Gynecologic Oncology 115 (2009) 362–366

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Tumor platinum concentration following intraperitoneal administration of cisplatin versus carboplatin in an ovarian cancer model

Danielle D. Jandial [a,*], Karen Messer [b], Salman Farshchi-Heydari [a], Minya Pu [b], Stephen B. Howell [c,1]

[a] Moores Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, La Jolla, CA 92093-0819, USA
[b] Moores Cancer Center, Department of Biostatistics, University of California, San Diego, La Jolla, CA 92093-0901, USA
[c] Moores Cancer Center, Department of Medicine, University of California, San Diego, La Jolla, CA 92093-0819, USA

ARTICLE INFO

Article history:
Received 7 July 2009
Available online 22 September 2009

Keywords:
Intraperitoneal chemotherapy
Cisplatin
Carboplatin
Penetration

ABSTRACT

Objective. Current intraperitoneal (IP) regimens for the treatment of ovarian cancer rely on cisplatin (DDP) whereas intravenous regimens rely on carboplatin (CBDCA). A major question in the field is whether CBDCA can replace DDP for IP treatment. We compared the uptake of IP administered DDP and CBDCA into human ovarian carcinoma nodules of various sizes growing on the peritoneal surface of nu/nu mice.

Methods. Human 2008 cells expressing GFP were inoculated IP in nu/nu mice. When small tumor nodules became visible by external imaging, a maximum tolerated dose of DDP, or either an equimolar or equitoxic dose of CBDCA, was injected IP. Platinum (Pt) concentration in tumor nodules was measured by inductively coupled plasma mass spectrometry.

Results. A total of 749 tumors harvested from 33 mice were analyzed for Pt concentration. DDP produced a 3.4-fold higher level of Pt in tumor nodules when compared to an equimolar dose of CBDCA ($p = 0.02$). However, when DDP and CBDCA were injected at doses that were equitoxic to the mice, tumor Pt levels were equivalent ($p = 0.63$). Although Pt concentrations of equal-sized nodules were highly variable, tumor Pt content (ng Pt/mg tumor) decreased with increasing nodule size following IP DDP, an effect not seen with IP administration of equitoxic doses of CBDCA ($p < 0.001$).

Conclusions. These results suggest that IP CBDCA has comparable or better drug penetration when compared to DDP given at equitoxic doses, and thus provide support for replacing DDP with CBDCA in the IP treatment of patients with ovarian cancer.

Introduction

There is very strong evidence from experimental models and clinical studies that the antitumor activity of the platinum (Pt)-containing drugs is closely related to the amount of drug reaching the tumor. Intraperitoneal chemotherapy for patients with small volume ovarian carcinoma is based on the concept that, when DDP is administered IP in adequate doses, drug will reach the tumor both by diffusion in from the free tumor surface in the peritoneal cavity and via capillary flow after the DDP enters the systemic circulation. The anticipated net effect is an increase in the total amount of drug reaching the tumor. This concept has been validated by the results of multiple prospective randomized clinical trials that demonstrated the therapeutic advantage of intraperitoneal (IP) chemotherapy for patients with small volume residual ovarian cancer after primary surgery [1–3]. Nevertheless, the incremental benefit of IP therapy with respect to progression-free and overall survival is small and there are concerns related to poor patient tolerance and catheter-related complications. When given IV, CBDCA has demonstrated therapeutic equivalence to DDP and has a more manageable toxicity profile. As a consequence, CBDCA has now largely replaced DDP for the primary therapy of patients with ovarian cancer.

