Intraoperative chemotherapy with cisplatin and epinephrine after cytoreductive surgery in patients with recurrent ovarian cancer: a phase I study

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Background **Intraperitoneal (i.p.) epinephrine was shown to increase the accumulation of i.p. cisplatin in tumours, and thus its antitumour effect in a model of peritoneal carcinomatosis in rats.**

Methods **To determine the tolerance to i.p. epinephrine with cisplatin, 18 patients with recurrent ovarian carcinoma were intraoperatively treated in this phase 1 study. After maximal cytoreductive surgery, the peritoneal cavity was filled twice for 1 h with 30 mg/l of cisplatin and increasing concentrations of epinephrine (0, 1, 2, 3 mg/l) in 3 l of saline solution at 37°C.**

Results **No deaths occurred. Three patients were treated at each of the 0, 1 and 2 mg/l epinephrine levels without adverse events. Two of the three patients who received 3 mg/l epinephrine experienced cardiac intolerance. Six additional patients received 2 mg/l of epinephrine without toxicity. A relationship between the serum concentration of epinephrine and occurrence of cardiac toxicity was established. A 60% decrease in serum area under the curve of platinum was calculated in patients receiving i.p. epinephrine compared with i.p. cisplatin alone. Renal toxicity from cisplatin was not increased by epinephrine. No haematological or neurological toxicity was recorded. The other grade 3–4 adverse events [thromboembolism (5), peritonitis (1), abdominal bleeding (1), bowel fistula (1)] occurred as often as usually reported for this heavy surgical procedure.**

Conclusion **The combination of i.p. epinephrine with cisplatin as intraoperative chemotherapy after optimal cytoreductive surgery is feasible. The recommended concentration for further studies is 2 mg/l for i.p. epinephrine. *Anti-Cancer Drugs* 21:320–325 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The peritoneal cavity is the main site of disease involvement in ovarian cancer [1]. Standard treatment includes surgery followed by intravenous (i.v.) platinum/taxane-based chemotherapy [2–5]. Postoperative intraperitoneal (i.p.) chemotherapy is an encouraging option [6–8]. The rationale for i.p. treatment is based on its ability to provide local high drug concentrations leading to an increased antitumour effect and limited systemic toxicity. However, it is often reported that postoperative i.p. chemotherapy distributes poorly in the peritoneal cavity owing to adhesion barriers and/or anatomic sanctuaries [9]. Moreover postoperative i.p. chemotherapy is hampered by frequent abdominal pain and catheter dysfunction [7]. Intraoperative i.p. chemotherapy has been proposed to overcome these problems. The clinical efficacy of i.p. chemotherapy is mainly observed in patients whose residual tumours are smaller than 5 mm in diameter after surgical debulking [6]. Most stage 3 ovarian cancers recur, often in the peritoneal cavity alone, despite complete initial surgery and adjuvant i.v. or i.p. chemotherapy. Secondary cytoreductive surgery has emerged as a salvage option for a subgroup of patients with recurrent ovarian cancer [10]. Meticulous resection of all macroscopic nodules during surgery is recommended. However, even in millimetric residual lesions, interstitial pressure and the rapid draining of drugs through the capillary network hamper drug penetration to deep inside the tumour [11].

We reported earlier that i.p. epinephrine lowered this functional barrier by decreasing tumour blood flow in a preclinical animal model [12–14]. Epinephrine increased platinum concentrations in peritoneal tumour nodules

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and in the peritoneum of rats that received i.p. cisplatin. The combination was able to cure animals with peritoneal tumour nodules smaller than 2 mm when i.p. cisplatin alone did not. A safe 2 h schedule of i.p. cisplatin and epinephrine has been established in pigs [14].

On the basis of these experimental data, a first phase I trial using i.p. cisplatin and epinephrine was performed in patients with recurrent and unresectable peritoneal carcinomatosis [15]. Both drugs were given i.p. every 4 weeks in nonanaesthetized patients through a Port-a-Cath device. However, the major problem was poor fluid distribution through the peritoneal cavity owing to adherences and major abdominal pain.

We initiated a second phase 1 trial in which a fixed dose of cisplatin was associated with increasing doses of epinephrine for intraoperative i.p. chemotherapy for recurrent ovarian carcinoma after peritoneal cytoreduction.

