurate as possible, in order to avoid a futile procedure or excessive morbidity and, on the other hand, to offer patients the best opportunity for optimal cytoreduction. The estimation should be based on the combination of a number of factors: clinical characteristics or findings from physical examination, imaging studies, serum markers, or laparoscopic findings.

Serum markers

Some biological markers have been studied in relation to the stage of disease, resectability, and survival. The elevation of these markers is frequently reported in direct association with advanced stage diseases, suboptimal resection of ovarian cancer or decreased survival. Nevertheless, different reports show variation in their diagnostic performance and levels of significance varied.

Inflammatory markers: Recently, the relationship between cancer development and inflammation has been recognized. This relationship is explained through an inflammatory process elicited by cancer cells. Cancer cells can trigger the host inflammatory response with the release of neutrophil-releasing inflammatory cytokines, leukocytic and other phagocytic mediators. These substances induce damage to cellular DNA, inhibit apoptosis and promote angiogenesis around cancer area. This will ultimately result in tumor growth, progression, and metastases[12-14]. Similarly, platelets can release growth factors such as platelet-derived growth factor, platelet factor 4, transforming growth factor β, vascular endothelial growth factor[15-17] and thrombospondin, which function as potent mitogens or as adhesive glycoproteins for various cell types including ovarian surface epithelium[18,19]. These growth factors can stimulate ovarian tumor cell proliferation and adhesion to other cells, leading to tumor growth and metastases, respectively[20].

Elevation of neutrophils[21], platelets[22-24], lymphocytes as well as of the neutrophil to lymphocyte ratio (NLR)[25,26], and the platelet to lymphocyte ratio (PLR)[27,28] were found to be associated with unfavorable clinico-pathologic features in ovarian cancer. In many early studies thrombocytosis was found to be associated with more advanced disease, inoperable cancer, and to be an independent prognostic factor for survival of epithelial ovarian cancer patients[22-24,28]. A possible prognostic role of NLR was also studied, but with inconsistent results[25,26,28]. One study found that elevated NLR (> 2.6) and cancer antigen (CA) 125 correlated with poor survival[26] while a second study failed to demonstrate any such association and only found significant association between elevated pre-operative NLR and advanced stage or suboptimal surgery[25]. Other studies also explored the role of PLR and found that it functioned better than platelet count[28] or NLR[27,28] as a prognostic factor for poor survival and other unfavorable clinico-pathological factors, such as, advanced stage and suboptimal residual disease.

Despite the association of elevated inflammatory markers with survival and suboptimal surgery, data on the levels of significance are inconsistent among studies. Different number of patients and non homogeneous patients' characteristic (*e.g.*, stage of disease and result of primary surgery) among the series might explain these differences. Larger studies and more homogeneous pop-

Table 1 Studies of cancer antigen 125 for predicting the result of surgery in epithelial ovarian cancer

First author, year	*n*	Preoperative CA 125 (U/mL)		Optimal surgery[3]	Sensitivity	Specificity	PPV	NPV
		Median	Cut-off					
Not clinically useful[1]								
Gemer *et al*[30], 2001	40	341	500	60%	62%	83%	71%	77%
Cooper *et al*[31], 2002	112	893	500	58%	49%	77%	74%	52%
Memarzadeh *et al*[32], 2003	99	-	912	73%	58%	54%	78%	31%
Rossi *et al*[33], 2004	82[2]	1351	500	40%	40%	64%	-	-
Alcázar *et al*[34], 2004	67	730	620	48%	60%	-	-	-
Gemer *et al*[35], 2005	424	495	400	57%	69%	57%	55%	71%
Everett *et al*[36], 2005	56	NA	500	52%	-	-	-	-
Barlow *et al*[37], 2006	164	364	500	47%	66%	59%	64%	36%
Gilani *et al*[38], 2007	90	500	500	47%	68%	62%	64%	35%
Arits *et al*[39], 2008	96	625	330	43%	80%	42%	-	-
Chi *et al*[40], 2009	277	731	500	80%	-	-	-	-
Probably clinically useful[1]								
Chi *et al*[41], 2000	100	819	500	45%	78%	73%	78%	73%
Saygili *et al*[42], 2002	92	494	500	52%	73%	77%	75%	75%
Obeidat *et al*[43], 2004	40	467	500	55%	72%	73%	68%	76%
Eltabbakh *et al*[44], 2004	72	680	500	81%	73%	74%	-	-
Brockbank *et al*[45], 2004	77	397	586	68%	80%	89%	86%	80%
Vorgias *et al*[46], 2009	426	650	500	42%	79%	90%	85%	85%

[1]Studies of not clinical useful and probably useful were arranged according to the comments of the authors in each study; [2]Diagnostic functions of cancer antigen (CA) 125 in the study were of the whole group (22% early stages and 78% advanced stages) while the numbers of patients (*n*) in other studies were of stage Ⅲ or stage Ⅲ-Ⅳ disease; [3]All studies defined residual disease ≤ 1 cm as optimal surgery. NPV: Negative predictive value; PPV: Positive predictive value; NA: Not available.

ulations are needed to validate the role of inflammatory markers as predictors for suboptimal surgery.

CA 125: Serum CA 125 is the most widely used biological marker in ovarian cancer and is abnormally high in more than 90% of patients with AOC[29]. Hence, many studies have attempted to find a reliable cut-off level of CA 125 which could predict the optimal resection of ovarian cancer.

However, the results are inconsistent among studies and it is not possible to define a single reliable cut-off value of CA 125 to predict optimal surgery (Table 1)[30-46]. Some reasons can explain these unsatisfactory results. First, all of these studies were retrospective in nature. Second, the number of patients in each study varied from less than 50 to over 400. Third, the rates of optimal cytoreduction ranged from less than 50% to 80% in the various centers. Fourth, the median value of CA 125 in the studies varied significantly. Most probably, these differences reflect the lack of homogeneity of tumor stages and in the extent of tumor burden, as well as the different criteria for operability adopted in the different centers.

Since the level of CA 125 is directly related to the stage of disease and to the amount of tumor burden, preoperative CA 125 levels in studies with a higher number of optimal cytoreductions should, theoretically, be lower than those in studies with more unresected tumors. Nevertheless, some studies suggest that the aggressiveness of the surgical procedures may be a confounding factor that affects the rates of optimal cytoreduction. One multicenter study by Gemer *et al*[35] reviewed records of 424 patients with AOC and found that clinical applicability of CA 125 for predicting suboptimal surgery was limited. The authors found only a 57% rate of optimal surgery. Although the median CA 125 serum levels in patients with optimally cytoreduced tumor was significantly lower than that in suboptimally debulked cases (304 U/mL *vs* 863 U/mL), the diagnostic accuracy of CA 125 as predictor of optimal debulking was only 62% with the best cut-off identified (400 U/mL). Another large study by Vorgias *et al*[46] also found significant association between CA 125 levels and surgical results in 426 patients: 84% of patients with CA 125 < 500 U/mL achieved optimal cytoreduction compared to only 15% of those with higher CA 125 levels. However, this study reported only a 42% overall rate of optimal cytoreduction. Once again, this might be the result of a less extensive surgical effort for peritoneal carcinomatosis and for metastatic lymph-nodes. The results from 2 other studies by the same groups of authors further demonstrated the importance of the surgical aggressiveness. In their first report in early 2000s, Chi *et al*[41] reported a 45% optimal cytoreduction in 100 AOC patients. The rate of optimal cytoreduction was significantly higher in patients with pre-operative CA 125 ≤ 500 U/mL than those with higher level: 73% *vs* 22%[41]. However, their subsequent study in 277 patients with similar characteristics demonstrated that the patients with a higher CA 125 level required more extensive upper abdominal surgery to achieve optimal surgery (< 1 cm residual tumor) compared to those with a lower CA 125 level, 50% *vs* 27%[40]. There was no CA 125 threshold which could predict the surgical outcome. Of note, their latter study reported a higher rate of cytoreduction (80%). These studies may be affected by selection bias, a com-

mon phenomenon in retrospective and in non-randomized prospective trials

It is therefore difficult to make any conclusion regarding the possible role of CA 125 in determining resectability in advanced ovarian cancer patients. One systematic review by Kang *et al*[47] determined the ability of pretreatment CA 125 level to predict optimal cytoreduction in AOC. The authors identified 122 articles in which 15 studies including their own series met the inclusion criteria, and 2192 patients were analyzed in the meta-analysis. The pooled optimal cytoreduction rate and the mean of median CA 125 levels were 53.7% and 580 U/mL, respectively. The authors did not find any significant heterogeneity factor (year of publication, numbers of patients, median CA 125 levels, percentage of stage Ⅳ disease, or rate of optimal cytoreduction) influencing the analysis. The diagnostic performance of CA 125 in predicting suboptimal cytoreduction was analyzed at 3 cut-off levels of 500, 1000 and 1500 U/mL. A direct association between CA 125 levels and likelihood of suboptimal cytoreduction was found. Increasing specificity and odds ratios along with decreasing sensitivity were observed with higher CA 125 cut-off levels. At a cut-off level of 500 U/mL, the odds ratio was 3.69 (95%CI: 2.02-6.73). The authors also demonstrated that the predictive role of CA 125 was not affected by the rate of optimal cytoreduction. The odds ratios were not different among the studies which had optimal cytoreduction rate ≥ 50% *vs* < 50%: 4.0 *vs* 4.5, respectively. Against all the odds, this might suggest that the effort of a surgeon probably has little to do with the accuracy of CA 125 in predicting the result of PDS. It should be noted that, despite the strong association of CA 125 and risk of suboptimal surgery, the meta-analysis showed that CA 125 showed only a low positive likelihood ratio and could not accurately predict the optimal or suboptimal surgery at any cut-off level[47].

From these retrospective studies and from the systematic review, we can conclude that although pre-operative serum CA 125 level is a reliable predictor for the extent of disease, it has limited accuracy in predicting a successful surgical outcome. The sensitivity and specificity in the various studies ranged from 40% to 80% and from 40% to 90%, respectively (Table 1). With a positive predictive value (PPV) of 55%-86% (approximate mean of 73%) an unsuccessful (unnecessary) surgical exploration would be performed in 27% of patients (false negative diagnosis). On the other hand, the negative predictive values (NPV) ranged from 31%-85% (approximate mean of 62%), suggesting that 38% of patients would be falsely interpreted to be inoperable and would miss their chance to undergo a successful operation. Hence, one should not use CA 125 as a single criterion to determine patient management: primary surgery *vs* NACT. Other clinical features, such as ascites or imaging studies, may add value to CA 125 in predicting an optimal cytoreduction. Nevertheless, a high level of CA 125 should warn a surgeon that aggressive surgery will probably be required to achieve an optimal resection. This will ultimately aid in planning the setting or level of the hospital where the operation should be performed.

Imaging studies

Imaging studies are very useful to evaluate the location, nature, and extent of disease. However, some common pitfalls are encountered depending on the location and size of the lesions. Aside from having an important role in the assessment of tumor response during or after the courses chemotherapy, imaging can be used to evaluate the extent or location of disease preoperatively to estimate whether the surgery can be achieved with minimal morbidity and with maximal outcome. An imaging study can be an indicator alone or in combination with other clinical features, such as CA 125, in trying to improve the predictive role of each.

Computed tomography: Computed tomography (CT) scan is a commonly used imaging tool in AOC. Many criteria have been used to select the patients who were unlikely to have a successful surgical outcome and NACT may be a better option. These include carcinomatosis, pelvic sidewall infiltration, ascites, and extensive upper abdominal disease over diaphragm, liver, porta hepatis, mesentery, and bowel[48]. Using spiral CT scan, the reported sensitivity in detecting peritoneal metastases, mesenteric, and diaphragmatic surfaces ranged from 85% to 93%[49,50]. This technique yielded improved sensitivity over previous reports that used 10-mm slice CT scanning, which may miss subcentimetric peritoneal nodules or plague-like lesions[51].

One of the earliest studies of CT scan for predicting optimal surgery in 42 ovarian cancer patients was reported by Nelson *et al*[52]. The authors found that CT scan could detect the presence of ascites, mesenteric, and omental disease. However, it was poor in detecting liver involvement, omental attachment to the spleen, gallbladder fossa disease, and peritoneal nodules smaller than 2 cm. The overall optimal cytoreduction rate was 69%. The sensitivity was as high as 92% with specificity of 79%, while the PPV and NPV were 67% and 96%, respectively. Notably, 8 of the 42 patients had stage Ⅰ / Ⅱ disease. In patients with advanced disease the specificity decreased from 79% to 71%.

A larger study by Salani *et al*[53] who included only stage Ⅲc/Ⅳ disease reported 92% overall rate of optimal cytoreduction in 180 ovarian cancer patients. The authors found varying rates of optimal surgery according to the location and number of lesions identified preoperatively: 91% optimal debulking in the presence of ascites or carcinomatosis, 94% in the presence of lesions over the diaphragm, 85% or 88% with spleen or liver involvement, and only 75% for lesions involving the porta hepatis or the lymph-nodes above the renal vessels. The rates of optimal debulking according to the number of lesions were: 95% for disease involving 1 site, 94% for 2 sites, and 82%, 93%, 80% for 3, 4, and 5 sites, respectively. The authors concluded that none of these features absolutely excluded the possibility of optimal resection.

Other studies have used several radiographic findings in combination to develop a score model to predict surgical outcomes. Dowdy *et al*[54] reported the role of CT scans in predicting suboptimal cytoreductive surgery in 87 patients with stage Ⅲ/Ⅳ ovarian cancer. The optimal cytoreduction rate was 71%. Among many radiographic criteria from CT scans, only diffuse peritoneal thickening was independently associated with suboptimal resection. Using this single criterion, the PPV and NPV were 57% and 85%, respectively. The PPV increased to 68% when ascites was added as a feature, and 79% with added ascites and diaphragmatic diseases. Interestingly, the authors made specific note that the predictive ability of CT criteria was dependent on other factors, especially the effort of the surgeon to perform extensive surgery[54]. Another study by Meyer *et al*[55] used a 10-score model composed of a score of 0 to 2 for a disease at each site of the following: omentum, liver, para-aortic nodes, diaphragm, and small-bowel mesentery. The rate of optimal cytoreduction or of having residual diseases ≤ 2 cm was 57%. Score ≥ 3 had sensitivity of 58% and a specificity of 100% in predicting residual disease > 2 cm. The area under the curve (AUC) was 0.94. Of note, nearly 40% of the patients in this study had early stage disease, and again, this may have led to overestimation of the role of pre-operative CT scan. Another study by Fujwara *et al*[56] created two models using various features of diffuse peritoneal thickening, infrarenal para-aortic or pelvic lymph node involvement, a bowel encasement tumor or bowel mesenteries or omental cake ≥ 2 cm, and ascites fluid. The two models using either 4 or 6 disease sites as criterion yielded greater than 90% accuracy in predicting suboptimal surgery.

Combined CT scan and clinical data: Some studies have evaluated the combined use of CT scans with clinical data, including CA 125, to improve the doctor's ability to predict the results of surgery. However, the results of these attempts to predict optimal cytoreduction were inconsistent[7,55,57-61].

As mentioned earlier, Meyer *et al*[55] used a 10-point scoring system from CT scan features and found an AUC of 0.94 in predicting a suboptimal surgery. The AUCs were not improved when the authors added age, ascites, or CA 125 to their index, with AUC scores of 0.91, 0.93, and 0.97, respectively[55]. A study by Byrom *et al*[57] evaluated CT scan findings in 51 ovarian cancers (49% having residual diseases). The sensitivity and specificity of the CT scan using a full model (the 4 CT features of ascites, omental cake, mesenteric disease, and diaphragmatic deposits) or a reduced model (only omental cake and mesenteric disease) in predicting residual disease were the same: 88% sensitivity, 98% specificity, 95% PPV, and 94% NPV. The specificity and PPV, at 98% and 95% respectively, were not improved by the addition of age and CA 125.