One approach to improving the tolerability of IP chemotherapy would be to substitute CBDCA for DDP in intraperitoneally administered regimens. CBDCA has been shown to be well tolerated when administered IP in patients, and the total drug exposure for the peritoneal cavity relative to plasma (AUC ratio) for CBDCA is similar to that of DDP [4]. However, concerns have been raised as to whether the two drugs have equal ability to penetrate from the peritoneal cavity into small tumor nodules growing on the peritoneal surface. The reasons for this are based primarily on the findings of two studies. The first was a study by Los and colleagues who measured the Pt concentration and depth of penetration of DDP and CBDCA into rat colon carcinoma nodules following IP administration of the drugs [5]. They determined that DDP was more effective than CBDCA at penetrating into the tumor nodules. When the rats were injected IP with equimolar doses of the two drugs, tumor nodules harvested from rats receiving DDP contained ~7-fold more Pt per mg wet weight than

* Corresponding author. Fax: +1 858 822 1111.
E-mail addresses: djandial@uci.edu (D.D. Jandial), showell@ucsd.edu (S.B. Howell).
[1] Requests for reprints: Moores UCSD Cancer Center, 3855 Health Sciences Drive, CA 92093-0819. Fax: +1 858 822 1111.

0090-8258/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2009.08.028

nodules from rats who received CBDCA. When equitoxic doses of the drugs were injected, the Pt level was ~1.5-fold greater in nodules from animals receiving DDP than from those receiving CBDCA. However, the experimental model used was a rat colon cancer not a human ovarian cancer model, and only a small number of tumor nodules were examined. These results prompted a retrospective clinical study that analyzed data from a series of 65 patients and found that the response rate in patients who received 100 mg/m^2 IP DDP was better than in those receiving an IP regimen containing 200–300 mg/m^2 CBDCA for macroscopic residual tumors >0.5 cm (71% vs. 32%), but equivalent in patients with microscopic residual disease (46% vs. 38%) [6]. However, in a retrospective analysis there is always the possibility that patient characteristics dictated which treatment was given, and so account for differences in outcome as well. To date, no prospective human trials comparing IP CBDCA to DDP have been published.

The objective of this study was to compare the ability of DDP and CBDCA to penetrate from the peritoneal cavity into tumor nodules using a human ovarian carcinoma growing on the peritoneal surface of nu/nu mice, a model whose biologic characteristics closely mimic those of ovarian cancers in patients.

Materials and methods

Drugs

DDP (Platinol) and carboplatin (Paraplatin) were gifts from Bristol-Myers Squibb (Princeton, NJ). The clinical formulation of Platinol containing 3.33 mM DDP was kept in the dark at room temperature. Paraplatin was reconstituted with sterile water to a 20 mM solution and stored at 4 °C.

Animal model

All animal studies were approved by the University of California Institutional Animal Care and Use Committee and performed in accordance with NIH guidelines. A subline of the 2008 human ovarian cancer cell line, derived from a serous cystadenocarcinoma [7], was engineered to express GFP and was inoculated IP into nu/nu mice. Prior studies showed no effect of the expression of GFP on the cellular pharmacology of DDP in this subline relative to the parental 2008 line *in vitro* [8]. Cells were grown in RPMI-1640 media supplemented with 10% fetal bovine serum with 500 μg/mL G418 at 37 °C and 5% CO_2. All tissue culture chemicals and reagents were obtained from Fisher Scientific (Tustin, CA). Female nu/nu mice (Charles River Laboratories, Wilmington, MA) aged 6–8 weeks were inoculated IP with 5×10^6 2008/GFP cells in 750 μL of serum free media. When there was evidence of IP tumor growth by optical imaging with the IVIS 200 (Caliper Life Sciences, Hopkinton, MA), typically 4 weeks post-inoculation, animals were treated with a single IP injection of DDP at the maximum tolerated dose (10 mg/kg) or either an equimolar dose of CBDCA (12.4 mg/kg) or an equitoxic dose of CBDCA (85 mg/kg). Both drugs were diluted with sterile 0.9% NaCl to a final injection volume of 500 μL to allow for adequate peritoneal distribution. Animals were sacrificed 2 h after injection and all tumors were removed for further analysis. Approximately 95% of the tumors analyzed (708 of 749) were 2–9 mm in their maximum measured dimension.