Methods

Patient selection

This study was conducted in two French university hospitals (Besançon, Dijon) and approved by the local ethics board (Comité de Protection des Personnes de Franche-Comté). All eligible patients had histologically confirmed recurrent epithelial ovarian cancer, and all had received i.v. chemotherapy with platinum-containing regimens earlier. Patients who had evidence of extra-peritoneal disease were not included. All of the following inclusion criteria were required: age $\geq$ 18 years, WHO performance status 0 or 1 and written informed consent. Normal haematological, renal and hepatic function was required. Patients with a history of cardiac insufficiency, heart rhythm disorders or chronic arteriopathy were excluded. Normal baseline electrocardiogram; cardiac ultrasonography; ambulatory cardiac rhythm; and Doppler-ultrasound of the lower limbs, renal arteries and neck vessels were required.

Treatment

The procedure was carried out either immediately after the diagnosis of the relapse or after i.v. induction chemotherapy using a platinum-containing regimen. Complete debulking surgery aiming to remove all peritoneal tumour nodules larger than 5 mm was performed. After surgical resection, the peritoneal cavity was filled with 3 l of isotonic saline solution preheated to 37°C, and then cisplatin and epinephrine were added after 1 min. The cardiac rhythm was closely monitored. The peritoneal cavity was bathed for 1 h at 37°C using an extracorporeal pump and a fluid heater to maintain the temperature. The peritoneal cavity was then emptied and refilled using the same procedure for 1 additional hour. The homogenous liquid distribution was obtained by continuous hand stirring. At the end of the procedure, the peritoneal cavity was emptied and rinsed with drug-free saline solution before closing. Concomitant i.v. hydration (to maintain > 100 ml/h urine output) was administered to prevent cisplatin renal toxicity. Continuous cardiac monitoring and serum troponin assays were performed during the procedure and for 24 h after its completion.

Study schedule

The concentration of i.p. cisplatin was fixed at 30 mg/l in the 3 l of saline solution for two sequences of 1 h (total dose 180 mg) on the basis of our earlier studies [16,17]. The first three patients were treated with cisplatin alone. The dose escalation of epinephrine was planned according to a Fibonacci sequence at 1, 2, 3, 5 and 8 mg/l. The starting dose was chosen on the basis of earlier preclinical and clinical studies [18,19]. A minimum of three assessable patients were entered at each dose level of epinephrine. Toxicity was assessed using the Common Toxicity Criteria of the National Cancer Institute, Version 3.0. Cardiovascular intolerance was predefined as a tachycardia over 120/min, systolic blood pressure over 190 mmHg, more than 2/min ventricular extrasystoles (VES), signs of left cardiac insufficiency, increase in serum troponin concentration, or electric signs of myocardial ischaemia. Occurrence of grade 3–4 intraoperative toxicity meant that a nontolerable dose had been reached. Follow-up was performed 1 month later and then every 3 months after the i.p. chemotherapy.

Pharmacokinetic study

Peritoneal and blood samples were taken 1, 30 and 59 min after starting each peritoneal bath. Blood samples were taken 4, 6, 8, 16 and 24 h after treatment. Samples were centrifuged and total (T-Pt) and ultrafiltered (Uf-Pt) platinum were separated using Amicon Ultra-4 units (Millipore, Billerica, Massachusetts, USA). Platinum assays were performed by inductively coupled plasma mass spectrometry [17]. Intraperitoneal epinephrine was determined using a high-performance liquid chromatographic assay [20]. Serum epinephrine was assayed with a radioenzymatic method [21]. The area under the curve (AUC) of T-Pt or Uf-Pt in serum was calculated during the 24-h period using a trapezoidal method. The half-life was estimated by means of linear regression from the slope of terminal decay.

Statistical analysis

Overall survival and disease-free progression were evaluated with Kaplan–Meier nonparametric methods using JMP software (SAS, Cary, North Carolina, USA). Nonparametric analysis of variance (Kruskall–Wallis followed by a Mann–Whitney post-hoc test) was used to compare pharmacokinetic parameters.