In addition to the chronological age of an individual, the performance status of a patient may affect the treatment outcome. One study by Aletti *et al*[7] examined the resectability of ovarian cancer by considering disease factors as well as patient status and the effort of the surgeon. Data taken into account were age, performance status, CA 125, ascites volume, carcinomatosis, diaphragmatic or mesenteric involvement, and the surgeon category (radical surgery in less than *vs* more than 50% of cases). Only performance status, carcinomatosis, and surgeon were independently associated with surgical outcome. The authors focussed on the surgical effort of the surgeon. Among the patients with high-risk factors of poorer performance status or with carcinomatosis, the rates of optimal cytoreduction varied from 42% to 67% depending on the willingness of the operating surgeons to perform aggressive surgery[7].

Another study by Bristow *et al*[58] included as many as 25 radiographic features from CT scans as well as clinical features including performance status and pre-operative serum CA 125 to predict optimal cytoreduction in 41 ovarian cancer patients. Based on the statistical probability of each factor in predicting cytoreductive outcome, performance status and 13 imaging features were selected for the final assessment model. Performance status ≥ 2, peritoneal thickening, ≥ 2 cm tumor implants on the peritoneum, small or large bowel mesentery, ≥ 1 cm suprarenal para-aortic lymph nodes, omental extension (spleen, stomach, or lesser sac), and pelvic sidewall involvement and/or hydroureter, which were most strongly associated with surgical outcome, had a score of 2 while the other CT features had a score of 1. Scores ≥ 4 had the highest overall accuracy at 93%, with 100% sensitivity, 85% specificity, 88% PPV, and 100% NPV. However, the predictive function of this model was not confirmed in other similar cross-validation studies[59,60]. Axtell *et al*[59] found disease over the diaphragm and large bowel mesentery as independent predictors of suboptimal cytoreduction. The authors also applied a different 14-criteria radiographic-based model to the original cohort of Bristow *et al*[58] as well as to the other cohorts, but found lower sensitivity, specificity, and accuracy. Another study by Gemer *et al*[60] compared the validity of four predictive CT scan models reported by Nelson *et al*[52], Dowdy *et al*[54], Bristow *et al*[58], and Qayyum *et al*[62]. Only the Dowdy study's criteria for predicting the results of surgery were confirmed. The predictive performances of the other models were lower.

Finally, one recent prospective study by Ferrandina *et al*[61] used several features from CT scans combined with clinical data to develop a predictive index. The CT scan features were: peritoneal thickening or implants > 2 cm, bowel mesentery involvement, omental cake, pelvic sidewall involvement and/or hydroureter, suprarenal aortic lymph nodes > 1 cm or infrarenal aortic lymph nodes > 2 cm, superficial liver metastases > 2 cm and/or intraparenchimal liver metastases of any size, and ascites > 500 mL. Clinical data included age, CA 125, and ECOG-performance status. Radiographic and clinical features which yielded a specificity > 75%, PPV and NPV > 50%, and accuracy > 60% in predicting surgical outcomes were assigned a score of 2. The AUC was 0.78 using only radiographic features and 0.81 using both radiographic and clinical data. The

Table 2 Studies of computed tomography scan with or without clinical features to predict surgical outcome in epithelial ovarian cancer

First author, year	*n*	OS	CT criteria ± clinical feature	Sensitivity	Specificity	PPV	NPV	Accuracy
Using 2 cm as criteria for OS								
Nelson *et al*[52], 1993	42[1]	69%	1 of 8 disease site	92%	79%	67%	96%	86%
Meyer *et al*[55], 1995	28[1]	57%	5 disease sites	58%	100%	100%	55%	79%
Byrom *et al*[57], 2002	51	51%	Full/reduced models (same values)	88%	98%	95%	94%	-
			CT with age and CA 125 (not useful)	88%	92%	85%	94%	-
Qayyum *et al*[62], 2005	137	15%	Either CT (n = 91) or MRI (n = 46)	76%	99%	94%	96%	95% (CT), 96% (MRI)
Using 1 cm as criteria for OS								
Dowdy *et al*[54], 2004	87	71%	3 disease sites (CA 125 not useful)	44%	95%	79%	81%	-
Fujwara *et al*[56], 2011	98	86%	4 or 6 disease sites (similar values)	-	-	50%	97% or 99%	91% or 94%
Bristow *et al*[58], 2000	41	49%	13 disease site (predictive index ≥ 4) (age and CA 125 not useful)	100%	85%	88%	100%	93%
Axtell *et al*[59], 2007	(3 cohorts)		2 disease sites					
	65	78%	Cohort A	79%	75%	-	-	77%
	48	41%	Cohort B	15%	32%	-	-	34%
	71	87%	Cohort C	72%	56%	-	-	64%
Gemer *et al*[60], 2009	123	73%	Nelson's criteria	64%	64%	-	-	64%
			Qayyum's criteria	67%	57%	-	-	60%
			Bristow's criteria	70%	64%	-	-	66%
			Dowdy's criteria	79%	60%	-	-	65%
Ferrandina *et al*[61], 2009	195	44%	9 disease sites ± age, CA 125, PS	AUC 0.78 for CT only and 0.81 when added with PS				

[1]19% of the patients in the study of Nelson *et al*[52] and 36% in the study of Meyer *et al*[55] had stage Ⅰ-Ⅱ diseases while all other studies included only advanced stage disease. OS: Optimal surgery; CT: Computed tomography; PPV: Positive predictive value; NPV: Negative predictive value; PS: Performance status; CA: Cancer antigen; MRI: Magnetic resonance imaging; AUC: Area under the curve.

authors concluded that adding performance status led to improvement in the diagnostic performance in predicting suboptimal surgery.

Magnetic resonance imaging: Magnetic resonance imaging (MRI) is not as commonly used as CT scans in ovarian cancer and there are fewer studies examining its role in predicting surgical outcome in patients with AOC. Qayyum *et al*[62] compared the possible role of CT scans (91 patients) and MRIs (46 patients) in predicting ≥ 2 cm suboptimal cytoreduction in 137 epithelial ovarian cancer patients. Using criteria from 14 different peritoneal and nodal diseases, the diagnostic performances of CT scan and MRI in predicting suboptimal diseases were similar, and optimal cytoreduction was achieved in 85% of the cases. However, these findings should be interpreted with caution because 32 patients in this study had early stage disease and only approximately one third of the patients underwent MRI. Furthermore, the results compared the findings from the two radiological techniques in all patients, rather than an individual comparison. Until we have a larger number of studies on the role of MRI in predicting surgical outcome, this technique cannot be recommended in place of CT scan as the first radiological imaging study.

Positron emission tomography and CT scans: The combined used of positron emission tomography and CT scans (PET/CT) has become more common in current clinical practice. This combination enables both sequential functional and anatomical imaging. In the primary treatment setting, the PET/CT combination is used to evaluate the extent of disease, to predict the surgical outcome, and to evaluate the response of a tumor to chemotherapy[63,64].

The few studies which compared PET/CT imagings with other imaging tools found that PET/CT was superior to previous methods for diagnosis of malignant ovarian tumors[65,66]. The results of PET/CT were the same as operative findings in 69% to 78% of the patients. One advantage of PET/CT over other imaging methods was that it could reveal extra-abdominal ovarian tumors or co-existing malignant tumors at other sites[65,66]. We found only one prospective study by Risum *et al*[67], which evaluated risk using a malignancy index comprising of 10 features from PET/CT to assess 54 patients with AOC. Large bowel mesentery implants, pleural effusion or ascites, and peritoneal carcinomatosis identified from PET/CT were predictive factors of suboptimal cytoreduction. However, large bowel mesenteric implant was the only independent predictor. The authors concluded that findings from PET/CT scans should not be used to exclude patients from primary cytoreductive surgery. Nevertheless, the identification unsuspected extra-abdominal metastases by PET/CT scan (which were found in approximately one-third of all patients or half of apparent stage Ⅲ patients) gave important information for making a decision on how to manage these patients[67].

Studies using a CT scan either alone or combination with other clinical features to predict the results of PDS are presented in Table 2[52,54-62]. The sensitivity and specificity of imaging studies from various studies ranged from 15% to 92% and 32% to 100%, respectively. The PPV of 50%-100% (approximate mean of 82%) could suggest that 18% of the patients had a false negative diagnosis and that the expected optimal cytoreduction

Table 3 Studies using laparoscopy to predict surgical outcome

Study	*n*	PDS (*n*)	Optimal surgery[1]	Criteria of residual diseases (cm)	Sensitivity	Specificity	PPV	NPV	Accuracy
Angioli *et al*[71], 2006	87	53	96%	0	-	-	-	-	-
Deffieux *et al*[72], 2006	15	11	91%	0	-	-	-	-	-
Fagotti *et al*[73], 2006[2]	64	61	67%	1	30%	100%	100%	70%	74%
Fagotti *et al*[74], 2008[2]	113	91	50%	1	30%	100%	100%	60%	75%
Brun *et al*[75], 2008[2]	55	26	69%	1	46%	89%	89%	44%	60%

[1]Percentage of optimal surgery was obtained only in the patients who had primary debulking surgery; [2]Diagnostic performance predictions in these studies used score ≥ 8 as cut-off value from the model of the study. PDS: Primary debulking surgery; NPV: Negative predictive value; PPV: Positive predictive value.

could not be achieved. On the other hand, the NPVs which ranged from 55%-100% (approximate mean of 89%) or false positive diagnosis would indicate that 11% of patients could miss their chance of successful PDS.

In conclusion, although some radiological features can predict the possibility of optimal or suboptimal resection, aggressive surgery also has impact on the surgical outcome regardless of the extent of diseases. Hence, a predictive model derived from imaging findings (which does take the effort of the surgeons into account) may not be applicable in all advanced stage ovarian cancer patients in different settings.

Laparoscopy

In the absence of any absolutely reliable preoperative imaging studies or serum markers to predict surgical outcomes in AOC, other means have sought. Laparoscopy (LPS) is an emerging technology which has become more widely practiced in gynecological oncology. Laparoscopic procedures have been practiced in early stage ovarian cancer for many years[68,69]. The minimally invasive nature of LPS yields an advantage over a laparotomy in terms of the rapid recovery of the patient. A balance between comprehensive surgery and maintenance of a locally confined ovarian tumor in early stage disease must be exercised. In recent years, LPS has also been applied in AOC[70]. A direct visualization before laparotomy of tumor location and other pathological findings in the peritoneal cavity will assist a surgeon to better assess the possibility of surgery, particularly for optimal cytoreduction.

Few studies have evaluated a role of LPS to predict the outcome of PDS. Angioli *et al*[71] in 2006 performed LPS on 87 women with AOC before making the decision for laparotomy. NACT was the alternative option in the presence of viscera lesions. As much as 96% of patients, whose tumors were deemed resectable from LPS, were actually optimally debulked by PDS, yielding an 80% rate of optimal cytoreduction. It should be noted that the definition of optimal surgery in this study was "no gross residual disease". This might have led to a higher frequency of NACT use compared to a scenario where 1 or 2 cm residual disease was used as the criterion for optimal cytoreduction. In the same year, two other studies also reported on the role of LPS in AOC[72,73]. Deffieux *et al*[72] estimated by LPS that 11 out of 15 AOC patients would have resectable peritoneal carcinomatosis. Ten of them actually had no residual disease from PDS. Another study by Fagotti *et al*[73] reported the results from their prospective study evaluating lesions over the omentum, diaphragm, peritoneum, mesentery, liver, bowel, and stomach in predicting the surgical outcomes in AOC. The rate of optimal cytoreduction was 67%. Using a scale of 0 to 12, a score ≥ 8 had PPV of 100%, NPV of 70%, and accuracy of 75% for optimal cytoreduction. This was confirmed by a subsequent validation study by these authors who used the same scoring model in 113 women with stage Ⅲ/Ⅳ disease[74]. The rate of optimal cytoreduction in this series was 56%. The PPV, NPV, and overall accuracy were 100%, 60%, and 93%, respectively. The authors concluded that a score ≥ 8 was the appropriate cut-off for predicting suboptimal cytoreduction in 100% of patients. The rate of futile exploration was only 40%. Of note, another cross-validation study by Brun *et al*[75], who used a score of ≥ 8 in predicting optimal surgery in stage Ⅲ/Ⅳ disease, reported an accuracy of only 60% with 89% PPV, 44% NPV, 46% sensitivity, and 89% specificity. The authors simplified the original Fagotti-scoring system and found a score ≥ 4 to be as accurate as Fagotti's score in predicting resectability. Table 3 shows studies which have determined the role of LPS to predict surgical outcome prior to PDS or NACT and IDS[71-75].

The limitations noted in the predictive role of LPS score across a number of studies were probably due to the involvement of different surgeons with various intentions and skills in that particular setting. Nevertheless, a direct visualization of disease by LPS should theoretically offer the best prediction of surgical outcome compared to other preoperative markers or imaging studies. Unnecessary laparotomies can probably be avoided with more confidence. One ongoing multicentre trial will randomize 200 patients with AOC to have a diagnostic LPS prior to a planned PDS[76]. Patients who are evaluated by LPS to have disease expected to be resectable to < 1 cm will undergo PDS followed by platinum based chemotherapy while the other patients will have NACT and IDS before continuing chemotherapy. The primary outcome will be the proportion of suboptimal surgeries in each arm of the study.

NACT: INDICATIONS AND SELECTION CRITERIA

As already mentioned, the standard treatment of advanced epithelial ovarian cancer (FIGO stage Ⅲ-Ⅳ) is a staging laparotomy with PDS, followed by platinum-based chemotherapy. The extent of tumour cytoreduction is considered to be the most relevant prognostic factor. The definition of optimal debulking has changed over time and it is currently defined by many authors as "no macroscopic residual tumour"[2]. In the last decade the dogma of PDS as the preferred "one-size-fits-all" approach to the primary treatment of AOC has been challenged by NACT, that is chemotherapy delivered prior to any attempt at surgical debulking.

Two meta-analysis[77,78] and two systematic reviews[79,80] addressed the question of the timing of surgery before or after chemotherapy in AOC patients. The Bristow and Chi meta-analysis included only phase Ⅰ/Ⅱ and retrospective studies involving 835 patients from 21 studies using platinum-based NACT after a primary surgery attempt[77]. The results showed that survival of patients who had NACT followed by IDS was inferior to those who had PDS. Furthermore each incremental chemotherapy cycle after the third course of NACT resulted in a 4.1-mo decrease in survival. This meta-analysis is, however, affected by severe methodological limitations as recognized by the authors themselves. In particular, the results are confounded by major selection biases (no information is given about criteria to establish NACT duration), by a large variety of different chemotherapeutic agents and administration schedules, and by the fact that prognostic factors such as performance status were not examined. It is also worth-noting that because of the limited number of studies the authors did not apply the multiple linear regression model and it is possible that one or more statistically significant variables associated with survival on simple linear regression could be irrelevant if interaction among variables were taken into account. In another meta-analysis on the same 21 studies conducted by Bristow *et al*[77], the random effect meta-regression analysis was used instead of simple linear regression[78]. The year of publication (more *vs* less recent), the stage (Ⅲ *vs* Ⅳ), the use of a taxane (*vs* not), and the optimal cytoreduction (*vs* not) were associated with a better overall survival. The detrimental effect of duration of NACT was not confirmed, indicating that the allocation of poorer prognosis patients to NACT and to a greater number of chemotherapy courses is a general phenomenon in non-randomized studies, leading to a severely confounding selection bias.