Measurement of tumor platinum concentration

Tumors were blotted free of excess moisture, weighed, measured, and digested overnight in 70% nitric acid at 65 °C. The digestate was diluted to a final concentration of 5% nitric acid with buffer containing water, 1 ppb indium as an internal standard, and 0.1% Triton X-100. Pt levels were then measured by inductively coupled mass plasma spectrometry (Element 2, Perkin Elmer Life Sciences) or inductively coupled optical emission spectrometry (model 3000DV, Perkin Elmer Life Sciences) and expressed as ng Pt per mg of tumor wet weight or tumor volume as calculated by $(\text{width}^2\times\text{length})/2$.

Statistical analysis

A Kruskal–Wallis test compared the number of tumors analyzed per mouse among the three dose groups. SAS PROC MIXED was used to model log-transformed Pt concentration as a linear function of tumor size for each group, and to test for differences in slope between treatment groups; a random intercept was used to account for correlated data within each mouse. Random intercept models also tested for mean differences in log transformed tumor volume, weight, and Pt concentration between groups. Conditional Studentized residuals were plotted to check model fit and to identify influential outliers (data not shown). Outliers were retained in the final models since they did not cause significant changes when excluded. Analyses used SAS version 9.2 (The SAS Institute, Inc., Cary, NC) and the statistical package R version 2.5.1, 2007 (The R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided at the 5% significance level.

Results

Tumor uptake of DDP compared to two doses of CBDCA

This study analyzed 749 tumors from 33 mice. Tumor characteristics are detailed in Table 1. No significant difference was noted between the three treatment groups with respect to the median number of tumors per mouse, mean tumor volume, or mean wet weight.

Preliminary studies established that a single IP dose of 10 mg/kg DDP or 85 mg/kg CBDCA reproducibly produced equal degrees of toxicity to nu/nu mice as judged by an average weight loss of 10% (data not shown). Mean log Pt tumor concentration was compared for DDP, 12.4 mg/kg CBDCA, and 85 mg/kg CBDCA and these are

Table 1
Tumor characteristics and mean platinum uptake, by treatment group.

Drug	Dose, mg/kg	No. tumors analyzed	Median no. tumors per mouse (range)	Median tumor length in mm (range)	Median tumor width in mm (range)	Mean[a] tumor volume in mm^3 (95% CI)[b]	Mean[a] tumor wet weight in mg (95% CI)[b]	Mean[a] tumor platinum in ng Pt/mg tumor weight (95% CI)[b]
DDP	10	129[c]	19.0 (2–23)	4 (2–11)	3 (2–10)	16.2 (11.5–22.8)	15.1 (12.3–18.6)	1.92 (0.85–4.32)
CBDCA	12.4	384[d]	34.0 (1–60)	4 (2–22)	3 (1–12)	14.0 (10.8–18.1)	16.6 (14.3–19.3)	0.57 (0.29–1.11)
CBDCA	85	236[d]	18.5 (6–45)	4 (1–20)	2 (1–9)	10.3 (7.8–13.5)	16.2 (13.8–19.0)	2.47 (1.28–4.79)

Abbreviations: DDP, cisplatin; CBDCA, carboplatin; Pt, platinum.
[a] Means and standard errors were calculated from log-transformed data using a random intercept model; values reported here are exponentiated model estimates and so estimate the geometric mean.
[b] $p>0.05$.
[c] $n=9$ mice.
[d] $n=12$ mice.

Table 2
Estimated ratios of mean tumor platinum concentration.

	Fold-increase in mean tumor Pt[a]	95% CI	*p*-value
CBDCA 85 vs. CBDCA 12.4 mg/kg	4.24	(1.70–11.04)	<0.01
DDP vs. CBDCA 85 mg/kg	0.78	(0.27–2.21)	0.63
DDP vs. CBDCA 12.4 mg/kg	3.37	(1.18–9.58)	0.02

[a] Mean differences and their standard errors were calculated from log-transformed data using a random intercept model; values reported here are exponentiated model estimates and so estimate the ratio of the geometric means estimated in this table.