Results

Patients and treatment

Twenty-five patients with recurrent and/or refractory advanced epithelial ovarian cancer were included between October 2004 and February 2007. One patient

refused the operation after having signed the informed consent form. Cytoreductive surgery was not possible in four patients and there was no evidence of residual disease after i.v. chemotherapy in two patients. Eighteen patients thus underwent surgery and received the i.p. treatment. The histological cancer types were serous (13), endometrioid (3), clear cell carcinoma (1) and mixed epithelial carcinoma (1). The median age was 60 years (range 27–69 years). The median interval between the first diagnosis of ovarian cancer and recurrence was 21.6 months (range 3–42 months). The median number of prior lines of i.v. chemotherapy was two (one to four), including induction and adjuvant chemotherapy.

Tolerance

No procedure-related deaths occurred. No patients enrolled at the 0, 1 and 2 mg/l i.p. epinephrine levels had cardiovascular intolerance (Table 1). No toxicity occurred in the first patient treated at the 3 mg/l concentration of epinephrine. The second patient had tachycardia over 120/min with more than 2/min VES, electric signs of myocardial ischaemia and increased levels of serum troponin. The third patient had tachycardia over 120/min with more than 2/min VES, but with no increase in serum troponin or electric signs of ischaemia. For these two patients with tachycardia, the i.p. procedure was immediately stopped by emptying the abdominal cavity and rinsing out the epinephrine. Six additional patients were included at the lower level of 2 mg/l of epinephrine, and none experienced limiting cardiac toxicity. No grade 3–4 haematological toxicity was observed. Recoverable grade 1–2 delayed renal toxicity occurred in four patients. The most frequent complication was urinary or pulmonary infection. Three patients developed peritonitis and intraabdominal abscess requiring a second laparotomy to clean up the peritoneal cavity. A second surgical intervention was necessary for intraabdominal bleeding in one patient. Surgical restoration for a bowel fistula was necessary in one patient. Thromboembolic events were reported in five patients, including pulmonary embolism in three patients.

Table 1 **Toxicity National Cancer Institute – common toxicity criteria grading)**

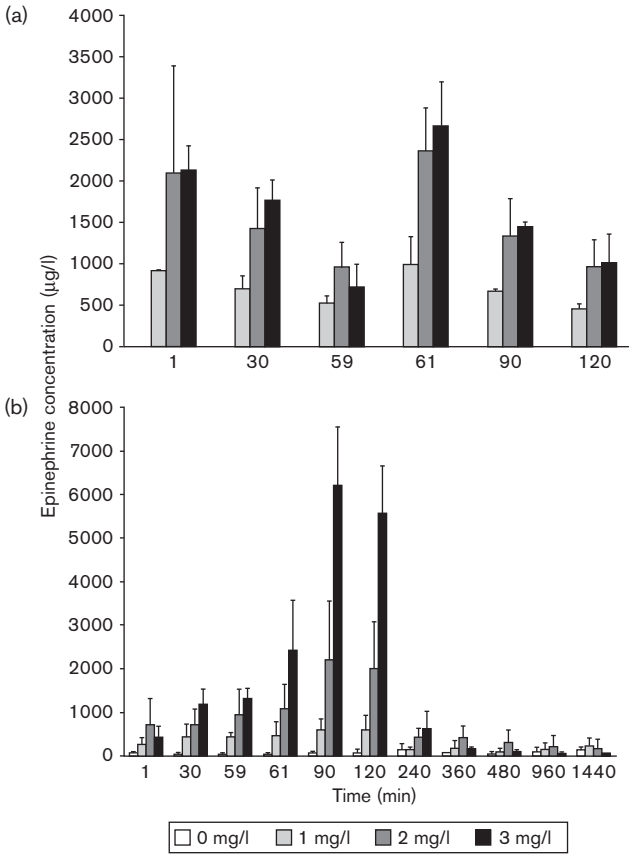
Toxicity	Grade (number of patients)
Vascular toxicity	
No epinephrine	0 (0/3)
Epinephrine = 1 mg/l	0 (0/3)
Epinephrine = 2 mg/l	0 (0/9)
Epinephrine = 3 mg/l	3 (2/3)
Renal toxicity	
No epinephrine	1 (2/3)
	2 (1/3)
Epinephrine: 1 mg/l	1 (1/3)
Epinephrine: 2 mg/l	1 (1/9)
Epinephrine: 3 mg/l	1 (1/3)
Infectious complications	
Urinary	2 (3/18)
Pulmonary	2 (3/18)
Intraabdominal abscess or peritonitis	4 (3/18)
Intraabdominal bleeding	4 (1/18)
Thromboembolic events	3 (2/18)
(Including pulmonary embolism)	4 (3/18)
Chronic diarrhoea	1 (3/18)
Chronic dysuria	2 (1/18)
Persistent abdominal pain	2 (2/18)
Bowel fistula	4 (1/18)
Haematological toxicity	0 (18)
Neurological toxicity	0 (18)