A systematic review of randomized controlled trials of chemotherapy *vs* surgery for the initial treatment in AOC patients was conducted by the Cochrane collaborative group in 2007[81] and was recently updated[80]. The first version of the review[81] identified only one randomized trial by Liu *et al*[82]. Patients were randomized to NACT by the intra-arterial route before IDS or conventional PDS followed by adjuvant chemotherapy. This study randomized just 85 women and could not demonstrate any significant difference in overall survival between the two treatment arms. However, optimal cytoreduction was achieved more often in the NACT/embolisation group, and this group had a shorter operating time, less blood loss and fewer blood transfusions. The updated review excluded this trial because the study findings might have been attributable to NACT, the iliac artery embolization, or both.

As a consequence the only RCT included in the Cochrane 2012 review is the Intergroup Study from Europe, Canada and South America (EORTC 55971/NCIC OV13). This is the only published randomized trial comparing NACT (3 courses) followed by surgery and by 3 more courses of adjuvant chemotherapy with PDS followed by 6 courses of adjuvant chemotherapy (with or without IDS)[10]. The trial randomized 718 patients with stage Ⅲc-Ⅳ AOC, primary peritoneal cancer or fallopian tube cancer with the goal of evelauting the NACT *vs* the control arm in terms of overall survival (primary end-point). Secondary end-points were progression-free survival, surgical morbidity and mortality, quality of life and adverse effects. Among 670 evaluable patients, no significant differences in terms of overall survival (HR 0.98; 95%CI: 0.82-1.18) or progression-free survival (HR 1.01; 95%CI: 0.86-1.17) were found, even though the complete resection rate was higher in the NACT group (52% *vs* 20%, RR 2.56; 95%CI: 2.00-3.28). Grade 3 and 4 haemorrhage, venous thromboembolism and infection were more frequent in the control arm. No differences were observed in the need for blood transfusions, operating times and quality of life.

The definition of selection criteria for NACT or PDS in clinical practice remains a matter of heated debate[83-85]. The supporters of PDS state that optimal debulking surgery can be achieved in most cases and must be pursued even when major debulking procedures and ultra-radical surgery are needed, restricting NACT to a minority of patients with diffuse extraperitoneal disease and/or too sick and elderly to tolerate a major debulking procedure[83]. According to this view, the lack of surgical skills among gynaecological oncologists is a critical issue that should be modified in order to improve the survival of ovarian cancer patients. The major criticism of this position is that it is based only on biased retrospective data and has never been prospectively validated in the context of a randomized controlled trial.

On the other hand, some are concerned about the feasibility of extensive surgery in a real clinical practice[84]. According to the EORTC/NCIC trial, the Leuven selection criteria for NACT[85] include: tumours larger than 2 cm around the superior mesenteric artery or behind the porta hepatis, or intrahepatic (multiple) metastases or several extra-abdominal metastases (excluding resectable inguinal or supraclavicular lymph nodes), or poor general conditions (*e.g.*, over 80 years of age), or extensive serosal invasion necessitating bowel resections greater than 1.5 m

or women who cannot be easily debulked to no residual tumor (*e.g.*, more than one bowel resection, expected operating time greater than 4 h). The last two Leuven criteria are probably the most controversial.

Even if the level of evidence in favour of NACT as a treatment option for patients with bulky stage Ⅲc-Ⅳ AOC is limited (one single RCT), the level of evidence in favour of major debulking surgery and ultra-radical surgery is even lower (retrospective data only). Supporters of NACT believe that it is not recommended to submit patients to the risk and costs of major surgical procedures based on such a low level of evidence.

Three more prospective randomized trials are comparing NACT *vs* PDS in AOC: the small Indian trial results[86] were partly presented in 2007 and in 2009 and should be published shortly (the anticipated results are similar to those of EORTC/NCIC trial). The Japanese trial JCOG0602 accrued 301 patients from November 2006 to October 2011, while the CHORUS trial recruited over 500 patients from March 2004 to July 2010 and the results are awaited[87,88]. All of these trials are investigating a short-term platinum-taxane NACT (3 courses in the Indian and in the CHORUS trials, 4 courses in the JGOG trial).

Hence, we can state that NACT can be considered as an option in patients whose disease appears to be extensive and when the PDS is not possible, expected to be suboptimal or requiring extensive surgical demolitions. NACT should not replace PDS whenever there is a chance for a patient to have a successful standard treatment by PDS followed by adjuvant chemotherapy.

IDS: SELECTION CRITERIA AND OPTIMAL TIMING

NACT has been promoted in order to avoid non-useful surgical procedures in patients expected to have a suboptimal surgical staging after establishing a diagnosis of AOC[89]. IDS or delayed PDS will be performed when the tumors have responded to induction or NACT in terms of complete or partial response as well as stable disease. Most studies to date have demonstrated that the advantage of NACT is the higher rate of optimal cytoreduction at IDS compared to PDS[11,79,90,91]. The possible benefit of IDS on survival is more controversial. Several non-randomized trials which attempted to evaluate the association of IDS and patient survival had inconsistent results. Some studies showed similar survival outcomes between patients who underwent IDS and those patients who had PDS[92-95]. Other studies reported significantly longer survival of patients who had IDS[90,96] and some showed lower survival rates for patients having IDS than for those having optimal PDS[97]. To date, only three randomized trial have focused on the prognostic role of IDS[98-100], and these trials did not agree on the benefit of IDS on survival outcomes. Two trials found similar survival rates between patients who had IDS and those who had conventional treatment[98,100], while the third showed significantly longer survival in the IDS group[99]. The positive effects found in the Van der Burg study persisted after a 10-year follow-up[101]. The Cochrane Collaboration Group conducted a systematic review and meta-analysis (including the three trials just noted) involving 853 women (781 evalauble)[11], and found no statistically significant difference of overall survival (HR 0.80, 95%CI: 0.61-1.06) and progression-free survival (HR 0.88, 95%CI: 0.57-1.33) between the patients who had or did not have IDS. IDS appeared to be beneficial when the PDS was not performed by a gynaecological oncologist or when the PDS was less extensive (HR 0.68, 95%CI: 0.53-0.87).

The timing of performing IDS is another unresolved issue. Previous studies reported the number of induction or NACT cycles ranging from 2-10, with the most common being 3-4 cycles[10,11,90,91,102]. Many reasons were proposed for the earlier timing of the IDS. First, chemotherapy induced fibrosis is less extensive after 3 than after 6 cycles[103]. Second, some tumor clones may develop chemoresistance after 6 cycles[104]. Lastly, indirect evidence from an earlier study investigating the role of tumor debulking at the time of second-look surgery after 6 cycles of chemotherapy did not show any survival improvement[8]. To date, only a few studies with data comparing early with late (after 6 cycles) IDS after NACT are available. One French multicenter study investigated the results of NACT in 54 AOC patients presenting with primary unresectable tumors[105]. The authors found a higher complete response rate from late (after 6 cycles) compared to early IDS (after 3-4 cycles), 61% *vs* 45%. However, the survival rates were the same in both groups at 22 mo. These results were consistent with the data of Stoeckle *et al*[106] who compared outcomes of AOC patients who were treated with platinum-based chemotherapy and underwent early (after 3 cycles) or late IDS (after 6 cycles). The authors also found a higher complete resection rate in the late IDS groups than that in the early IDS gropus, 58% *vs* 36%. These findings suggest that the chance of achieving an optimal debulking increases in a direct relationship with the number of cycles before surgery. However, one randomized trial which was unable to demonstrate different response rates or rates of optimal surgery (residual tumors ⩽ 1 cm) between 2 cycles and 3 cycles of NACT[107]. With inconsistent results regarding the benefit of more cycles of NACT, it should be noted that higher rates of responses and optimal debulking were not translated into an improved rate of survival[105,106]. Hence, based on the EORTC randomized trial[10], limiting NACT to 3 cycles is a reasonable practice until further data prove otherwise. Longer NACT treatment should be explored in the context of clinical trials.

Generally when the disease shows some response to induction chemotherapy or NACT, IDS can be performed unless clinical signs of progressive disease are evident. Criteria for selection of patients who are likely to have successful IDS are also important[9,108]. Patients who are still deemed inoperable or cannot have optimal IDS may be better receiving a new chemotherapy regimen. To

Table 4 Laparoscopic parameters assigned a predictive index score

Predictive index parameter	Point value	Sensitivity	Specificity	PPV	NPV	Accuracy
Omental cake	0	72.7%	68.3%	55.8%	82.0%	69.9%
Diaphragmatic carcinosis	0	77.1%	71.2%	61.4%	84.0%	73.4%
Mesenteral retraction	2	64.3%	98.2%	94.7%	85.0%	87.2%
Bowel infiltration	2	69.7%	86.0%	74.2%	84.1%	80.8%
Stomach infiltration	2	17.6%	100%	100%	67.4%	69.6%
Superficial liver metastasis	2	22.8%	100%	100%	68.9%	71.6%

NPV: Negative predictive value; PPV: Positive predictive value.

predict the results of IDS, Rodriguez *et al*[91] studied the role of CA 125 in 103 AOC patients who were treated with platinum-based NACT followed by IDS. Ninety-nine patients (96%) had optimal cytoreduction, defined as residual disease ≤ 1 cm (47 patients or 48% had no residual disease). There was no statistical difference in CA 125 at diagnosis between those without residual disease and those with optimal surgery but with macroscopic disease. However, the CA 125 level before IDS was significantly lower in patients with no residual disease than that in patients with optimal but macroscopic disease, 92 U/mL compared to 233 U/mL ($P = 0.001$). Using CA 125 of ≤ 100 U/mL as a cut-off level, a significantly higher percentage of patients without residual tumors had low pre-IDS CA 125 than the group with macroscopic residual disease, 80% *vs* 63%. The authors suggested that patients with pre-IDS CA 125 ≤ 100 U/mL were likely to have successful optimal cytoreduction to no residual disease. Another study by Bland *et al*[109] evaluated and constructed 3 algorithms using CA 125, CT scan, and LPS findings in 128 AOC women after initial chemotherapy but before surgery. The authors found that failure of CA 125 to decline dramatically was significantly associated with suboptimal surgery: 89% of the patients with optimal surgery had a decline of CA 125 > 50% compared to only 57% in the suboptimal group[109]. In the same vein, a significantly higher percentage of patients with suboptimal surgery had more small-bowel mesentery disease identified from by CT scan than found in those with optimal surgical outcome, 38% *vs* 6%. Other findings which were missed in pre-operative CT scans and were found in patients with suboptimal surgery were diseases on the liver surface, small-bowel surface, large-bowel mesentery, bladder peritoneum, spleen, and diaphragm. Finally the authors proposed a predictive algorithm for identifying patients most likely to have suboptimal surgery following chemotherapy using criteria: < 50% reduction in CA 125, stable or progressive disease on CT scan, and diseases on the bladder peritoneum or liver surface identified at the time of LPS[109]. However, the number of patients in this study having either serum CA 125, CT scan, or LPS surgery before exploration was limited and further study is required to confirm these data.

In addition to tumor markers and imaging studies, a recent study by Fagotti *et al*[9] reported a role for LPS in AOC patients who had partially stable/stable disease after NACT. The authors set a predictive index score based on various features identified from staging LPS to select patients who were likely to have successful IDS (Table 4). The LPS parameters of mesentery retraction, bowel and stomach infiltration, and superficial liver metastasis were strongly associated with unresectable diseases. Using a staging LPS after serological response with NACT, the authors found the rate of inappropriate exploration was reduced from 18% to 0%. Moreover, a predictive index score > 4 could absolutely predict the probability of optimally cytoreduction at laparotomy in all patients.

Unlike the important prognostic role of the size of residual disease after PDS[2], only limited information regarding the size of residual disease after IDS is available. Most studies have used the same traditional definition of "optimal cytoreduction" in IDS as that in PDS. A recent randomized study and one retrospective study found that complete resection of all macroscopic disease at the time of IDS was the single most important independent prognostic factor in AOC[10,110].

In conclusion, standard management of advanced ovarian cancer is primary surgery followed by adjuvant chemotherapy. The aim of surgery should be a removal of all gross visible tumors because this is one of the most important prognostic factors. Prediction of surgical outcome is crucial especially when the benefit of optimal surgery and the risk of extensive surgery are equivocal. NACT followed by surgery is an alternative option with less morbidity and comparable survival outcome. IDS is another approach for patients who have suboptimal primary surgery and who have no progressive disease after induction chemotherapy. This interval surgery yields survival benefits particularly in patients who have had less extensive primary surgery or less than maximal efforts made by an expert surgeon.

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BRIEF ARTICLE

Cytoreductive surgery and HIPEC after neoadjuvant chemotherapy for advanced epithelial ovarian cancer

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Abstract

AIM: To reduce postoperative complications and to make possible an optimal cytoreduction, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery has been applied with encouraging results.

METHODS: Between December 2009 and February 2012, patients with stage ⅢC-Ⅳ epithelial ovarian cancer (EOC) underwent diagnostic laparoscopy, to assess the feasibility of optimal debulking surgery. The modified Fagotti score was applied to assess the feasibility of resection with zero residual tumor. Patients who were not candidate for upfront debulking surgery were submitted to NACT, then reassessed according to the RECIST 1.1 criteria and submitted to cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) if they showed clinical response or stable disease. The remaining cycles of adjuvant systemic chemotherapy (ASCT) were administered postoperatively, to complete 6 cycles of systemic chemotherapy.

RESULTS: Nine patients were included. Clinical response to NACT was complete in 3 patients and partial in 5 patients; one patient had stable disease. All patients underwent CRS resulting in CC0 disease prior to HIPEC. Average operative time was 510 min. Average intensive care unit stay was 2 d. Average postoperative hospital stay was 25 d. No postoperative mortality was observed. One patient experienced pelvic abscess. One patient refused ASCT. The remaining 8 patients started ASCT. Average time to chemotherapy was 36 d. All patients are alive, with an average follow up of 11 mo. Eight patients are disease-free at follow up.

CONCLUSION: HIPEC after CRS for advanced EOC is feasible with acceptable morbidity and mortality. NACT may increase the chance for achieving complete cytoreduction. Phase 3 studies are needed to determine the effects of HIPEC on survival.

Key words: Peritoneal carcinomatosis; Ovarian cancer; Cytoreductive surgery; Intraperitoneal chemotherapy; Hyperthermic intraperitoneal chemotherapy; Hyperthermia

Core tip: This is a report of a phase 2 prospective observational study, which served as a pilot study for the CHORINE trial protocol (http://www.chorine.org). Our pilot study supports the feasibility of neoadjuvant chemotherapy (NACT) followed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for upfront treatment of advanced epithelial ovarian cancer. This combined therapy does not reduce the possibility to start the postoperative systemic chemotherapy in an acceptable period of time. We believe that in the upfront setting NACT can better select chemoresponsive patients, increasing their chance to take advantage from HIPEC, reducing the surgical stress and the perioperative complications.

Lotti M, Busci LM, Campanati L, Catena F, Coccolini F, Bakrin N, De Iaco P, Ercolani G, Grosso G, Pisano M, Poiasina E, Rossetti D, Rossi M, Zamagni C, Bertoli P, Pinna AD, Frigerio L, Ansaloni L. Cytoreductive surgery and HIPEC after neoadjuvant chemotherapy for advanced epithelial ovarian cancer. *World J Obstet Gynecol* 2013; 2(4): 167-175 Available from: URL: http://www.wjgnet.com/2218-6220/full/v2/i4/167.htm DOI: http://dx.doi.org/10.5317/wjog.v2.i4.167

INTRODUCTION

Ovarian cancer is the third commonest gynecological neoplasm[1] and accounts for 5% of all female cancer deaths. Epithelial ovarian cancer (EOC) accounts for more than 70% of all ovarian cancers. EOC typically presents with unclear gastrointestinal and constitutional symptoms, like abdominal bloating, distension, weight loss, and fatigue[2]. Due to heterogeneity of these symptoms, nearly 70% of patients with EOC are diagnosed with advanced stage disease (stage Ⅲ or Ⅳ)[3,4].