presented in Table 1; the concentration ratios are presented in Table 2. As expected, average Pt tumor concentration in the DDP treated mice was higher, by an estimated factor of 3.37 (95% CI, 1.18–9.58), than for mice treated with an equimolar dose of 12.4 mg/kg CBDCA. Pt concentration was also significantly higher in the tumor nodules of mice treated with 85 mg/kg CBDCA than in those treated with 12.4 mg/kg CBDCA (estimated ratio, 4.24; 95% CI, 1.70–11.04). No significant difference in Pt concentration was noted between mice treated with DDP when compared with mice treated with the higher dose CBDCA (estimated DDP/CBDCA ratio, 0.78; 95% CI, 0.27–2.21).

Platinum concentration as a function of tumor size

Fig. 1 shows tumor Pt concentration (ng Pt/mg wet weight) as a function of tumor weight for animals treated with DDP (10 mg/kg), equimolar (12.4 mg/kg) CBDCA, and equitoxic (85 mg/kg) doses of CBDCA. Although average Pt concentration did not differ significantly between the two treatment groups receiving equitoxic doses of DDP and CBDCA, a significant difference was observed when comparing the tumor Pt concentration as a function of tumor weight. As shown in Fig. 1, for the mice treated with DDP, average Pt content decreased significantly as tumor wet weight increased (estimated slope on the log scale, −0.26; 95% CI, −0.38 to −0.13). In contrast, no statistically significant relationship was detected between Pt concentration and tumor wet weight in mice treated with CBDCA at the higher dose (estimated slope on the log scale, 0.03; 95% CI, −0.04 to 0.09). At the lower CBDCA dose, a small but statistically significant decrease in Pt concentration was observed as tumor wet weight increased (estimated slope on the log scale, −0.08; 95% CI, −0.13 to −0.03); however, this was significantly less than the decrease observed for DDP ($p = 0.004$, test for slope differences). The remaining pairs of slopes (DDP vs. high dose CBDCA; high vs. low dose CBDCA) also differed significantly ($p < 0.001$ and $p = 0.02$, respectively).

Discussion

Consistent with a previous study using a murine colon cancer model, the results of this study demonstrate that the mean Pt accumulation in human ovarian cancer nodules was 3.4-fold higher in mice receiving DDP than those receiving CBDCA when mice were injected with equimolar doses of the two drugs [5]. However, the mean Pt concentration increased as the CBDCA dose was escalated, and when DDP and CBDCA were given at doses that were equitoxic to the mice, the mean tumor nodule concentration of Pt did not differ significantly, although it was higher for CBDCA. Therefore, it is reasonable to conclude that equal Pt levels can be achieved with IP CBDCA if equitoxic doses are given, at least for tumor nodules in the 2–9 mm range.

CBDCA is less potent than DDP with respect to its toxicity to both normal tissues and ovarian carcinoma cells. When given to patients intravenously every 3 weeks, DDP is generally tolerated at a dose of 75–100 mg/kg whereas CBDCA can be given at doses of ~400 mg/m^2 which correspond to an area under the plasma concentration times time curve (AUC) of 6 mg × min/mL [9]. Thus, when compared with the commonly used doses of DDP, the dose of CBDCA needed to achieve therapeutic equivalence is up to ~5.3 times higher in humans. Similarly, in this animal model, the observation that equitoxic doses of IP CBDCA produced equivalent levels of tumor Pt when compared to mice receiving IP DDP reflects a trend that is consistent with clinical data from patients with regard to differences in dose ratios required for therapeutic equivalency.

