Table 2
Adverse events and response to IP carboplatin-based chemotherapy

Bone marrow toxicity	Number	Percentage
All patients (n = 165)		
Grade 3/4 neutrocytopenia	94	57.0%
Grade 3/4 thrombocytopenia	64	38.8%
Platelet transfusion	35	21.1%
	Carboplatin	
	<400 mg/m^2 (n = 70)	>=400 mg/m^2 (n = 95)
Grade 3/4 neutrocytopenia (P = 0.5247)	54.2% (n = 38)	60.0% (n = 57)
Grade 3/4 thrombocytopenia (P = 0.0014)	25.7% (n = 18)	50.5% (n = 48)
Platelet transfusion (P = 0.0043)	10.6% (n = 8)	30.5% (n = 29)
	Number (%)	
Termination of IP chemotherapy	24 (14.5%)	
Cause of termination of IP chemotherapy		
Catheter related complication	16 (9.7%)	
Obstruction	8	
Infection	4	
Pain	3	
Ileus	1	
Progression of disease	6 (3.6%)	
Chemotherapeutic response in 54 evaluable cases	Number	Percentage
CR	13	24.1%
PR	25	42.3%
NC	10	18.5%
PD	6	11.1%

400 mg/m^2 (median survival = 25 months) (P = 0.0137, Fig. 2a and Table 3). Similarly, PFS also was worse when patients received carboplatin <400 mg/m^2 (P = 0.0083). This tendency was consistent when stage III/IV patients were grouped according to the residual tumor size (Fig. 2b and c). In patients with residual disease <2 cm the median survival was not reached when the carboplatin dose was ≥400 mg/m^2, but it was 24.5 months when the dose of carboplatin was <400 mg/m^2 (P = 0.0543). In patients with residual disease ≥2 cm, median survival of patients who received carboplatin doses of ≥400 mg/m^2 and <400 mg/m^2 were 37 and 30 months, respectively, (P = 0.0469).

When performance status, age, and tumor grades were compared between stages III/IV patients who received IP

Table 3
Median survival of patients

Factors (patient number)	Median progression free survival (months) (5-year PFS)	P Value	Median overall survival (months) (5-year survival)	P value
Stage I (54)	Not reached (81.1%)		Not reached (94.4%)	
II (21)	Not reached (78.4%)		Not reached (87.9%)	
III (72)	22		44	
IV (17)	20	<0.0001	30	<0.0001
Stage III/IV				
Size of residual disease				
<2 cm (37)	22		51	
≥2 cm (53)	19	0.1148	34	0.3422
Dose of carboplatin				
<400 mg/m^2 (38)	14		25	
≥400 mg/m^2 (52)	22	0.0083	51	0.0137
Histological type				
Non clear Cell (76)	22		49	
Clear cell (14)	11	0.0695	13	0.0006
Stage I/II				
Non clear Cell (59)	Not reached (79.8%)		Not reached (91.9%)	
Clear cell (16)	Not reached (87.5%)	0.6556	Not reached (93.8%)	0.6666

Note. P values were calculated by log rank test.

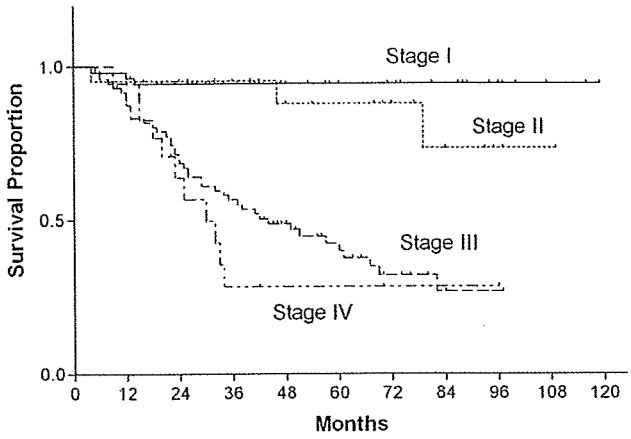

Fig. 1. Overall survival based on the clinical stage of patients who underwent IP carboplatin-based chemotherapy.

carboplatin ≥ 400 mg/m^2 and <400 mg/m^2, they were not significantly different (P = 0.564, 0.562, and 0.776, respectively), although the number of patients with performance status of two receiving IP carboplatin <400 mg/m^2 was slightly more than those who received carboplatin at ≥400 mg/m^2 (eight vs five).