It is well known that primary cytoreductive surgery (CRS) followed by platinum-based systemic adjuvant chemotherapy (SACT), when indicated, is the mainstay of treatment for EOC: in this setting, the aim of primary surgery is to remove as much tumor as possible (possibly all the tumor), since the amount of residual tumor is one of the most important prognostic factors for survival[5-7]. Unfortunately, the achievement of optimal cytoreduction (residual tumor less than 1-2 cm), mainly in advanced EOC, is not always possible, due to the amount of disease at presentation, patient's co-morbidities, and the experience of the surgeon[8-11]. Not performing optimal or complete CRS results in loosing the chance for longer survival.

To help achieving complete resection rate, the concept of neoadjuvant chemotherapy (NACT) followed by interval CRS (ICRS) has been developed for patients deemed to have unresectable disease (stage ⅢC/Ⅳ EOC). From several retrospective and prospective case-control studies, along with recent meta-analyses, it appears that NACT-ICRS compared to primary CRS offers less postoperative morbidity to patients[12]. Moreover, results of the prospective randomized controlled trial (RCT) EORTC 55971 are consistent with the majority of the previous studies, suggesting that NACT-ICRS results in the same survival but fewer complications than primary CRS in patients with stage ⅢC/Ⅳ EOC[13].

During its natural history, EOC tends to be chemosensitive and to confine itself to the surface of the peritoneal cavity for a long period of time. These features make it an obvious target for intraperitoneal chemotherapy (IPCT), which is given by infusion of the chemotherapeutic agents directly into the peritoneal cavity. This may increase the anticancer effect with fewer systemic adverse effects in comparison to intravenous therapy. To optimize drug distribution, IPCT has also been applied intraoperatively, immediately after CRS. Different techniques have been used for intraoperative IPCT. An advantage of intraoperative use is that IPCT can be administered even under hyperthermic conditions, which are poorly tolerated by a patient who is awake. Hyperthermia is directly cytotoxic and enhances the efficacy and penetration depth of many drugs, while the mild locoregional hyperthermia that is used has no significant adverse effects.

The feasibility of hyperthermic intraperitoneal chemotherapy (HIPEC), as a treatment for peritoneal carcinomatosis, was first demonstrated by Spratt *et al*[14]. Its development continued under Dr. Sugarbaker in the mid-1990s, who advocated a combined procedure of CRS with peritonectomy procedures (aimed at resecting peritoneal surfaces with tumor implants) and associated visceral dissections, with maximal surgical effort to remove as much tumor as macroscopically possible, followed by direct instillation of heated IPCT to address microscopic residual disease[15]. This treatment has already been shown to be beneficial for patients with peritoneal carcinomatosis from gastric cancer[16] appendiceal cancer[17], colorectal cancer[18] and peritoneal mesothelioma[19].

The rationale to use CRS and HIPEC in EOC stands on a few considerations. First, phase 3 RCTs have established the superiority (improved progression-free and overall survival) of intraperitoneal cisplatin-based chemotherapy compared to the systemic delivery of the agent in the treatment of small-volume residual advanced EOC[20-22]. Second, a number of prospective phase 2 studies and retrospective institutional experiences have shown the feasibility of employing HIPEC[23-28], when complete macroscopic cytoreduction is achieved prior to the delivery of the antineoplastic agents. However a few concerns still exist about the application of IPCT because of the fear of possible complication linked to this way of chemotherapy administration. The prospected main risk is to delay or to definitively obstacle the possibility to start systemic chemotherapy as soon as possible after the surgery.

For these reasons we performed a bi-centric prospective observational pilot study combining NACT with carboplatin (CBCDA) and paclitaxel (PTX) to CRS and HIPEC with cisplatin (CDDP) and PTX in upfront treatment of advanced EOC. The aim of this study was to evaluate the feasibility of CRS and HIPEC in patients

with stage ⅢC/Ⅳ EOC, who showed partial or complete response after NACT, in terms of percentage of complete cytoreduction (residual disease < 2.5 mm), toxicity, postoperative complications, postoperative mortality, and time elapsed till the start of systemic chemotherapy (time to chemotherapy, TTC).

MATERIALS AND METHODS

The Study design was approved by our local Ethics Committee. The selection criteria were the following: (1) Inclusion criteria. Female adult women (18 to 70 years old) patients, with EOC (FIGO stage ⅢC or Ⅳ), performance status (ECOG) 0, 1 or 2, signed informed consent, body mass index < 35 kg/m^2; and (2) Exclusion criteria. Impossibility of an adequate follow-up, presence of other active neoplasms, active infection or other concurrent medical condition that could interfere in the ability of patients to receive the proposed treatment according to protocol, complete bowel obstruction, abnormal bone marrow indices or renal and liver function, ASA Ⅳ or Ⅴ.

Patients with advanced EOC (stage ⅢC-Ⅳ) were submitted to a diagnostic laparoscopy, to assess the feasibility of optimal debulking surgery with no residual disease at the end of the procedure.

Laparoscopy was performed by trained gynecologists and surgeons. In presence of ascitic fluid, a sample for cytology was obtained; otherwise, a lavage of the peritoneal cavity was performed; biopsy of eventual pelvic and peritoneal masses was obtained.

The modified Fagotti scoring system was applied[29], to assess the feasibility of resection with zero residual tumor. Patients with a score ≥ 4 were judged not candidate for debulking surgery: a score ≥ 4 was chosen as a compromise to warrant adequate accrual, because the higher risk of inappropriate lack of exploration (27.3%) was likely to be balanced by the documented efficacy of NACT in this type of tumor.

After laparoscopic evaluation, patients who were not candidate for upfront debulking surgery were submitted to NACT with CBCDA AUC-5 and PTX 175 mg/m^2, administered every 21 d.

After 3-6 cycles of chemotherapy, patients were re-assessed by clinical, radiologic [computed tomography (CT) scan] and laboratory (CA 125) evaluation and assigned to one of four subgroups, according to the RECIST 1.1 criteria: complete clinical response (cCR), partial clinical response (cPR), clinically stable disease (cSD), clinically disease progression (cDP)[30]. Patients with cCR, cPR or cSD after NACT, were submitted to CRS with radical intent.

After laparotomy, a detailed pattern of peritoneal diffusion of the disease was drawn according to the Peritoneal Cancer Index (PCI) scoring system[31] and then CRS was as follows: hysterectomy, bilateral salpingoophorectomy, pelvic and peri-aortic lymphadenectomy, radical omentectomy, random biopsy of peritoneal surfaces, associated to any surgical procedure needed to obtain a ≤ 2.5 mm residual tumor (peritonectomy, bowel resection, diaphragmatic stripping, gastric resection, *etc.*).

After CRS, patients with adequate cytoreduction (CC0, no residual disease; CC1, residual tumor ≤ 2.5 mm)[29] were submitted to HIPEC with CDDP (100 mg/m^2 of body surface area) and PTX (175 mg/m^2 of body surface area) at 42 ℃, with an intraperitoneal infusion time of 90 min. HIPEC was delivered using an open abdomen (coliseum) technique.

Toxicity was recorded in accordance to the National Cancer Institute Common Toxicity Criteria (NCI CTC). Surgical complications were considered as a component of the total toxicity and also registered in accordance of the NCI CTC. Treatment-related death was defined as death due to toxicity following cytoreduction and HIPEC without time interval restrictions.

As soon as the conditions of the patients allowed it (and in any case at least 4 wk after surgery) the remaining cycles of SACT were administered with the same schedule of NACT, to complete 6 cycles of systemic chemotherapy.

RESULTS

Between December 2009 and February 2012, 36 patients with advanced EOC (stage ⅢC-Ⅳ) were evaluated and submitted to a diagnostic laparoscopy: 15 patients were selected who were not candidate for upfront debulking surgery (13 stage ⅢC, 2 stage Ⅳ) and submitted to NACT with CBCDA AUC-5 and PTX 175 mg/m^2, administered every 21 d.

After three cycles of NACT, 6 patients were excluded for evidence of cDP; in the remaining 9 patients, cCR was observed in 3 cases, cPR was observed in 5 cases, one patient had cSD: these 9 patients were enrolled in our pilot study.

Six patients underwent CRS and HIPEC after four cycles of NACT, 2 patients after three cycles of NACT and 1 patient after six cycles of NACT, in order to achieve optimal clinical response (> 50%, according to the RECIST 1.1 criteria). Average age was 55.8 years (median 55 years, range 45-65 years).

At operation, average PCI was 14 (median 13, range 5-28). All patients underwent CRS resulting in CC0 disease prior to HIPEC. Supramesocolic compartment peritonectomy was required in 5 patients. Six patients underwent colorectal resection and anastomosis, with temporary diverting ileostomy. More clinical details are available in Table 1.

All patients underwent HIPEC with CDDP 100 mg/m^2 of body surface area and PTX 175 mg/m^2 of body surface area at 42 ℃, with an intraperitoneal infusion time of 90 min.

Average operative time was 510 min (median 520 min, range 400-595 min). Average intensive care unit stay was 2 d (median 2 d, range 1-5 d). Average postoperative hospital stay was 25 d (median 22 d, range 9-35 d).

No postoperative mortality was observed. One patient

Table 1 Clinical characteristics of the ovarian cancer patients

Patient	Age (yr)	BMI (kg/m^2)	Stage	Histology	Grade	PCI	No. of cycle NACT	Clinical response (%)	CC
1	47	23	IIIC	Sierous	3	15	4	100	0
2	50	31	IV	Sierous	3	12	4	> 50	0
3	53	31	IV	Endometrioid	3	6	4	100	0
4	65	19	IIIC	Sierous	2	8	4	> 50	0
5	55	24	IIIC	Sierous	3	21	4	100	0
6	55	21	IIIC	Undifferentiated	3	28	4	< 50	0
7	47	22	IIIC	Endometrioid	3	5	3	> 50	0
8	62	22.9	IIIC	Sierous	3	14	6	> 50	0
9	65	20	IIIC	Sierous	3	13	3	> 50	0

BMI: Body mass index; PCI: Peritoneal cancer index; NACT: Neoadjuvant chemotherapy.

Table 2 Postoperative adverse events *n* (%)

	Patients	CTCAE grade	Treatment
Postoperative death	0 (0)		
Reoperation	1 (11)		
Types of complications	5 (56)		
Grade 3-5 morbidity	5 (56)		
Pelvic abscess	1 (11)	3	Reoperation
Leukopenia	3 (33)	3	G-CSF
Thrombocytopenia	2 (22)	3	Observation

G-CSF: Granulocyte colony-stimulating factor.

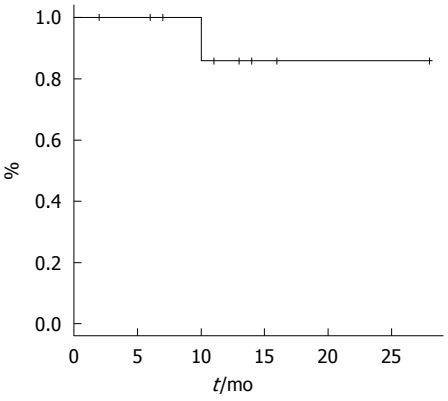

Figure 1 Disease free survival curve.

experienced a grade 3 postoperative complication (pelvic abscess), requiring reoperative debridement and drainage. Grade 3 leukopenia was observed in 3 patients and was treated with administration of granulocyte colony-stimulating factor; one of these patients had also grade 3 thrombocytopenia. One more patient experienced Grade 3 thrombocytopenia, which resolved spontaneously (Table 2).

One patient refused SACT. The remaining 8 patients started SACT. Average TTC was 36 d (median 29 d, range 25-62 d). All patients are alive, with an average follow up of 12 mo (median 11 mo, range 2-28 mo). Eight patients are disease-free to date. One patient showed a raising CA 125 after 10 mo of follow up. The disease-free survival curve for the 9 patients included in the study is shown in Figure 1.

DISCUSSION

In our presented study, 36 women with advanced EOC were evaluated by means of laparoscopy and 15 of them (41.6%) were judged not suitable for optimal CRS, adopting the modified Fagotti score with a cut-off of 4. These 15 patients were treated with NACT, and then 9 of them (those with cCR, cPR or cSD) underwent CRS and HIPEC with complete cytoreduction (CC0), few postoperative complications and no mortality. All patients but one, who refused it, were able start SACT in an average time of 36 d after CRS + HIPEC. All of them were able to complete SACT after CRS and HIPEC. Eight out of 9 patients are disease free to date and all of them are alive after a median follow up of 11 mo.

Even if the number of patients enrolled is small, our study shows that performing CRS and HIPEC after NACT was safe and led to a 100% rate of optimal cytoreduction, in patients with advanced EOC previously judged not suitable for complete cytoreduction at diagnostic laparoscopy. Except for the patient who refused postoperative SACT, all of the patients were able to complete SACT after CRS and HIPEC, with an acceptable TTC.

The strategy adopted in our study is not the recognized standard treatment of advanced EOC, namely maximal CRS followed by platinum-based SACT: nevertheless, patients are selected for this strategy only if they are judged not suitable for complete CRS by means of laparoscopy and a recognized scoring system[29]. Those patients are offered CRS after NACT and HIPEC is added to address microscopic residual disease: our study shows that this strategy is feasible, safe and does not flaw the completion of systemic CT.

Follow up is short, but preliminary results are encouraging and comparable to those achieved in other phase 2 studies available in the literature.

A recent article by Deraco *et al*[32] reported the results of a multi-center phase 2 trial using CRS and closed-abdomen HIPEC with CDDP and doxorubicin, in front-line treatment of advanced EOC. The authors accrued 26 patients over 6 years in four different Italian centers, achieving macroscopically complete cytoreduction in 15

Table 3 Studies on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in upfront setting

Ref.	Patients (neoadjuvant)	Type of NACT	HIPEC (technique, drug and dose, temperature, lenght of infusion time)	Period	Country
Steller *et al*[46]	2		C, carboplatin 800-1200 mg/m^2, 41-43 ℃, 90 min	NR	United States
Look *et al*[44]	4		O, doxorubicin, NR, NR	1988-2001	Singapore
Piso *et al*[45]	8 (1)	*iv* TPB	O, cisplatin 75 mg/m^2, NR, 90 min	1995-1999	Germany
Reichman *et al*[43]	9 (9)	*iv* PB	O, cisplatin 50 mg/m^2, 40 ℃, 90 min	2001-2004	United States
Rufián *et al*[42]	19		O, paclitaxel 60 mg/m^2, 41-43 ℃, 60 min	1997-2004	Spain
Roviello *et al*[47]	45 (31)	*iv* TPB	C, mitomycin C 25 mg/m^2 + cisplatin 100 mg/m^2, 41-43 ℃, 60 min	2000-2009	Italy
Pavlov *et al*[39]	31		C, doxorubicin 0.1 mg/kg (+ EPIC 15 mg/m^2 × 5 d), NR, NR	1995-2007	Serbia
Guardiola *et al*[40]	31 (31)	*iv* TPB	O, cisplatin 180 mg, 37 ℃, 120min	2003-2006	France
Di Giorgio *et al*[41]	22 (4)	*iv* TPB	C, cisplatin 75 mg/m^2, 42-43 ℃, 60 min	2000-2007	Italy
Lim *et al*[48]	30 (14)	NR	C, cisplatin 75 mg/m^2, 41.5 ℃, 90 min	2007-2009	Korea
Frenel *et al*[49]	7 (7)	*iv* TPB	O, oxaliplatin, 360-460 mg/m^2, 41-43 ℃, 30 min	2005-2008	France
Muñoz-Casares *et al*[50]	10 (10)	*ip* TB (+ in 5 pts *iv* PB)	O, paclitaxel, 60 mg/m^2, 41-43 ℃, NR	2004-2009	Spain
Parson *et al*[38]	51		C, carboplatin 1000 mg +mitomycin C 30 mg, 41-42 ℃, 60-120 min	1996-2009	United States
Deraco *et al*[32]	26		C, cisplatin 40 mg/L of perfusate + doxorubicin 15 mg/L of perfusate), 42.5 ℃, 90 min	2004-2010	Italy

NACT: Neoadjuvant chemotherapy; O: Open method; C: Closed method; TPB: Taxanes and platinum based; PB: Platinum based; TB: Taxanes based; NR: Not reported; HIPEC: Hyperthermic intraperitoneal chemotherapy.

patients and only minimal residual disease (≤ 2.5 mm) in the remaining 11.