Peritoneal and blood pharmacokinetics

Epinephrine concentrations in the peritoneal cavity decreased with time after the bolus injection into the peritoneal liquid (Fig. 1a). The mean epinephrine half-life was 0.95 h (± 0.02 h), with no difference according to the dose or the order of the bath.

The mean endogenous concentration of epinephrine was 62.4 ± 38.3 pg/l in the serum of patients who received cisplatin alone (Fig. 1b). The addition of 1, 2 and 3 mg/l of i.p. epinephrine to the peritoneal bath led to a dramatic increase in its concentration in the serum.

Fig. 1

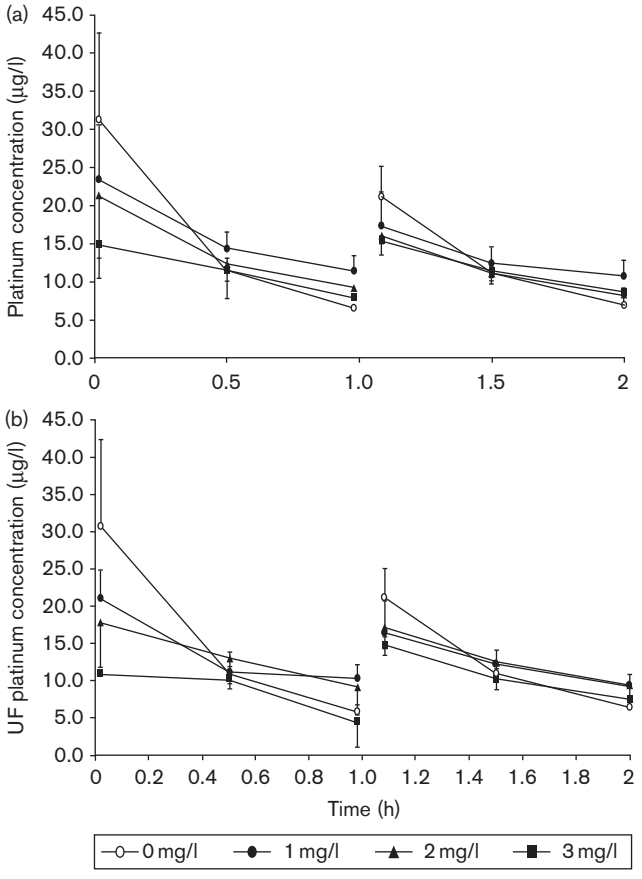


Epinephrine concentration in the peritoneal cavity (a) and serum (b). Each value is the mean (± SD) from two [3 mg/l intraperitoneal (i.p.) epinephrine], three (0 or 1 mg/l i.p. epinephrine) or nine patients (2 mg/l i.p. epinephrine).

The mean peak concentration was 606 pg/l and 2225 pg/l for 1 and 2 mg i.p. epinephrine, respectively. A higher epinephrine serum concentration, 6327 and 7162 pg/l, was recorded in the two patients who experienced cardiac toxicity at the 3 mg/l level. Epinephrine concentrations in serum returned to the baseline 4 h after completion of the i.p. treatment.

Platinum concentrations in the peritoneal cavity decreased with time after the bolus injection of cisplatin into the bath. The pharmacokinetics was approximately the same in the first and second bath, except for the first determination performed 1 min after the drug injection (Fig. 2). As observed earlier [17], the values of T-Pt and Uf-Pt were very close in this protein-poor medium (always < 5 g/l despite contamination of the peritoneal liquid with blood). The half-life of T-Pt and Uf-Pt in the peritoneal liquid was approximately doubled in the presence of i.p. epinephrine (Table 2). Platinum concentrations in the peritoneal liquid were generally above 10 mg/l.

Fig. 2



Concentration of total (a) and ultrafiltered (b) platinum in the peritoneal cavity. Each value is the mean (± SD) from two [3 mg/l intraperitoneal (i.p.) epinephrine], three (0 or 1 mg/l i.p. epinephrine) or nine patients (2 mg/l i.p. epinephrine).