Because Japanese study showed a poorer prognosis for cases with clear cell histology [14], we tested if similar observations could be obtained. The PFS of stage III/IV patients with clear cell histology was marginally worse than the PFS of those with nonclear cell histology (Table 3), but the OS was significantly worse (Table 3 and Fig. 3). However, the survival was not different in stage I/II patients (Table 3).

Univariate and multivariate analyses for stages III/IV cases are summarized in Table 4. Significantly poorer prognostic factors determined by multivariate analysis were advanced clinical stage, clear cell histology, and dose of carboplatin <400 mg/m^2. Residual tumor size was a significant factor in PFS but not in OS.

Discussion

Because IP chemotherapy is a reasonable approach for ovarian cancer, a large number of studies have been published. In fact, in addition to the three large randomized trials that have shown survival advantages in IP arms [1–3], Barakat et al. demonstrated an excellent survival of patients who underwent IP chemotherapy as a consolidation setting [14]. The main reason why IP chemotherapy has not become a standard treatment in spite of this clinical evidence seems to be due to the toxicity of cisplatin, frequently used as an IP chemotherapy agent. Although several phase II studies demonstrated satisfactory responses by IP use of the less toxic agent, carboplatin [15–17], it has not been used

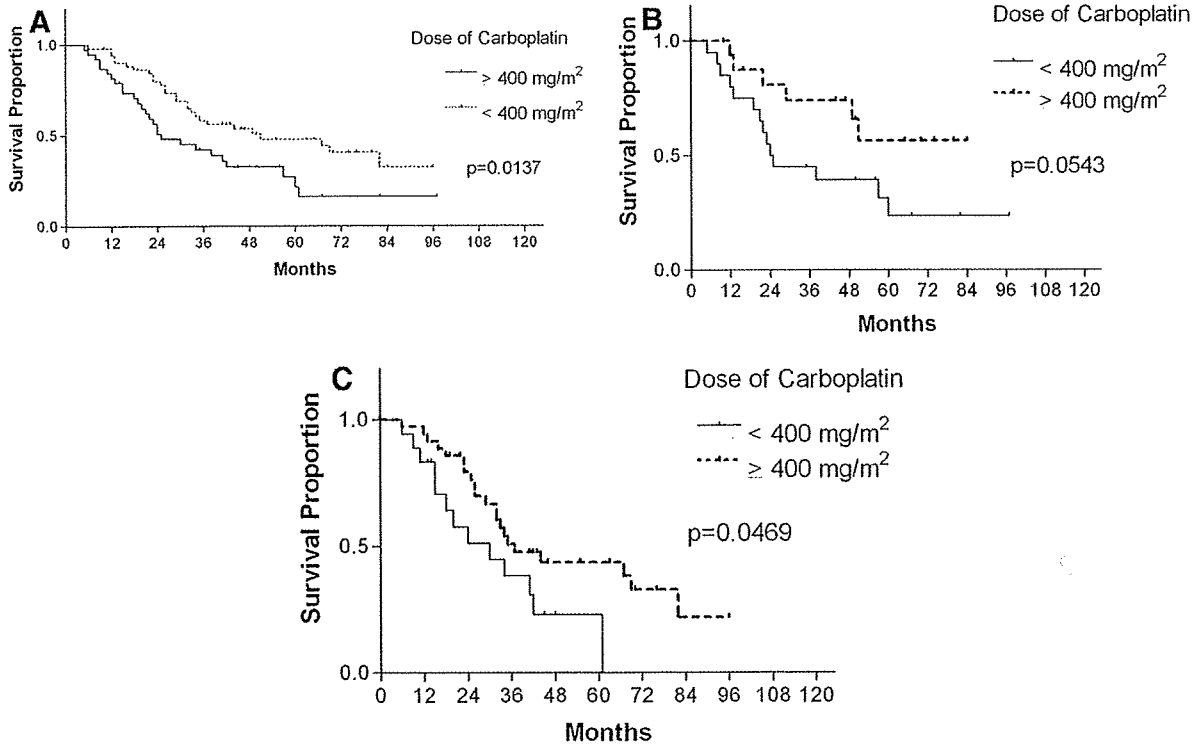

Fig. 2. (a) Overall survival based on the dose of carboplatin (either <400 mg/m^2 or ≥400 mg/m^2) in patients with stage III/IV disease. (b) Overall survival based on the dose of carboplatin (either <400 mg/m^2 or ≥400 mg/m^2) in stage III/IV patients with residual disease <2 cm. (c) Overall survival based on the dose of carboplatin (either <400 mg/m^2 or ≥400 mg/m^2) in stage III/IV patients with residual disease ≥2 cm.

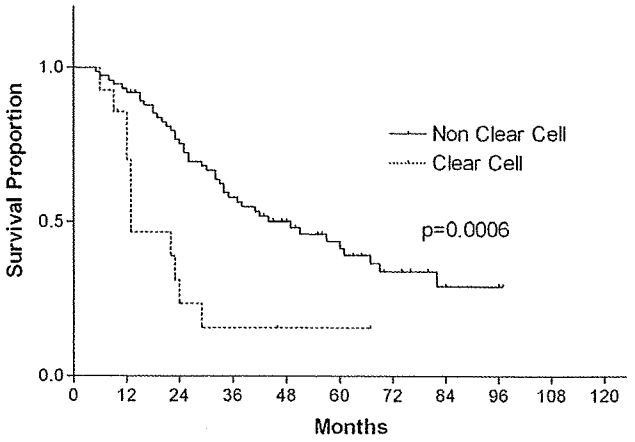

Fig. 3. Overall survival based on clear cell or nonclear cell histological subtypes in patients with stage III/IV disease who underwent IP carboplatin-based chemotherapy.

because of the lack of a sufficient number of clinical data showing efficacy and detailing toxicities.