Four patients experienced major complications, including one postoperative death. 25 out of 26 patients started SACT after CRS + HIPEC, with a median TTC of 46 d. Five-year overall survival was 60.7% and progression-free survival was 15.2%. Although these results are encouraging, in absence of a phase 3 trial, before suggesting that CRS + HIPEC could be a valid strategy for upfront treatment of advanced EOC a few considerations should be done.

It is well known that CRS, especially in very advanced cases, is associated to a high incidence of postoperative morbidity and mortality[33-35] and that the HIPEC procedure could even increase the incidence of perioperative complications[36]. For these reasons, HIPEC should be considered a burdensome procedure and before performing it, every effort is needed to select which patients will achieve the maximum benefit from it.

Although the majority of patients with EOC (up to 80%) respond to first-line systemic platinum based chemotherapy, 20% of them are resistant or refractory[37]. According to these data, a certain percentage of women with chemoresistant tumor cells will not benefit from administration of high dose HIPEC after upfront CRS for advanced EOC.

Even if not detailed in the article by Deraco *et al*[32], the survival curve of the patients accrued in their phase 2 study shows that almost 30% of the patients recurred at 1 year. It is reasonable to suppose that these patients were not chemo-sensitive.

HIPEC should be active on chemosensitive cells and the procedure could be avoided in women with insensitive tumor cells. Even if NACT followed by CRS + HIPEC did not show better results in terms of PFS and OS[13], the evaluation of patients' response to NACT could be a strategy to select for HIPEC only the patients who show a chemo-sensitivity to platinum and taxanes.

There are some phase 2 observational studies[32,38-51] in the literature reporting a total of 295 patients with primary EOC treated with CRS and HIPEC in upfront setting, with an approach that is similar to the study of Deraco *et al* (Table 3).

All these phase 2 observational studies include patients where in most cases a great surgical effort has been made and the chemosensibility state was not known: in only 107 cases (36.3%) the patients had undergone NACT to test *in-vivo* chemosensitivity before CRS and HIPEC.

The idea of proposing NACT in patients with very advanced EOC and performing ICRS associated to HIPEC, like in our study, could have various advantages. First, NACT can select "*in vivo*" chemosensitive patients, thus making possible to offer the HIPEC procedure only to those patients that are highly responsive to the chemotherapeutic molecules. Second, NACT reduces the surgical load and consequently surgery obtains no residual tumor in the vast majority of this set of patients. Third, the less radical surgery required is associated to lesser perioperative complications, permitting shorter recovery to start with postoperative chemotherapy. And last, this strategy could be offered to an high proportion of women with advanced EOC[13,52].

In our study, 6 out of 15 women (40%) showed cDP after NACT: this percentage of non-responders to NACT is low compared to those of previous studies including EORTC trial[13]. Anyway, we should consider that the decision to adopt the RECIST criteria in our study was made to clearly select highly responsive patients. In fact, after CRS all women were CC0.

If we consider the EORTC study, 295 out of 334 women were submitted to CRS after NACT, and residual tumor < 1 cm was achieved in 80.6% of 295 women: this means that 97 out of 334 women assigned to NACT (30%) were non-responders. Moreover, it is reasonable to think that if a residual tumor < 2.5 mm (CC1) or no residual

tumor (CC0) was used in the EORTC trial to define optimal cytoreduction after CRS, a higher percentage of non-responders to NACT could have been found.

Although according to the results of our study, NACT could offer the opportunity to reduce the surgical load needed to achieve optimal cytoreduction and make possible to perform CRS and HIPEC with only minor complications and no postoperative mortality, many scientists agree that RCTs are needed to confirm the potential advantages of HIPEC associated to CRS in all time points of the natural history of advanced EOC, but especially in upfront setting[53-55]. Only RCTs will clarify the role of CRS and HIPEC in advanced EOC, as already has been done for colon and gastric cancer[56,57].

To our knowledge, regarding the use of CRS and HIPEC in advanced EOC, at least four RCTs are ongoing. The first study is a Korean RCT including primary and recurrent EOC[58]. Two different RCTs have been proposed by St George Hospital in Sydney (Australia), to test HIPEC in primary and recurrent EOC[59]. A third multicentric RCT (CHIPOR trial), testing HIPEC in recurrent EOC, has been planned by French surgeons[60]. The fourth RCT, conceived by the Netherlands Cancer Institute (OVHIPEC trial), evaluates the efficacy of secondary cytoreduction, with or without HIPEC, in patients with advanced EOC, eligible for interval debulking surgery either following primary chemotherapy or following incomplete primary debulking and chemotherapy. The experimental group undergoes interval debulking with HIPEC (CDDP 100 mg/m^2) at the end of CRS, while the control group is treated only with interval debulking surgery[61].

Similarly to the last described RCT, where HIPEC is used in upfront setting after primary chemotherapy, our groups have recently proposed the transformation of our above mentioned pilot study (following its philosophy) in a RCT called CHORINE Study (Cytoreduction and Hipec in the treatment of OvaRIaN cancEr). This study project is a multicentre phase 3 prospective RCT, comparing CRS and HIPEC (CDDP+PTX) *vs* CRS alone in stage ⅢC unresectable EOC with partial or complete response after 3 systemic cycles of CBCDA + PTX (NACT), followed by further 3 cycles of CBCDA + PTX (SACT). The choice to add PTX to CDDP in the HIPEC perfusate takes count of the negligible toxicity observed in our pilot study and the efficacy of PTX reported in the literature, where a significant increase in survival is observed when heated intraperitoneal PTX is administered after CRS[62-67]. In the CHORINE study the primary outcome is 2-year disease-free survival.

Only patients with complete or cPR after the 3 cycles of NACT will be eligible for the study and, after signing the informed consent form, will be submitted to CRS with radical intent. The randomization (HIPEC *vs* no HIPEC) will be applied during the surgical procedure after adequate CRS (residual tumor ≤ 2.5 mm): patients with suboptimal cytoreduction (residual tumor > 2.5 mm) are considered not suitable for randomization and will be excluded.

The drug schedule elected in the CHORINE study is CDDP 100 mg/m^2 of body surface area and PTX 175 mg/m^2 of body surface area with an intraperitoneal infusion time length of 90 min.

A sample size of 47 patients for each group has been calculated to reach a confidence level of 95% with a power of 80%, considering a 45% and 75% disease-free survival at 2 years of follow-up in non-HIPEC and HIPEC group respectively.

On the one hand the advantages of CHORINE study are the following: (1) NACT selects for inclusion in the study only patients in whom there is a clinical response (test of *in-vivo* chemosensitivity) and then a response to HIPEC is expected; (2) response to NACT should make the cytoreductive effort less demanding, increasing the occurrence of complete CRS and presumably lowering the morbidity; and (3) HIPEC is the only variable between groups in the study, making it possible to evaluate its effectiveness regardless of CRS, because a radical and complete cytoreduction is required either in the experimental arm than in the control group (as requested by many authors in the literature[53]).

On the other hand, the major limitation of the study is that the control group is not the recognized standard treatment for advanced EOC, namely maximal CRS followed by platinum-based SACT.

The CHORINE study has been approved by our review board and we are in the process to complete the administrative requirements and recruiting the other participating centers.

In conclusion, our pilot study supports the feasibility of NACT followed by CRS and HIPEC for upfront treatment of advanced EOC. This combined therapy does not reduce the possibility to start the post-operative systemic chemotherapy in an acceptable period of time. We believe that in the upfront setting NACT can better select chemoresponsive patients, reducing thus the surgical stress and the perioperative complications.

Based on the results of this pilot study, our proposed phase 3 trial (the CHORINE study) will clarify the relative benefits of HIPEC, that have been though to support the course of action of CRS by targeting microscopic residual tumoral intraperitoneal disease in advanced EOC.

COMMENTS

Background

Ovarian cancer is the third commonest gynecological neoplasm and accounts for 5% of all female cancer deaths. Epithelial ovarian cancer (EOC) accounts for more than 70% of all ovarian cancers. Primary cytoreductive surgery (CRS) followed by platinum-based systemic adjuvant chemotherapy (SACT), when indicated, is the mainstay of treatment: unfortunately, the achievement of optimal cytoreduction (residual tumor less than 1-2 cm), mainly in advanced EOC, is not always possible. To help achieving complete resection rate, the concept of neoadjuvant chemotherapy (NACT) followed by interval CRS has been developed for patients deemed to have unresectable disease (stage ⅢC/Ⅳ EOC). A number of prospective phase 2 studies and retrospective institutional experiences have shown the feasibility of employing hyperthermic intraperitoneal chemotherapy (HIPEC) when complete macroscopic cytoreduction is achieved; however a few concerns still exist. For these reasons the authors performed a bi-centric prospective observational pilot study combining NACT with carbo-

platin (CBCDA) and paclitaxel (PTX) to CRS and HIPEC with cisplatin (CDDP) and PTX in upfront treatment of advanced EOC. The aim of this study was to evaluate the feasibility of CRS and HIPEC in patients with stage ⅢC/Ⅳ EOC, who showed partial or complete response after NACT, in terms of percentage of complete cytoreduction (residual disease < 2.5 mm), toxicity, postoperative complications, postoperative mortality, and time elapsed till the start of systemic chemotherapy (time to chemotherapy, TTC).

Research frontiers

Based on the results of this pilot study, the authors developed the CHORINE study protocol (www.chorine.org), a multicentre phase 3 prospective RCT, comparing CRS and HIPEC (CDDP + PTX) *vs* CRS alone in stage ⅢC unresectable EOC with partial or complete response after 3 systemic cycles of CBCDA+PTX (NACT), followed by further 3 cycles of CBCDA + PTX (SACT). Only RCTs will clarify the role of CRS and HIPEC in advanced EOC, as already has been done for colon and gastric cancer.

Innovations and breakthroughs

The cornerstones of developing the CHORINE study protocol are the following: (1) NACT selects for inclusion in the study only patients in whom there is a clinical response (test of *in-vivo* chemosensitivity) and then a response to HIPEC is expected; (2) response to NACT should make the cytoreductive effort less demanding, increasing the occurrence of complete CRS and presumably lowering the morbidity; and (3) HIPEC is the only variable between groups in the study, making it possible to evaluate its effectiveness regardless of CRS, because a radical and complete cytoreduction is required either in the experimental arm than in the control group (as requested by many authors in the literature).

Applications

The study results suggest that NACT followed by CRS and HIPEC is a feasible strategy for upfront treatment of advanced EOC.

Terminology

CRS: the aim of surgery for advanced EOC is to remove as much tumor as possible, since the amount of residual tumor is one of the most important prognostic factors for survival. HIPEC: during its natural history, EOC tends to be chemosensitive and to confine itself to the surface of the peritoneal cavity for a long period of time. These features make it an obvious target for intraperitoneal chemotherapy (IPCT), which is given by infusion of the chemotherapeutic agents directly into the peritoneal cavity. This may increase the anticancer effect with fewer systemic adverse effects in comparison to intravenous therapy. To optimize drug distribution, IPCT has also been applied intraoperatively, immediately after CRS. An advantage of intraoperative use is that IPCT can be administered even under hyperthermic conditions, which are poorly tolerated by a patient who is awake. Hyperthermia is directly cytotoxic and enhances the efficacy and penetration depth of many drugs, while the mild locoregional hyperthermia that is used has no significant adverse effects.

Peer review

The authors presented preliminary results from a pilot study evaluating the feasibility and safety of HIPEC after NACT and CRS in 9 patients with advanced ovarian cancer. They showed that this strategy was feasible and safe and had acceptable TTC. The topic of HIPEC after CRS for advanced ovarian cancer is interesting and worth being evaluated in a large-scale clinical study.

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BRIEF ARTICLE

Surgical repair of pelvic organ prolapse and follow-up: An institutional multi-center experience

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Abstract

AIM: To investigate the effects of the Elevate Anterior and Posterior transvaginal mesh procedure on 30 patients affected by pelvic organ prolapse (POP) at 12 mo follow-up.

METHODS: Between September 2011 and September 2012, a prospective multicenter observational study enrolled 30 consecutive patients with POP-Q ⩾ stage Ⅱ. After a preoperative evaluation, patients underwent prolapse repair utilizing the Elevate Anterior and Posterior Prolapse Repair System (American Medical Systems, Minnetonka, MN, United States). Operative technique was standardized and performed by the same surgical team under spinal or general anesthesia. Patients were evaluated postoperatively at 1, 3, 6 and 12 mo.

RESULTS: All 30 patients completed the 12 mo follow-up. The mean age was 65.3 years (range 49-81 years) and average hospital stay was 4.5 d. The mean operative time was 65 min (range 40-120 min). Related adverse events reported were mesh extrusions (6.7%) and post void residual urine volume (13.3%). There were no visceral injuries, no infection of the mesh, and no symptoms of recurrent prolapse. All quality-of-life scores significantly improved from baseline.

CONCLUSION: One year's follow-up of our 30 patients confirms the safety and the efficacy of the Elevate Anterior and Posterior transvaginal mesh procedure for POP treatment. Our final results are comforting but longer term follow-up is ongoing.

Key words: Pelvic organ prolapse; Pelvic organ prolapse; Mesh; Vaginal mesh erosion

Core tip: Our initial results show that the vaginal repair of anterior/apical and posterior wall prolapse utilizing a wall mesh placed *via* the Elevate system is an effective, safe and minimally invasive procedure for the treatment pelvic organ prolapse and shows excellent anatomical and functional results. Recent studies of the anatomical and physiological pelvic floor characteristics favored new generation prosthetic surgical techniques with advanced tools and biocompatible mesh in order to allow lower recurrence rates. Our final results are interesting and comforting but longer term follow-up is ongoing.

Gustapane S, Leombroni M, Falò E, Santarelli A, Frondaroli F, Liberati M, Perrone E, Tinelli A. Surgical repair of pelvic organ prolapse and follow-up: An institutional multi-center experience. *World J Obstet Gynecol* 2013; 2(4): 176-180 Available from: URL: http://www.wjgnet.com/2218-6220/full/v2/i4/176.htm DOI: http://dx.doi.org/10.5317/wjog.v2.i4.176

INTRODUCTION

Pelvic organ prolapse (POP), including anterior and/or posterior vaginal prolapse, uterine prolapse and enterocele, is a common group of clinical conditions affecting millions of women worldwide[1,2]. Data from the Women's Health Initiative revealed anterior POP in 34.3%, posterior wall prolapse in 18.6%, and uterine prolapse in 14.3% of women[3].