Peak concentration (Fig. 3) and AUC (Table 2) of platinum in the patient serum were dramatically decreased in the presence of i.p. epinephrine, whatever the epinephrine dose (Fig. 3).

Clinical outcome

After a median follow-up of 14.7 months (2–27 months), disease recurrence was recorded in 10 of the 18 patients. The median duration of the response was 8.4 months (2.2–19.8 months). The sites of relapse were the peritoneum (five patients), retroperitoneal lymph nodes (two patients), liver metastasis (four patients) and pleural effusion (one patient). The median overall survival was 26.2 months (7.1–40.2 months).

Discussion

This study describes for the first time the use of epinephrine combined with cisplatin for intraoperative peritoneal chemotherapy in recurrent ovarian carcinoma as a complement to surgical debulking. The role of peroperative i.p. chemotherapy remains controversial owing to the lack of randomized trials and the multitude of proposed methods, varying in drugs, doses, schedules and temperature. This study is an original step in the search for an optimal intraoperative i.p. chemotherapy regimen. The choice of the procedure using two successive 1-h baths for i.p. cisplatin was based on earlier clinical studies [16,17,20]. The 1-h bath did not allow sufficient exposure to cisplatin above a targeted 10 mg/l threshold. This threshold was previously determined using a clonogenic assay to be the minimal concentration that kills 95% of resistant human ovarian cancer cells after 2 h of exposure [20]. Interestingly, platinum concentration in the abdominal cavity exceeded this effective threshold most of the time, with a slight advantage in the presence of epinephrine. However, the 2-bath procedure increased renal toxicity [16]. The predictive parameter for renal toxicity was serum T-Pt 24-h AUC with a threshold value of 25 mg h/l. We show here that i.p. epinephrine dramatically decreased the peak concentration and AUC (about 60%) of serum platinum. This effect was related to vasoconstriction of the peritoneal microvasculature and the consecutive reduction in cisplatin diffusion, which might explain the moderate renal toxicity. The mild renal grade 1 toxicity recorded in four patients is lower than that reported in an earlier protocol in which cisplatin was administered with the same pattern and dose but without epinephrine [20]. Despite the relative systemic and renal protection offered by epinephrine, the total dose of i.p. cisplatin did not exceed 180 mg in this trial.

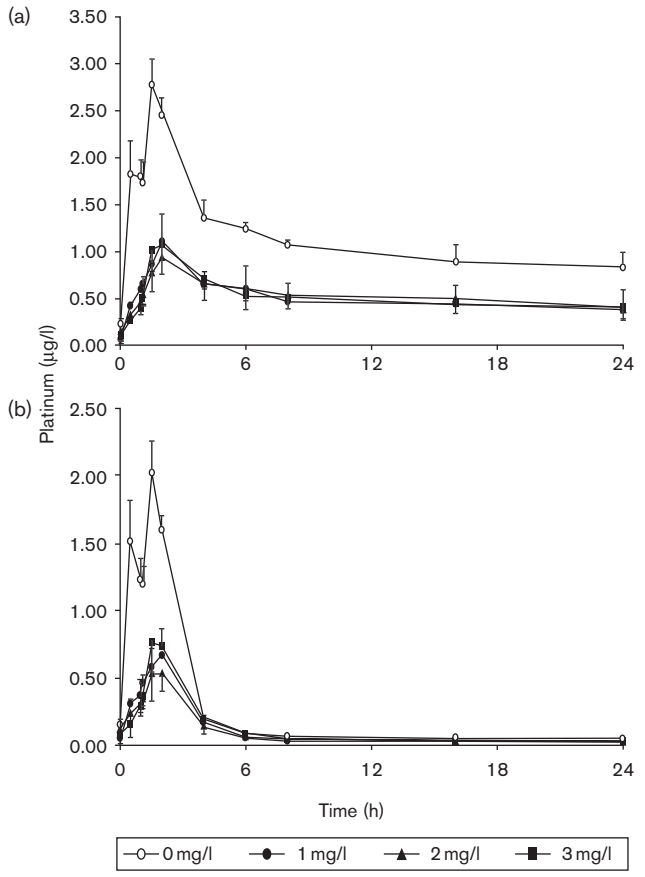
As expected, cardiac toxicity resulting from epinephrine was dose limiting. One and 2 mg/l i.p. epinephrine was well tolerated, whereas two of the three patients who received 3 mg/l i.p. epinephrine experienced tachycardia and VES, with an increase in serum troponin for one