One of the most important observations made in this study was that Pt levels decreased significantly with increasing tumor size after

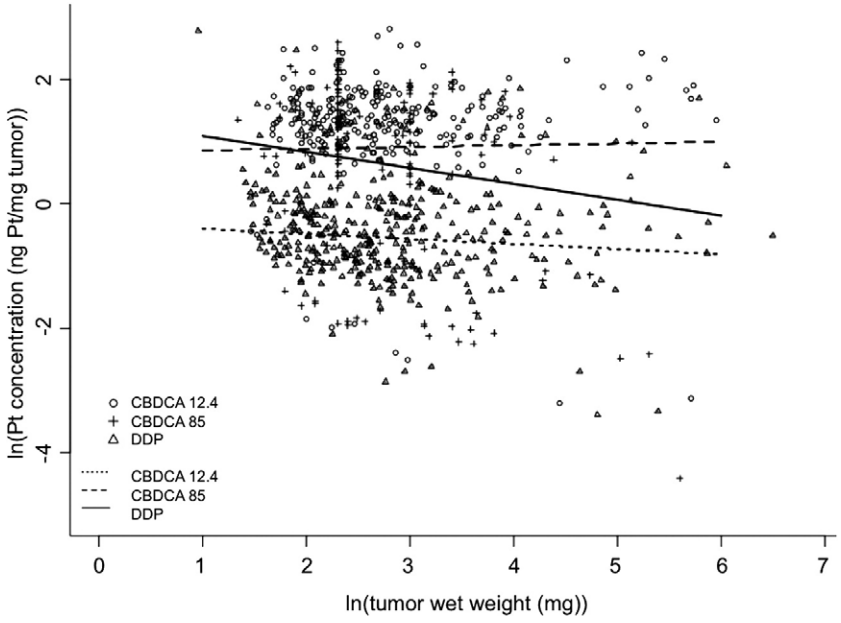

Fig. 1. Natural log of Pt concentration per tumor as a function of natural log tumor wet weight, by treatment group. Regression lines were estimated from a mixed model containing a random intercept for each mouse. DDP 10 mg/kg group: solid line, open triangle; estimated slope, −0.26 units ln(Pt concentraion) per unit ln(tumor weight); 95% CI on slope, −0.38 to −0.13. CBDCA 85 mg/kg group: heavy dashed line, '+'; estimated slope, 0.03; 95% CI on slope, −0.04 to 0.09. CBDCA 12.4 mg/kg group: dotted line, open circle; estimated slope, −0.08; 95% CI on slope, −0.13 to −0.03. On the original scale, the estimated slope for DDP corresponds to a statistically significant 16.5% decrease in Pt concentration for each doubling of tumor weight, for CBDCA 85 mg/kg, a non-significant increase in Pt concentration as tumor weight increases (by 5.7% for each doubling of tumor weight), and a small but statistically significant 5.3% decrease in Pt for each doubling of weight for CBDCA 12.4 mg/kg.

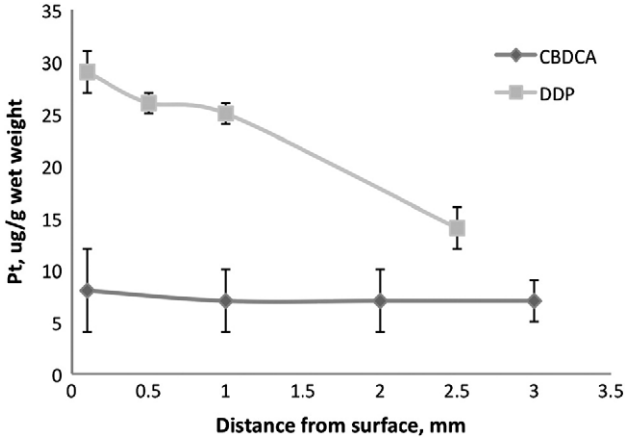

Fig. 2. Graphical representation of data from Table 2 in Los et al. [5]. Error bars: SEM.