There are approximately 250000 procedures annually in the United States for POP, with a prevalence of 11.1%[1]. POP includes a range of disorders, from asymptomatic disturbed vaginal anatomy to complete vaginal eversion associated with considerable degrees of urinary, defecatory and sexual dysfunction. The pathophysiology of prolapse is multifactorial, including neuromuscular dysfunction and fascial defects in the integrity of the uterosacral-cardinal complex[4]; however, genetically susceptible women more exposed to life events results in the development of a clinically significant prolapse.

Main risk factors are age, obstetric history[5], obesity[6], chronic lung and intestinal disease, history of hysterectomy[7], history of previous prolapse operations, and race[8]. Estrogens have a protective role[9,10] and so menopausal women are mainly involved. The support mechanisms reduction predisposes the herniation of the pelvic organs in the vaginal canal[11], causing several symptoms related to the severity of the prolapse. The most reliable symptom is "to see or to feel a budge in the vagina"[12,13]. The evaluation of women with a prolapse requires a comprehensive approach, focusing on the function in all pelvic compartments based on a detailed patient history, physical examination and investigations.

Detailed *presurgical evaluation* is required to select the *most appropriate treatment* from a variety of medical and *surgical* options[14]. Non-surgical therapy of POP is considered in women with a mild to moderate prolapse, those who desire preservation of future childbearing, those in whom surgery may not be an option, or those who do not desire surgical intervention, and includes conservative behavioral management and the use of mechanical devices. Surgical therapy of POP includes vaginal, abdominal and laparoscopic approaches, or a combination of these approaches, with the aim to relieve or improve symptoms and restore normal vaginal anatomy.

The aim of our study is to assess the efficacy, safety and tolerability of the Elevate Anterior and Posterior transvaginal mesh procedure on 30 patients affected by POP repair at the 12 mo follow-up.

MATERIALS AND METHODS

This study is a prospective multicenter observational experience of 30 consecutive women with symptomatic stage 2 or greater of prolapse that underwent anterior and/or posterior repair using the Anterior and Posterior Prolapse Repair System (American Medical Systems, Minnetonka, MN, United States).

Table 1 Anamnestic data and classification of the patients according to pelvic organ prolapse quantification system

Age (yr)	65.3 ± 8.2 (range 49-81)
Previous hysterectomy	2 (6.7)
Menopausal	28 (93.3)
Pre-menopausal	2 (6.7)
Parity	2.3 ± 0.9 (range 0-4)
Pelvic organ prolapse's stage	
Ⅱ	7 (23.3)
Ⅲ	20 (66.6)
Ⅳ	3 (10)

Data are expressed as absolute *n* (%) or mean ± SD.

Comprehensive preoperative urogynecological exams were completed, including an evaluation of anamnestic data, obstetric history, BMI and chronic disease, a pelvic exam with prolapse quantification utilizing the Half Way System or Baden-Walker scales[15,16], and a ultrasound evaluation. Inclusion criteria were patients with symptomatic anterior or posterior compartment prolapse ≥ stage 2. Our patients received the Anterior and Posterior Elevate surgical procedure, with a consecutive 1 year follow-up at our center.

Operative technique was standardized and the surgery was performed by an expert surgical team under spinal or general anesthesia, according to anesthetist decision and patient's preference. The procedure began with injection of 40-60 cc of hydrodissection solution (25 cc of 1% lidocaine with epinephrine 1:200000 diluted in 250 cc of saline) into the anterior vaginal wall. A 3 to 4 cm vertical incision is then made in the anterior vaginal wall with a full-thickness hydrodissection. Elevate Anterior and Apical utilizes self-fixating tips that allow safe, simple and precise mesh placement in the sacrospinous ligament and the obturator internus muscle. In the Elevate Posterior procedure, the apical mesh arms are anchored to the sacrospinous ligaments and the distant portion of the graft was trimmed at the discretion of surgeon to fit vaginal length attached to the perineal body and rectovaginal septa bilaterally. A prophylactic antibiotic (ceftriaxone 2 g + metronidazole 500 mg) was administered. Subjects were evaluated postoperatively at 1, 3, 6 and 12 mo.

Statistical analysis

The analyzed data were collected and evaluated by an external statistician independent reviewer. Descriptive statistical analysis was performed with continuous variables, summarized using mean ± SD or median, and discrete variables were reported using numbers and percentages.

RESULTS

The mean age of the 30 patients was 65.3 years (range 49-81 years) and their mean parity was two deliveries (range 0-4). The demographic characteristics are summarized in Table 1. Of the 30 patients, 7 (23.3%) had stage Ⅱ prolapse, 20 (66.6%) stage Ⅲ and 3 (10%) had stage Ⅳ

on pre-operative pelvic examination. Two patients (6.7%) had a previous hysterectomy. No patients had a history of previous anterior or posterior vaginal wall repair. Fourteen patients (46.7%) had urinary problems, in particular urinary retention with a preoperative post void residual volume. Twenty-four (80%) patients underwent prolapse repair with Anterior and Apical Prolapse Repair ± Posterior Prolapse Repair System.

Concurrent colpohysterectomy was performed in 6 (20%) patients. There were no major intraoperative complications and the mean duration of operations was 65 min (range 40-120 min). There were no post-operative bleeds or hematomas and the mean postoperative body temperature was 37.1 ± 0.5 ℃.

The average hospital stay was 4.5 ± 1.38 d and the Foley catheter was removed after 72 h. All 30 patients completed the 12 mo follow-up. During follow-up, no patients had symptoms of recurrent prolapse or urinary problems. Four patients (13.3%) had a minimal asymptomatic post void residual urine volume. Two patients (6.7%) had partial mesh erosion; these women were treated with local application of 1 g of vaginal Promestriene (Colpotrophine, TEVA, Milan, Italy) twice a day for 1 mo.

After this therapy, patients returned to the surgery room for partial mesh excision, then the edges of the vaginal epithelium were trimmed where appropriate and re-approximated, with good results in their follow up. No mesh had to be removed secondary to allergic reaction or infections.

DISCUSSION

Over the years, numerous surgical techniques were used in the management of POP but few controlled studies were designed to assess the complexity, costs and long-term efficacy of individual procedures[17].

Surgical mesh has been used since the 1950s to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP and in the 1990s, gynecologists began using surgical mesh for surgical treatment of stress urinary incontinence and transvaginal POP repair. Over the next few years, surgical mesh products for transvaginal POP repair became incorporated into "kits" that included tools to aid in the delivery and insertion of the mesh. Surgical mesh kits continue to evolve, adding new insertion tools, tissue fixation anchors, surgical techniques and absorbable and biological materials.

Recent studies of the anatomical and physiological pelvic floor characteristics[18] favored new generation prosthetic surgical techniques. These involve the use of advanced tools and biocompatible mesh and allow better results and lower recurrence rates. As the implementation of synthetic materials in POP surgery has increased, so has the reporting of complications.

From 2008 to 2010, the most frequent complications reported to the Food and Drug Administration (FDA) from the use of surgical mesh devices for POP repair included vaginal mesh erosion (also called exposure, extrusion or protrusion), pain (dyspareunia), infection, urinary problems, bleeding and organ perforation. There were also reports of recurrent prolapse, neuro-muscular problems, vaginal scarring and shrinkage, and emotional problems. Based on evaluation of adverse event reports and assessment of the scientific literature, the FDA has not seen conclusive evidence that using transvaginally placed mesh in POP repair improves clinical outcomes any more than traditional POP repair that does not use mesh, and it may expose patients to a greater risk, as mesh erosion or extrusion.

For instance, when minor mesh erosion or extrusion occurs, observant management alone or the use of topical estrogens cream particularly in asymptomatic women are viable options. More commonly, the excision of exposed mesh with re-approximation of the vaginal defect is performed. However, in severe cases such as infection, complete or total excision of the mesh is required[19].

While the literature suggests an anatomical benefit to anterior repair with mesh augmentation, this anatomical benefit may not result in superior clinical outcomes and the associated risk of adverse events should be considered. Based on these findings, the FDA is considering regulatory changes that may improve our understanding of the safety and effectiveness of these devices and has specific recommendations for patients and healthcare providers[20].

Our surgical treatment utilizing the Elevate Anterior and Posterior Prolapse Repair System showed excellent anatomical and functional results and an objective cure rate of 100% within 12 mo. Subjectively, no patients complained of symptomatic prolapse (100% subjective cure rate) and no patients had urinary symptoms during follow-up.

Olsen *et al*[1] described as many as 29% of women treated with traditional surgical techniques having to undergo repeat surgery. Traditional anterior and posterior compartment repair utilizing the patient's own tissue is a compensatory procedure that utilizes weakened and/or damaged tissue and has reported failure rates in the range of 40%-60%[21]. Additionally, techniques like plication or colporrhaphy do not provide any apical support, which may also contribute to the failure rates seen with this type of repair[22].

Compared to other techniques utilizing synthetic mesh, Moore *et al*[22] believe the Anterior Elevate procedure to be less invasive and a more simplified technique for placing a wall graft.

Our mesh erosion rate (6.7%) was similar with the literature data; Stanford *et al*[23] reported a 5.6% of erosion rate in a 12 mo multicenter study on 142 patients at ICS 2011.

In our practice, the demand for uterine preservation during surgical management of uterovaginal prolapse is increasing. However, the current data of medical literature on this clinical problem are inadequate to assist a surgeon in determining which patients are ideal for uterine preservation[24].

At present, the decision is usually influenced by the patient's preferences, the surgeon's experiences[24] and the presence of uterine or cervical pathology. The current study is limited by its medium term follow-up.

In conclusion, although limited by its short follow-up period, our initial results show that the vaginal repair of anterior/apical and posterior wall prolapse utilizing a wall mesh placed *via* the Elevate system is an effective, safe and minimally invasive procedure for the treatment POP. It allows restoration of the vaginal length without compromising its caliber.

We find our research needs more study for determining the ideal utilized material and the optimal way to place and attach the graft vaginally. However, it can be expected that improvements in technology and techniques will continue. We recommend further prospective studies with longer term follow-up to delineate more deeply the Elevate Anterior and Posterior Prolapse Repair System role in clinical practice.

COMMENTS

Background

Pelvic organ prolapse (POP), including anterior and/or posterior vaginal prolapse, uterine prolapse and enterocele, is a common group of clinical conditions affecting millions of women worldwide. Over the years, numerous surgical techniques were used in the management of POP.

Research frontiers

Further prospective studies are needed to delineate more deeply the Elevate Anterior and Posterior Prolapse Repair System role in clinical practice, with longer term follow-up.

Innovations and breakthroughs

The authors' surgical treatment utilizing the Elevate Anterior and Posterior Prolapse Repair System showed excellent anatomical and functional results and an objective cure rate of 100% within 12 mo. Subjectively, no patients complained of symptomatic prolapse (100% subjective cure rate) and no patients had urinary symptoms during follow-up.

Applications

The initial results show that the vaginal repair of anterior/apical and posterior wall prolapse utilizing a wall mesh placed *via* the Elevate system is an effective, safe and minimally invasive procedure for the treatment POP and showed excellent anatomical and functional results. Recent studies of the anatomical and physiological pelvic floor characteristics favored new generation prosthetic surgical techniques with advanced tools and biocompatible mesh in order to allow better results and lower recurrence rates.

Terminology

POP, including anterior and/or posterior vaginal prolapse, uterine prolapse and enterocele, is a common group of clinical conditions affecting millions of women worldwide, with a prevalence of 11.1%. POP includes a range of disorders, from asymptomatic disturbed vaginal anatomy to complete vaginal eversion associated with considerable degrees of urinary, defecatory and sexual dysfunction. The pathophysiology of prolapse is multifactorial and the main risk factors are age, obstetrics history, obesity, chronic lung and intestinal disease, history of hysterectomy, history of previous prolapse operations, and race. Estrogens have a protective role and so menopausal women are mainly involved.

Peer review

The authors present a prospective multicenter observational study of 30 consecutive female patients with symptomatic stage 2 or greater of prolapse that underwent anterior and/or posterior repair using a new minimally invasive technique with a single vaginal incision. Overall, the results of the study are interesting and clinically relevant. The study design appears clear and straightforward, the statistics are basic, the results are interesting and clinically relevant, and the background review of the literature sufficient and supportive of the specific aims and results.

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BRIEF ARTICLE

Characteristics of semen parameters of Malawian men from couples seeking assisted reproduction

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Abstract

AIM: To profile semen parameters of Malawian men seeking fertility testing.

METHODS: Semen analysis is a key element in the fertility evaluation of men and permits male reproductive potential to be evaluated. Semen samples were collected from consenting men after 3-5 d of sexual abstinence. The samples were collected from 130 males; 78 were male partners of infertile couples while 52 were healthy semen donors. Seminal volume, motility and morphology were assessed. The results were analyzed on Prism 5. All data are expressed as mean ± SD. Student's *t*-test was used for statistical analysis. Differences were regarded as statistically significant if $P < 0.05$.

RESULTS: Semen volume, sperm concentration, progressive motility and normal morphology were significantly higher in the control group when compared to the participant group. On the other hand, no statistically significant difference was found between the control group total sperm motility when compared to the participant group. Oligozoospermia was found in 25 cases, teratozoospermia detected in 17 cases and abnormal seminal plasma in 16 cases. Asthenozoospermia and azoospermia were found in 12 and 8 participants, respectively. This study has shown that most of the infertile patients seeking fertility testing had oligozoospermia. Teratozoospermia was the second most common abnormality found in the patients seeking fertility testing.

CONCLUSION: Our study is in agreement with previous studies which reported that these parameters have been shown to be good predictors for fertilization.

Key words: Infertility; Human spermatozoa; Assisted reproduction; Semen analysis

Core tip: In recent years there has been an increase in infertility and some of the causes are due to male factors. Even although some causes of male infertility can be established, others are idiopathic. It has therefore become imperative to investigate infertility patterns in different countries. This paper reports the common causes of male infertility in Malawian men seeking fertility testing.

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INTRODUCTION

Infertility is defined as the inability to conceive after at least 1 year of unprotected intercourse. It affects about 8%-12% of all married couples[1]. In about one third of these couples, a male factor is the primary cause and in another one quarter, both the male and female partner

contribute to the infertility[1]. It is noteworthy that even today, recognizable causes of male infertility are present in only 40% of cases[2]. In the other 60%, infertility presented as an isolated abnormality in the semen analysis without diagnosable pathology[2]. This would explain why male infertility is generally regarded as a condition that is difficult to treat, especially in the low-cost settings of many developing countries where advanced methods of assisted reproductive techniques, such as intracytoplasmic sperm injection, are not available.

In developing countries, patterns of infertility are quite different from those in developed countries. That is to say, the incidence of preventable infertility is much higher in developing countries[3]. Recently, estimates of infertility in Malawi show a level of primary infertility or childlessness in women aged 20-44 years of 2%, as measured by the proportion of women who remained childless after at least 7 years of marriage[4]. However, secondary infertility or infertility subsequent to the birth of at least one child, was at 17%, ranging from a low 7% in women aged 20-24 years to 60% in women aged 40-44 years[5]. These figures put Malawi in the upper-middle range of infertility prevalence compared to other sub-Saharan African countries.

In African countries women carry the main burden of infertility since they are usually blamed for a couple's childlessness[6]. It has been reported that self-identified infertility in Malawi varied greatly by sex. None of the men who reported infertility was certain that they were the infertile partner, whereas 60% of the women were certain that they were the infertile one[5].

Semen analysis is a key element in the fertility evaluation of men and permits male reproductive potential to be evaluated in association with possible risk factors. However, semen samples are difficult to obtain in general population studies and the participation rate which is usually less than 20% may invalidate conclusions when extrapolated to the general population[7]. Studies of populations in which men are seeking infertility treatment avoid this problem because semen analysis is a key part of their fertility evaluation. Therefore, the aim of this study was to profile semen parameters of Malawian men seeking fertility testing.