Table 2 Pharmacokinetic parameters of ultrafiltered and total platinum

	Serum		Peritoneal cavity	
Epinephrine doses (number of patients)	AUC of total platinum (mg/h/l)	AUC of ultrafiltered platinum (mg/h/l)	Half-life of total platinum (h)	Half-life of ultrafiltered platinum (h)
0 mg/l (3 patients)	28.50 (24.63–28.70)	6.16 (5.89–6.59)	1.31 ± 0.46	1.23 ± 0.44
1 mg/l (3 patients)	10.58 (8.71–7.27)*	2.41 (2.02–3.09)*	2.98 ± 1.11*	2.83 ± 1.14*
2 mg/l (9 patients)	12.03 (8.73–6.96)*	2.35 (1.97–2.75)*	3.28 ± 1.16**	2.83 ± 1.14**
3 mg/l (2 patients)	12.39 (10.50–14.52)	3.01 (2.43–3.19)	2.78 ± 0.77*	2.22 ± 1.00*

Serum AUC was calculated over 24 h and expressed as the median (with range). Half-life of cisplatin in the peritoneal cavity was expressed as the mean ± SD.
AUC, area under the curve.
*$P < 0.05$ and **$P < 0.01$ between the groups with or without intraperitoneal epinephrine (Mann–Whitney post-hoc test).

Fig. 3



Concentration of total (a) and ultrafiltered (b) platinum in the serum. Each value is the mean (± SD) from two [3 mg/l intraperitoneal (i.p.) epinephrine], three (0 or 1 mg/l i.p. epinephrine) or nine patients (2 mg/l i.p. epinephrine).

patient. Postoperative cardiovascular examinations did not reveal any signs of cardiac necrosis. Intraperitoneal epinephrine in the peritoneal bath dramatically increased its serum concentration compared with the endogenous baseline level. A link between i.p. epinephrine concentrations and clinical cardiac toxicity was assumed. A serum concentration of approximately 2000 ng/l for the 2 mg/l i.p. epinephrine dose seemed to be well tolerated, whereas a concentration that peaked at more than 6000 ng/l after 3 mg/l epinephrine was deleterious. Non-cardiac morbidity was mostly related to the extensive peritoneal surgery, and is common with this procedure [18,19,21,22]. There was no evidence of a significant increase in morbidity owing to epinephrine compared with hyperthermia alone, which is also used to potentiate the antitumor effect of cisplatin. For example, Lim *et al.* [19] reported 40% of grade III adverse events in 30 patients who received 75 mg/l of i.p. intraoperative cisplatin at 41.5°C for 90 min.

In conclusion, 2 mg/l seems to be the maximal tolerated dose for i.p. epinephrine in association with 30 mg/l cisplatin for an intraoperative i.p. chemotherapy procedure with two successive 1-h peritoneal baths. However, the 1 mg/l epinephrine concentration could be sufficient, as it produced the same reduction in platinum AUC in serum and extended the half-life of cisplatin in the peritoneal cavity. A phase III study could be designed to compare an i.p. epinephrine/cisplatin regimen versus i.p. cisplatin alone versus no i.p. chemotherapy as a complement to cytoreductive surgery in patients with recurrent ovarian carcinoma.

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References

1 Cannistra SA. Cancer of the ovary. *N Engl J Med* 2004; **351**:2519–2529.
2 McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, *et al.* Cyclophosphamide and cisplatin versus paclitaxel and cisplatin: a phase III randomized trial in patients with suboptimal stage III/IV ovarian cancer (from the Gynecologic Oncology Group). *Semin Oncol* 1996; **23**:40–47.

3 Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, *et al*. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003; **21**:3194–3200.

4 Stuart GC. First-line treatment regimens and the role of consolidation therapy in advanced ovarian cancer. *Gynecol Oncol* 2003; **90**:S8–S15.

5 Thigpen T. The if and when of surgical debulking for ovarian carcinoma. *N Engl J Med* 2004; **351**:2544–2546.

6 Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. *Lancet Oncol* 2003; **4**:277–283.