IP DDP administration, whereas Pt levels remained nearly constant with increasing tumor size following injection of either dose of CBDCA. This finding is consistent with the observations of Los and colleagues [5] who measured Pt levels at various distances from the periphery of tumor nodules in animals treated with both DDP and CBDCA. A graph of data presented in tabular form in their report (Fig. 2) shows that the concentration of Pt decreased more rapidly as a function of distance from the surface of the nodule for DDP than for CBDCA, even under circumstances where CBDCA yielded a lower concentration of Pt near the nodule surface. Thus, while total tumor accumulation was the same when the two compounds were given at equitoxic doses, the data from both the current and prior study suggest that CBDCA may in fact be more effective than DDP in penetrating tumor nodules from their surface and that this advantage may be particularly important for the larger tumor nodules. However, it is important to note that it is not just the amount of drug in the tumor nodule that is the final determinant of cell kill, but rather the amount reaching the DNA or other critical targets in the tumor. This is related to both the penetration of drug and the residence of the drug in the nodule, neither of which was measured in our study.

Multiple factors influence the penetration of drug into tumor nodules, including drug size, the rate of uptake into tumor cells, binding in the extracellular matrix, and wash-out of drug by the tumor vasculature [10]. While there is a small difference in the molecular weight of DDP (300.1 Da) and CBDCA (371.25 Da), this is unlikely to significantly affect their tissue diffusion rate [11]. Also, while CBDCA is slightly less lipid soluble than DDP, neither compound crosses lipid membranes readily. The statistically significant difference in Pt concentration as a function of tumor size observed with DDP but not with CBDCA may be explained by the relatively lower rate of the uptake of CBDCA into cells [5] and its reduced proclivity to react with nucleophilic targets. Given that CBDCA is ~10–20 times less reactive than DDP, proportionally more drug is likely to remain available to penetrate deeper into the center of the nodule. In contrast, the more reactive DDP would be expected to become sequestered at a much more rapid rate, thereby decreasing the amount of drug available to penetrate through each successive deeper layer of the tumor.

Another factor that could account for a difference in the Pt gradient from the surface to the interior of the tumor nodule between DDP and CBDCA is the difference in duration of exposure. Both CBDCA and DDP have favorable pharmacokinetic parameters for IP delivery, with the peritoneal/plasma AUC ratios in the range of 10–18 and 12–15, respectively [4,12–14]. However, the peritoneal residence time of CBDCA is significantly longer than that of DDP as the peritoneal clearance of CBDCA is ~2.9 times lower than that of DDP [4,12]. Thus, the period of time during which there is a favorable peritoneal:tumor concentration gradient would be expected to be longer for CBDCA than for DDP.

It is important to note that there was heterogeneity in tumor Pt uptake both within tumors of the same size from the same animal and between animals. In particular, each of the three treatment groups contained one or two animals (5 of 33 total) in which the tumor nodules absorbed very little Pt. Our statistical models incorporated this between-animal variability by including an appropriate random effect; whereas *p*-values or confidence intervals which did not incorporate a similar random effect would have questionable validity, in particular tending to find statistically significant effects even if none were present. As a sensitivity analysis, we also estimated the slope of Pt concentration as a function of tumor wet weight for each mouse separately using ordinary regression, and compared slopes between groups. This less statistically efficient analysis gave similar estimates of the differences between groups, although *p*-values were now significant only at the 10% level, confirming the robustness of our estimates. The origin of this between-animal heterogeneity is unknown but is likely related to positional differences in the location of the tumor nodules within the peritoneal cavity and differences in the degree of tumor vascularization. When the outlier mice were excluded in a sensitivity analysis, the qualitative results did not change although the magnitude of the differences in slopes was attenuated.

Given that the majority of the tumors evaluated were 2–9 mm in maximum dimension, our findings are most directly relevant to patients with small volume residual disease. It remains to be determined whether similar effects will be seen in larger tumors. It is also important to point out that the ratio of the doses that produced equal toxicity in the mice used in this study (8.5) is different from the ratio of the usual doses used in ovarian cancer patients (5.3). This is due to the fact that identification of equal toxicity in mice is assessed using body weight loss whereas it is based on neurotoxicity and myelosuppression in patients. Therefore, although equitoxic doses of DDP and CBDCA produced equal concentrations of Pt in the tumor nodules in this mouse model, the same may not be true when the commonly used doses of DDP and CBDCA are administered to patients.