MATERIALS AND METHODS

Study area, setting and subjects

The study was carried out at the College of Medicine Andrology Laboratory in Blantyre, Malawi, the first andrology laboratory in Malawi. The study sample consisted of 130 males. Seventy-eight were male partners of infertile couples who had infertility for more than 1 year and who sought their first infertility evaluation between January 2010 and December 2011, while 52 were healthy semen donors of proven fertility. Approval for this study was obtained from the Institutional Review Board. All men enrolled in this study gave written consent after the procedures had been described to them.

Table 1 Different possible causes of infertility in the participant group *n* (%)

Group	Semen analysis	Data
Participants (n = 78)	Azoospermia[1]	8 (10.3)
	Oligozoospermia[2]	25 (32.0)
	Asthenozoospermia[3]	12 (15.4)
	Abnormal seminal plasma[4]	16 (20.5)
	Teratoozoospermia[5]	17 (21.8)
Controls (n = 52)	Normal semen	52 (100.0)

[1]Total absence of sperm in the semen; [2]Sperm concentration of < 20×10^6/mL; [3]< 50% spermatozoa with forward progression; [4]Seminal volume less than 2.0 mL or abnormal physical characteristics of semen with normal spermatozoa; [5]Reduced percentage (< 14%) of morphologically normal spermatozoa.

Semen collection and analysis

Two semen analyses of not less than fourteen and not more than 90 d apart were routinely undertaken. Semen samples were obtained by masturbation in a room next to the laboratory after 3-5 d of sexual abstinence. Semen assessment was performed as soon as the samples were liquefied but within 1 h from collection according to the routine method described by the World Health Organization[8]. Seminal volume was measured in a graduated pipette accurate to within 0.1 mL. Sperm concentration was determined by a hemocytometer (improved Neubauer counting chamber) after an appropriate dilution. Sperm motility and progressive motility were assessed by direct observation under a microscope (× 400). Smears were made on clean slides and air dried, after which they were stained with hemacolor (Merck, Darmstadt, Germany). Morphology was analyzed by oil immersion light microscopy according to the Tygerberg strict criteria[9].

Statistical analysis

Data are expressed as mean ± SD and the level of significance for comparison set at $P < 0.05$. Comparisons between the two groups were made using the χ^2 test for categorized independent variables and the t-test for continuous independent variables.

RESULTS

Characteristics of the population

The general characteristics of the men seeking fertility testing and health semen donors enrolled in this study are as follows. The mean age for infertile men was 34 ± 0.3 *vs* 33 ± 0.4 for the normal fertile donors ($P > 0.05$). There was no statistically significant difference between the groups in age. The number of years they had been married did not statistically differ between the two groups ($P > 0.05$).

Semen analysis

Table 1 shows the different possible causes of infertility in the patients seeking fertility testing. The most commonly detected abnormality was oligozoospermia, which was found in 25 cases (32%). In the remaining cases,

Table 2 Different semen parameters

	Controls	Participants	*P* value
Volume (mL)	3.52 ± 0.17	1.8 ± 0.23	< 0.05
Concentration (10^6/mL)	56.89 ± 4.34	34.21 ± 6.45	< 0.05
Total motility (%)	82.56 ± 4.32	76.45 ± 8.95	> 0.05
Progressive motility (%)	59.92 ± 3.54	44.34 ± 4.56	< 0.05
Normal morphology (%)	19.12 ± 2.45	7.35 ± 4.45	< 0.05

teratozoospermia was detected in 17 (21.8%) cases and abnormal seminal plasma in 16 (20.5%) cases. Asthenozoospermia and azoospermia were found in 12 (15.4%) and 8 (10.3%) patients, respectively.

Table 2 shows the different semen parameters of the participants seeking fertility testing compared to the controls. Semen volume, sperm concentration, progressive motility and normal morphology were significantly higher in the control group when compared to the participant group ($P < 0.05$). On the other hand, no statistically significant difference was found between the control group total sperm motility when compared to the participant group ($P > 0.05$).

DISCUSSION

This study has shown that most of the infertile participants seeking fertility testing had oligozoospermia (sperm concentration of $< 20 \times 10^6$/mL). In recent years there have been reports of declining sperm concentration in men around the world[10,11]. With assisted reproduction, participants with severe oligozoospermia can still do well in terms of fertilization and pregnancy outcome if enough sperm can be obtained with separation techniques. Kruger *et al*[12] reported that no impact could be found on pregnancy outcome after assisted reproduction using the concentration/mL in the initial sample as a yard stick.

Teratozoospermia [reduced percentage (< 14%) of morphologically normal spermatozoa] was the second common abnormality found in the participants seeking fertility testing. In this study, the Tygerberg strict criteria were used to assess sperm morphology. Using this criterion it has been reported that participants with fewer than 14% normal morphological forms are found to have a decreased fertilization rate[13]. Morphological characteristics of spermatozoa have been reported to be the best predictor for fertilization[13,14].

The findings of our study indicate that oligozoospermia was the most prevalent abnormality in the semen of the infertile participants, followed by teratozoospermia (reduced percentage of morphologically normal spermatozoa). Our study is in agreement with previous studies which reported that these parameters have been shown to be good predictors for fertilization[13-15]. Apart from known factors that contribute to male infertility, idiopathic factors also contribute to infertility. A study in Poland trying to investigate the pattern of infertility reported that 16% of male infertility was due to idiopathic causes[16]. Thus, we speculate that the infertility of the participants who took part in this study was mainly due to oligozoospermia and teratozoospermia. This study involved only 78 participants seeking fertility testing. A larger sample size would probably produce more conclusive results. We recommend that studies should be carried out to establish infertility patterns in different countries. These studies should involve large sample sizes in order to come up with conclusive results that can be extrapolated to the general population.

COMMENTS

Background

In recent years there has been an increase in infertility and some of the causes are due to male factors. Even although some causes of male infertility can be established, others are idiopathic. It has therefore become imperative to investigate infertility patterns in different countries.

Research frontiers

Semen analysis is a key element in the fertility evaluation of men and permits male reproductive potential to be evaluated in association with possible risk factors. However, semen samples are difficult to obtain in general population studies and the participation rate which is usually less than 20% may invalidate conclusions when extrapolated to the general population.

Innovations and breakthroughs

This study has shown that most of the infertile patients seeking fertility testing had oligozoospermia. Teratozoospermia was the second most common abnormality found in the patients seeking fertility testing.

Applications

Studies of populations in which men are seeking infertility treatment avoid this problem because semen analysis is a key part of their fertility evaluation.

Peer review

It is a descriptive study that analyzes the semen of 78 male partners of infertile couples who had infertility for more than 1 year and the controls who were 52 healthy semen donors of proven fertility.

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BRIEF ARTICLE

Pelvic arterial embolization in obstetric hemorrhage

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Abstract

AIM: To analyze safety and efficacy of pelvic arterial embolization (PAE) in preventing and treating obstetrical hemorrhage.

METHODS: A consecutive study of eight cases undergoing pelvic artery embolization from January 2010 to October 2012 in Department of Obstetric and Gynecology of Maulana Azad Medical College for intractable obstetric hemorrhage was done. All embolization were carried out in cath lab of cardiology Department at associated GB Pant Hospital.

RESULTS: Clinical success was defined as arrest of bleeding after PAE without need for repeat PAE or additional surgery which was 75% in our series. PAE was successful in controlling obstetrical hemorrhage in all except one who had mortality. Other had hysterectomy due to secondary hemorrhage. Five resumed menstruation. None of the women intended to conceive, hence are practicing contraception.

CONCLUSION: PAE is minimally invasive procedure which should be offered early for hemostasis in intractable obstetrical haemorrhage unresponsive to uterotonic. It is a fertility sparing option with minor complications.

Key words: Pelvic artery embolization; Uterine artery embolization; Obstetric hemorrhage; Placenta accreta; Post partum hemorrhage

Core tip: Historically obstetric hysterectomy was definitive treatment in morbid adherent placenta, cervical ectopic pregnancy and post partum hemorrhage refractory to medical and conservative surgical measures. Emergence of Pelvic arterial embolization as a minimally invasive procedure had led to alternative use of use of embolizing agents in controlling significant hemorrhage in various etiologies of obstetric hemorrhage thereby conserving fertility and reducing maternal mortality and morbidity. We used P- particle and coil as embolizing material with 75% success in our series. Our study further strengthens our confidence in pelvic artery embolization for its applicability in managing obstetric hemorrhage.

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INTRODUCTION

Pelvic arterial embolization (PAE) mainly uterine (UAE) or internal iliac artery is minimally invasive angiographic procedure which is used prophylactically and therapeutically in controlling obstetric hemorrhage (OH). Major causes of obstetrical hemorrhage include post partum hemorrhage (PPH), abruptio

Table 1 Demographic characteristics

Cases	Indication	Age (yr)	Parity	Period of gestation	Previous sections
Case 1	Cervical ectopic	30	G6P3A2L2, 11 wk	12 wk	2
Case 2	Placenta percreta	28	G3P2L1	36 wk	1
Case 3	Placenta percreta	38	P3L3	28 wk	3
Case 4	Placenta accreta	30	G3P1L1A1	27 wk	1
Case 5	Placenta accreta	30	G3P1L1A1	36 wk + 5 d	1
Case 6	PPH (Atonic + traumatic)	30	G2P1L1	36 wk	-
Case 7	PPH (Atonic + traumatic)	30	PRIMI	36 wk	-
Case 8	PPH (Atonic + traumatic)	28	G3P2L1	40 wk	-

PPH: Post partum hemorrhage.

Table 2 Clinical characteristics

Cases	Shock	Comorbidity	Blood loss (mL)	Coagulopathy	Mode of Delivery
Case 1	-	-	1300	-	NA
Case 2	-	Anaemia	300	-	Classical cs
Case 3	+	Anaemia	1000	+	Classical cs
Case 4	+	Anaemia	1500	+	Classical cs
Case 5	-	Anaemia	500	-	Classical cs
Case 6	+	Anaemia, precipitate labor	1000	+	NVD
Case 7	+	Jaundice, anaemia	1500	+	NVD
Case 8	+	-	2500	+	Forceps

NVD: Normal vaginal delivery; NA: Not applicable.

placenta, ectopic pregnancy and incomplete abortion[1,2]. PPH has been managed by uterine massage, uterotonics and packing. In refractory cases uterine suturing, stepwise vascular ligation and finally hysterectomy has been employed[3]. Placenta accreta and cervical pregnancy have been dealt by hysterectomy in past which causes loss of reproductive potential. PAE has emerged as a safe and effective alternative to surgery in controlling obstetric hemorrhage[4]. Ever since its first use by Brown *et al*[5], many have reported high success rates of PAE in obstetrical hemorrhage[6-8]. The purpose of this study was to evaluate the efficacy and safety of PAE in treatment of obstetric hemorrhage and analyze its outcomes.

MATERIALS AND METHODS

A consecutive study of eight cases undergoing embolization from January 2010 to October 2012 in Department of Obstetric and Gynecology of Maulana Azad Medical College for obstetric hemorrhage was done. Study was approved by our institutional review board. Causes of hemorrhage, comorbidities, preembolization treatments, technique, outcome and complications of embolization were analyzed. All embolization were done in cath lab of cardiology Department at associated GB Pant Hospital.

Eight cases underwent embolization for obstetrical emergencies (Table 1). Initial assessment and resuscitation were carried at our obstetric unit. Hemodynamic status, comorbidities, and presence or absence of disseminated intravascular coagulopathy (DIC) were assessed. The shock was managed by administration of crystalloid or colloid and transfusion of specific blood units. Obstetric assessment included inspection of the vagina, cervix, and perineum for lacerations, hematomas and exploration of the uterine cavity for retained products. A multispecialty team including obstetric consultant, intensive care anesthetist and cardiologist decided the need for embolization after informed consent. The criteria for selection were active hemorrhage, deterioration of hemodynamic or clotting status despite treatment and high risk cases with anticipated hemorrhage. Angiography under C-arm was performed. Bilateral femoral approach using 5-French femoral arterial introducer was used. The internal iliac artery and uterine artery were catheterized *via* two puncture sites (one on each side). Angiography was performed to detect the site of bleeding from pelvic arteries. Highly selective angiography of uterine artery was attempted in four patients. Others had embolization of internal iliac artery (anterior branch) due to presence of severe uterine artery spasm not relieved by vasodilators. Coil embolization was done in all. Three had additional Polyvinyl Alcohol particle instillation. All except three patients were transferred to intensive care unit (ICU) or high dependency obstetric units for management after procedure.

RESULTS

Mean age was 30.5 years. Five patients had history of previous caesarean and abortions (Table 1). In five cases emergent embolization was done as all had massive hemorrhage following surgery or delivery despite conservative measures and developed coagulopathy (Table 2). Three

Table 3 Procedural characteristics

Cases	Type of embolization	Type	Additional treatment	Time from presentation to start of embolization	Embolic agent
Case 1	Uterine	Prophylactic	Methotrexate	4 h	Coil + PVA particle
Case 2	Uterine	Prophylactic	Methotrexate + uterotonic	3 h	Coil
Case 3	Uterine	Emergency	Methotrexate + uterotonic	1 h	Coil+PVA
Case 4	Internal iliac artery	Emergency	Methotrexate + uterotonic	1 h	Coil
Case 5	Uterine artery	Prophylactic	Methotrexate + uterotonic	30 min	Coil + PVA
Case 6	Internal iliac artery	Emergency	Uterotonic + cervical tear repair	2 h	Coil
Case 7	Internal iliac artery	Emergency	Uterotonic + cervical tear repair	22 h	Coil
Case 8	Internal iliac artery	Emergency	Uterotonic + cervical tear repair	26 h	Coil

PVA: Polyvinyl alcohol.

had Prophylactic embolization for cervical ectopic and after classical section for placenta accreta percreta (n = 2). Conservative measures were uterotonic, cervical and vaginal tear repair in delivered cases and classical section with leaving placenta *in situ* for placenta accreta.

All but one had primary hemorrhage. Secondary hemorrhage occurred on day forty post classical preterm section done for placenta percreta. Six patients were moderately anaemic. Five patients were build up to adequate levels by packed cell transfusion prior to labor or section. Other presented in shock due to secondary hemorrhage and had correction after emergent embolization. All adherent placentas were previa as diagnosed by Doppler ultrasound and supplemented by magnetic resonance imaging (MRI) in two cases. All underwent conservative surgical management with embolization. One had secondary hemorrhage post classical section which responded to primary embolization. Placenta resorbed in all.

Three cases underwent embolization for Atonic and traumatic PPH due to cervical tears unresponsive to uterotonic and repair (Table 3). Emergent CT revealed unilateral broad ligament hematoma in two. Both had massive blood loss following delivery. Traumatic PPH was initially controlled in first. Constant trickling reappeared after twenty hours, so underwent embolization while on ventilatory support. Bleeding stopped and hematoma resolved spontaneously. Second case underwent immediate embolization due to persistent bleeding despite repair, with success. Third case had massive PPH following forceps delivery and had cardiac arrest forty minutes later because of hemorrhagic shock and was on ventilatory support. Clinically pelvic hematoma was suspected as evident by uterine deviation and abdominal fullness. Poor general condition prevented immediate imaging and surgical intervention. Patient was shifted to ICU where bleeding continued and hematocrit continued to fall in spite of blood transfusion. Emergency CECT pelvis revealed left supra-levator pelvic hematoma of size 12 cm × 10 cm. Patient underwent embolization but had cardiac arrest and expired shortly. Arrest was not related to embolization. Five patients were in coagulopathy which was corrected in two prior to embolization. Three underwent emergent PAE in coagulopathy unresponsive to conservative measures and had ongoing correction during and after embolization with success.