7 Markman M, Walker JL. Intraperitoneal chemotherapy of ovarian cancer: a review, with a focus on practical aspects of treatment. *J Clin Oncol* 2006; **24**:988–994.

8 Rao G, Crispens M, Rothenberg ML. Intraperitoneal chemotherapy for ovarian cancer: overview and perspective. *J Clin Oncol* 2007; **25**:2867–2872.

9 Markman M, Jones W, Lewis JL Jr, Rubin S, Hakes T, Reichman B, *et al*. Impact of laparotomy finding of significant intraabdominal adhesions on the surgically defined complete response rate to subsequent salvage intraperitoneal chemotherapy. *J Cancer Res Clin Oncol* 1992; **118**:163–165.

10 Salani R, Santillan A, Zahurak ML, Giuntoli RL, Gardner GJ, Armstrong DK, *et al*. Secondary cytoreductive surgery for localized, recurrent epithelial ovarian cancer: analysis of prognostic factors and survival outcome. *Cancer* 2007; **109**:685–691.

11 Boucher Y, Brekken C, Netti PA, Baxter LT, Jain RK. Intratumoral infusion of fluid: estimation of hydraulic conductivity and implications for the delivery of therapeutic agents. *Br J Cancer* 1998; **78**:1442–1448.

12 Chauffert B, Favoulet P, Polycarpe E, Duvillard C, Beltramo JL, Bichat F, *et al*. Rationale supporting the use of vasoconstrictors for intraperitoneal chemotherapy with platinum derivatives. *Surg Oncol Clin N Am* 2003; **12**:835–848.

13 Duvillard C, Benoit L, Moretto P, Beltramo JL, Brunet-Lecomte P, Correia M, *et al*. Epinephrine enhances penetration and anti-cancer activity of local cisplatin on rat sub-cutaneous and peritoneal tumors. *Int J Cancer* 1999; **81**:779–784.

14 Favoulet P, Magnin G, Guilland JC, Beltramo JL, Osmak L, Benoit L, *et al*. Pre-clinical study of the epinephrine–cisplatin association for the treatment of intraperitoneal carcinomatosis. *Eur J Surg Oncol* 2001; **27**:59–64.

15 Molucon-Chabrot C, Isambert N, Benoit L, Zanetta S, Fraisse J, Guilland JC, *et al*. Feasibility of using intraperitoneal epinephrine and cisplatin in patients with advanced peritoneal carcinomatosis. *Anticancer Drugs* 2006; **17**:1211–1217.

16 Guardiola E, Delroeux D, Heyd B, Combe M, Lorgis V, Demarchi M, *et al*. Intra-operative intra-peritoneal chemotherapy with cisplatin in patients with peritoneal carcinomatosis of ovarian cancer. *World J Surg Oncol* 2009; **7**:14.

17 Royer B, Guardiola E, Polycarpe E, Hoizey G, Delroeux D, Combe M, *et al*. Serum and intraperitoneal pharmacokinetics of cisplatin within intraoperative intraperitoneal chemotherapy: influence of protein binding. *Anticancer Drugs* 2005; **16**:1009–1016.

18 Gusani NJ, Cho SW, Colovos C, Seo S, Franko J, Richard SD, *et al*. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. *Ann Surg Oncol* 2008; **15**:754–763.

19 Lim MC, Kang S, Choi J, Song YJ, Park S, Seo SS, *et al*. Hyperthermic intraperitoneal chemotherapy after extensive cytoreductive surgery in patients with primary advanced epithelial ovarian cancer: interim analysis of a phase II study. *Ann Surg Oncol* 2009; **19**:993–1000.

20 Royer B, Delroeux D, Guardiola E, Combe M, Hoizey G, Montange D, *et al*. Improvement in intraperitoneal intraoperative cisplatin exposure based on pharmacokinetic analysis in patients with ovarian cancer. *Cancer Chemother Pharmacol* 2008; **61**:415–421.

21 Bijelic L, Jonson A, Sugarbaker PH. Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. *Ann Oncol* 2007; **18**:1943–1950.

22 Di Giorgio A, Naticchioni E, Biacchi D, Sibio S, Accarpio F, Rocco M, *et al*. Cytoreductive surgery (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of diffuse peritoneal carcinomatosis from ovarian cancer. *Cancer* 2008; **113**:315–325.