In summary, multiple randomized trials have demonstrated superior outcomes with IP DDP-based chemotherapy in optimally debulked ovarian cancer patients. Prospective randomized trials are now under development in the Gynecologic Oncology Group to investigate the feasibility and safety of IP CBDCA rather than DDP as a component of primary therapy in these patients. Given the established therapeutic equivalence and improved toxicity profile of CBDCA when injected by the IV route, IP CBDCA has the potential to decrease the toxicity of IP therapy and make it more widely accepted. This study provides important new evidence that comparable concentrations of Pt are produced in ovarian cancer nodules at doses which parallel the dose differences used clinically for CBDCA and DDP. While caution should always be exercised when extrapolating data obtained in animal models to patients, these results nevertheless provide a further rationale for adopting CBDCA in place of DDP in IP ovarian cancer therapy but still leave open the question of whether DDP and CBDCA deliver equivalent amounts of Pt to the tumor DNA.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

Acknowledgments

This work was supported in part by grants CA95298 and T32 CA121938 from the National Institutes of Health. The authors would like to thank Marieke Pouw for her time and assistance with tumor preparation and analyses.

References

[1] Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and

intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:1001–7.
[2] Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34–43.
[3] Elit L, Oliver TK, Covens A, Kwon J, Fung MF, Hirte HW, et al. Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. Cancer 2007;109:692–702.
[4] Elferink F, Vander Vijgh WJF, Klein I, Ten Bokkel Huinink WW, Dubbleman R, McVie JG. Pharmacokinetics of carboplatin after intraperitoneal administration. Cancer Chemother Pharmacol 1988:4157–60.
[5] Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. Cancer Chemother Pharmacol 1991;28:159–65.
[6] Markman M, Reichman B, Hakes T, Rubin S, Lewis Jr JL, Jones W, et al. Evidence supporting the superiority of intraperitoneal cisplatin compared to intraperitoneal carboplatin for salvage therapy of small-volume residual ovarian cancer. Gynecol Oncol 1993;50:100–4.
[7] Disaia PJ, Sinkovics JG, Rutledge FN, Smith JP. Cell-mediated immunity to human malignant cells. Am J Obstet Gynecol 1972;114:979–89.
[8] Katano K, Safaei R, Samimi G, Holzer A, Tomioka M, Goodman M, et al. Confocal microscopic analysis of the interaction between cisplatin and the copper transporter ATP7B in human ovarian carcinoma cells. Clin Cancer Res 2004;10: 4578–88.
[9] Bookman MA, McGuire III WP, Kilpatrick D, Keenan E, Hogan WM, Johnson SW, et al. Carboplatin and paclitaxel in ovarian carcinoma: a phase I study of the Gynecologic Oncology Group. J Clin Oncol 1996;14:1895–902.
[10] Minchinton AI, Tannock IF. Drug penetration in solid tumours. Nat Rev, Cancer 2006;6:583–92.
[11] Dedrick RL, Myers CE, Bungay PM, DeVita Jr VT. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 1978;62:1–11.
[12] Howell SB, Pfeifle CE, Wung WE, Olshen RA. Intraperitoneal *cis*-diamminedichloroplatinum with systemic thiosulfate protection. Cancer Res 1983;43:1426–31.
[13] DeGregorio MW, Lum BL, Holleran WM, Wilbur BJ, Sikic BI. Preliminary observations of intraperitoneal carboplatin pharmacokinetics during a phase I study of the Northern California Oncology Group. Cancer Chemother Pharmacol 1986;18:235–8.
[14] Miyagi Y, Fujiwara K, Kigawa J, Itamochi H, Nagao S, Aotani E, et al. Intraperitoneal carboplatin infusion may be a pharmacologically more reasonable route than intravenous administration as a systemic chemotherapy. A comparative pharmacokinetic analysis of platinum using a new mathematical model after intraperitoneal vs. intravenous infusion of carboplatin—a Sankai Gynecology Study Group (SGSG) study. Gynecol Oncol 2005;99:591–6.