Post embolization angiogram revealed arrest of bleeding in all patients (Figure 1). Transfusion was required in all patients. No major complications during or post embolization was noted. Minor complications were fever (n = 2), mild groin pain (n = 2) and correctable sepsis (Table 4). Initially, PAE was successful in controlling hemorrhage and partial resolution of cervical ectopic as evident by falling beta- HCG levels. Patient presented with secondary intractable hemorrhage on day twenty one and hysterectomy was undertaken as there was technical difficulty in shifting to cath lab.

Clinical success was defined as cessation of bleeding after PAE without need for repeat PAE or additional surgery. PAE was successful in controlling obstetrical hemorrhage in all except one who had mortality as this patient was severely hemodynamically compromised. One required hysterectomy due to secondary hemorrhage. Clinical success in our series was 75%. In six cases mean time was three hours and twenty four hours in two. Five resumed menstruation and two are at present lost to follow up. None of the women intended to conceive, hence are practicing contraception.

DISCUSSION

Obstetrical hemorrhage is a major cause of maternal morbidity and mortality worldwide. PPH is major contributor[1]. Primary PPH is defined as excessive bleeding from genital tract of 500 mL or more in first 24 h following delivery[4]. Management is centered on administration of uterotonic, uterine packing and conservative surgical vessel ligations. Internal-iliac-artery ligation may not be effective in controlling severe PPH in half of patients as blood flow in the distal vessel is decreased to 48% due to rich collateral network. Uterine artery ligation has 80% success in uterine atony, but is less effective in placenta accreta. Last resort is hysterectomy which causes significant morbidity and loss of reproductive potential. With advances in interventional radiology, PAE has emerged as an accepted option in refractory PPH[9]. Its advantage lies in its high success rates relative to ligation and hysterectomy[10].

Embolization was first used in 1972 to control arterial bleeding in pelvic fractures. First successful use of femo-

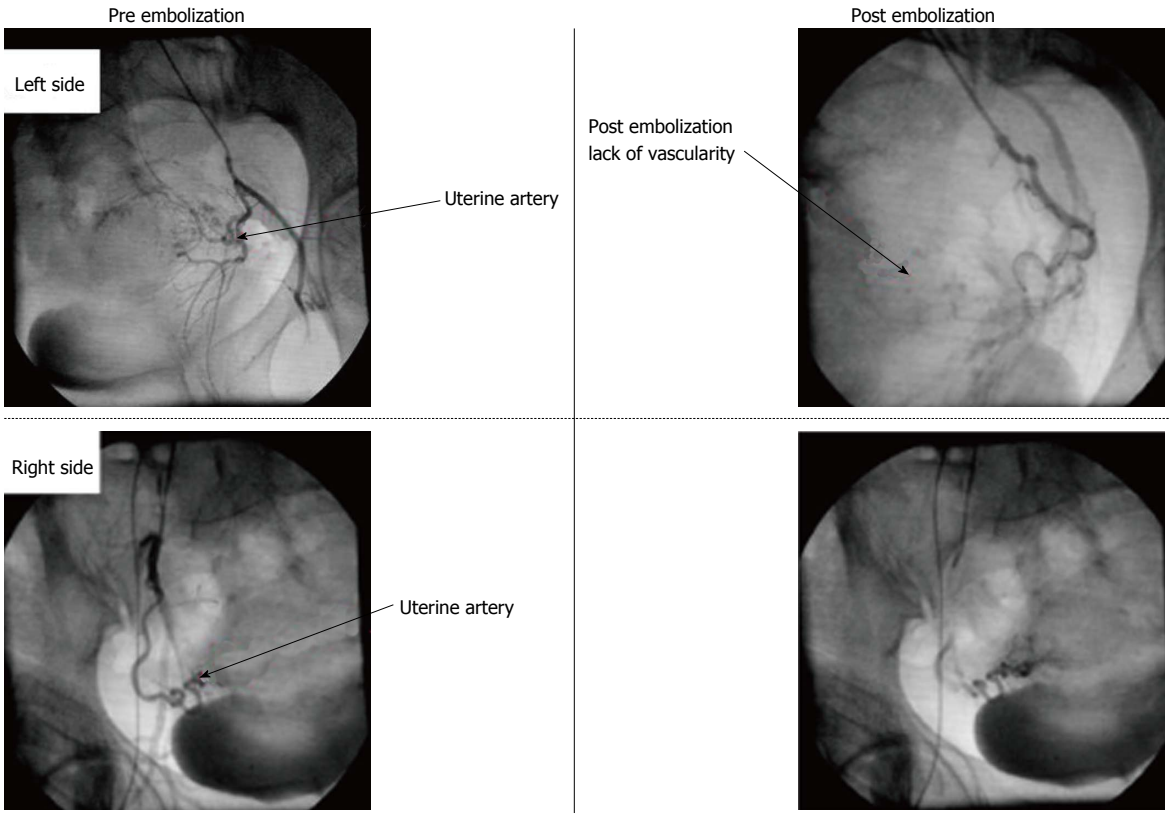

Figure 1 Pre and post embolization Angiogram showing arrest of flow through uterine arteries after selective uterine artery embolization.

Table 4 Outcomes

Cases	Hemorrhage controlled	Rebleeding after embolization	hysterectomy	Transfusion of blood and its products	Post embolization fever	Sepsis	Groin pain	Resumption of menstrual cycles	Mortality
Case 1	+	+	+	+	-	-	_	-	-
Case 2	+	-	-	+	+ (Non embolization)	+ (UTI)	+	+	-
Case 3	+	Mild, Hemostatics uterotonics	-	+	+	-	_	+	-
Case 4	+	+ Mild, Hemostatics uterotonics	-	+	-	-	_	-	-
Case 5	+	Mild, Hemostatics uterotonic	-	+	-	-	_	+	-
Case 6	+	-	-	+	+Non embolization cause	+ UTI, Puerperal Sepsis post exploration	+	+	-
Case 7	+	-	-	+	+	-	_	+	-
Case 8	Expired after embolization		Not applicable						+

UTI: Urinary tract infection.

ral transcatheter pelvic arterial embolization in PPH was described by Brown in 1979[5]. The reported success rate of UAE is over 90% to 100% in PPH due to atony[6,11]. Arterial embolization is performed at a more distal and specific location than vessel ligation which prevents bleeding through collaterals. Pelage *et al*[6] evaluated the efficacy and safety of selective arterial embolization in thirty-five women with intractable PPH. Hemostatic embolization of uterine arteries was performed in all including two cases which underwent hysterectomy. Bleeding stopped immediately. Two patients required repeat embolization. Delayed hysterectomy was undertaken in case of placenta accreta[6]. Lee *et al*[8] published largest retrospective single-center study in women who underwent PAE

for primary PPH in terms of efficacy and factors associated with failure of embolization procedure. Thirty-two patients had a clinical diagnosis of DIC. Overall bleeding control was achieved in 98.0% of the patients. Clinical success was 86.5%. Bleeding vessels, commonly bilateral uterine arteries as seen on angiography were embolized.

Embolization has a significant success in Secondary PPH. It is defined as excessive bleeding from the genital tract, with a blood loss of 500 mL or more, occurring after the first 24 h following delivery until the 6th-12th week of the puerperium. It affects 1%-3% of all deliveries[7]. Secondary PPH is managed with uterotonics and curettage. If bleeding persists vascular ligation or hysterectomy is required. Hence, transcatheter embolization of the uterine or pelvic arteries is an alternative in controlling secondary hemorrhage. Its first successful use was described by Pelage *et al*[7] in fourteen women unresponsive to uterotonic drugs or uterine curettage. We in one case of secondary hemorrhage in conservatively managed placenta percreta used UAE with success.

Angiographic embolization is effective in managing obstetric hemorrhage due to pelvic hematomas. It is difficult to identify bleeding vessel during exploration of hematoma due to friable genital tissues. Obstetrician must repair cervical and vaginal tears and correct coagulopathy prior to embolization to achieve therapeutic success[2,8]. But with ongoing hemorrhage and coagulopathy, emergent embolization can be used as it stems hemorrhage and causes hematoma resolution, facilitates uterine contractions releasing procoagulant factors into circulation[8]. Deux reported rapid improvement in clotting disorders and hemodynamic status after PAE[2]. Therapeutic success was 96%. Vascular spasms were dealt with injecting vasodilator thereby allowing selective catheterization[6,12].

Abnormal placentation is one of the etiological factors in intractable PPH. Placenta accreta is characterized by villi abnormally adherent to the myometrium due to the absence or defects in the normal decidual basalis and fibrinous Nitabuch layer[13,14]. Recently, rate of placenta accreta has increased in conjunction with the rate of cesarean deliveries at a frequency of 1 per 2500[15]. Placenta accreta has become leading cause of failed vessel ligation and peripartum hysterectomy[13,15]. Presence of placenta previa and prior cesarean delivery exponentially increases the risk. Antenatal diagnosis by doppler ultrasound or MRI allows either scheduled conservative management or hysterectomy thereby decreasing morbidity[15]. Management recommended is a cesarean-hysterectomy with placenta in situ in multiparous women not willing to conceive[16,17]. However hysterectomy is associated with significant morbidity like bladder and ureteric injury and renders woman sterile. Recent literature shows that leaving adherent placenta in utero followed by embolization avoids hysterectomy, maintains fertility with successful pregnancies in women desirous to conceive[18]. Leaving placenta in situ may result in infection and secondary PPH, which are dealt with appropriate antibiotics and repeat embolization. In a large multicenter study by Sentilhes *et al*[13] conservative methods were successful in avoiding hysterectomy in 78.4% of women, with a severe maternal morbidity rate of only 6%. In subsequent follow up of women contacted, 92% resumed menstruation. Eighty-eight point nine percent of women achieved successful pregnancy among who wished to conceive. Placenta accreta recurred in 28% of cases. They concluded conservative treatment for placenta accreta doesn' t compromise patients' subsequent fertility or obstetric outcome[17]. Prophylactic insertion of balloon catheters before cesarean section is effective method in controlling anticipated bleeding[19]. Embolization can be carried out without delay after uterine closure. We in two cases of adherent placenta carried prophylactic embolization immediately after classical section. It had less blood loss, surgery time and minimal complication. Methotrexate has been proposed as adjuvant treatment to hasten the postpartum involution of the uterus. No evidence currently supports its efficacy in conservative management of accreta. All our cases of adherent placenta received methotrexate with no complications. We believe conservative approach has less morbidity and preserves reproductive function and should remain first line management in adherent placenta.

Embolization is an emerging modality in conservative management of cervical ectopic. On reviewing literature PAE with methotrexate is effective in reducing the ectopic cervical mass. There is always a risk of haemorrhage which can be dealt with repeat PAE. Hysterectomy should be last resort if all conservative methods fail[20].

Clinical success of PAE for treatment of severe PPH lies in rapid transfer and timely decision for embolization. The time from decision for embolization to achievement of hemostasis should be in the order of 2-6 h[21].

Several prognostic factors are associated with clinical success of embolization. Shock, DIC, Massive blood transfusion, genital tears, caesarean delivery, and placenta accreta are poor prognostic factors in embolization in different case series[6,8,22]. Lee *et al*[8] showed that DIC and massive transfusion of more than ten red blood cell units were significantly related to clinical failure.

Abnormal placentation accounts for over half of the failures of UAE[6]. Failure is thought to be due to myometrial injury caused by difficult digital separation of the placenta. Massen performed juxta renal angiogram in UAE failures and occluded ovarian arteries in PPH[23]. PAE after a failed surgical procedure is not associated with unfavorable clinical outcome[24]. In our series embolization was successful in patients with hemodynamic shock, coagulopathy, abnormal placentation and prevented morbidity. PAE should be considered in hemodynamically unstable patients and in patients with coagulopathies but these patients require close monitoring in an ICU set up.

Embolization is associated with complications. Minor complications are pain, transient fever, mild transient numbness of the buttock, foot or thigh, hematoma formation at the site of common femoral artery puncture,

and pelvic infection[11,25]. Lee *et al*[8] reported asymptomatic dissection of the uterine artery and edema of the lower legs after PAE with no major complications. Complications from embolus migration to general blood circulation are very rare. Early intervention in form of confirmation of embolus by angiogram, anticoagulation and embolectomy can prevent loss of limb or its function[23]. Serious complications like uterine and bladder necrosis, delayed vesicovaginal fistula after PAE are reported[23,25]. Proper informed consent from patient must be taken before embolization.

The effects of PAE on menstruation and fertility are unclear. Successful pregnancies and resumption of menstruation have been reported unanimously in many case series studying long term effects of PAE[12,17,26-28]. Lee *et al*[8] reported resumption of regular menstruation in 97.3% of women after PAE. Sentilhes *et al*[12] analyzed sixty eight women who underwent embolization for PPH. 92% resumed menstruation. Those who desired pregnancy were able to conceive. Delotte in his review article included thirteen articles. Fertility follow-up of a total of one sixty eight women after PAE were analyzed. Clinical success of embolization was in 92%. Total forty five pregnancies were described of which thirty two cases resulted in live births[28]. Embolization doesn't seem to affect fertility and menstruation.

In conclusion, we present two failures and six successes in various etiologies of obstetric hemorrhage in our series. Correction of shock and DIC increases success but embolization should not be delayed while attempting to correct above. Embolization should be done in rebleeding. Non selective embolization of anterior branch of internal iliac artery can be attempted if there is technical difficulty in accessing uterine artery in vascular spasm. It has similar efficacy and has minimal complications. We believe planned embolization in case of morbid adherent placenta irrespective of parity leads to less morbidity and early recovery. Caesarean hysterectomy should be an alternative choice if embolization fails in morbid adherent placenta. Use of embolization as last resort is to be discouraged and should be early means of hemostasis in obstetric hemorrhage unresponsive to uterotonic.

Pelvic arterial embolization is minimally invasive procedure in modern obstetrics, which is a safe alternative to surgical methods in conditions causing intractable obstetrical hemorrhage and is a fertility sparing option with minor complications.

COMMENTS

Background

Uterine artery embolization in obstetrics was first described by Pelage *et al* in primary postpartum hemorrhage. Subsequently its use in obstetrics have been extended to embolization of pelvic arteries in management of primary and secondary post partum hemorrhage ,traumatic hemorrhage, placenta accreta and cervical ectopics thereby conserving fertility and reducing morbidity.

Research frontiers

Pelvic arterial embolization immediately stems hemorrhage arising from pelvic arteries and has emerged an effective hemostatic option in developing countries at tertiary level hospital. Research area is directed towards long term effects of embolization for which randomized control data is needed.

Innovations and breakthroughs

Authors' paper highlights the clinical success in managing cases with obstetric hemorrhage using embolization which otherwise might have needed hysterectomy. Its advantage lies in its high success rates relative to ligation and hysterectomy in controlling hemorrhage.

Applications

Pelvic arterial embolization (PAE) can be applied as minimally invasive choice in post partum hemorrhage refractory to medical measures, prior to classical section in placenta accreta and in live cervical ectopics. Hemodynamic instability should not be considered a contraindication for PAE.

Terminology

Pelvic arterial Embolization- embolization of internal iliac, uterine artery and its branches using polyvinyl alcohol particles or coil.

Peer review

This study was a case series to assess efficacy of PAE for varying etiologies of obstetric hemorrhage. It was a useful intervention option in hemorrhaging patients as it stemmed hemorrhage, reduced surgical morbidity, thereby conserving fertility in 75% of the patients.

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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