To the best of our knowledge, this is the largest series that has shown long-term follow-up survival of ovarian cancer patients who underwent IP carboplatin-based chemotherapy. The most impressive observation in this study was the differences in survival for different doses of carboplatin. In stage III/IV ovarian cancer patients, the PFS and OS were significantly worse in those treated with carboplatin doses smaller than 400 mg/m^2 than in those treated with doses ≥ 400 mg/m^2. Incidence of platelet toxicity was significantly higher in patients with carboplatin dose ≥400 mg/m^2. Most patients in this study received carboplatin administration alone or with cyclophosphamide. Incidence of thrombocytopenia may be less when paclitaxel is combined as paclitaxel is known to have a platelet sparing effect [18]. The toxicity of IP carboplatin in combination with paclitaxel must be carefully evaluated before a large clinical trial is performed.

The survival of these patients who had undergone IP carboplatin therapy was excellent. The estimated 5-year survival, calculated by the Kaplan-Meier method, was 94.4% for high-risk stage I patients and 87.9% for stage II patients. These results suggest that IP-carboplatin-based therapy may be an excellent option as an adjuvant therapy for high-risk early ovarian cancer patients.

Also, in the stage III/IV patients with residual disease <2 cm, the median survival was 51 months. This is a little shorter than the median survival of optimally debulked patients with IP chemotherapy arm in the GOG114 study (63.2 months), in which cisplatin and paclitaxel were used as IP therapy. However, in the GOG114, suboptimal cases were defined as those with residual disease <1 cm. Additionally, in our study, paclitaxel was used in only 20% of the patients, because it was not commercially available before 1998. As demonstrated in the United States and European studies [19,20], a combination of paclitaxel with platinum agents improved the survival. Therefore, under these circumstances, it is possible that survival will be better than in our study by combining IP carboplatin therapy with paclitaxel in patients with residual disease <1 cm, particularly if the dose of carboplatin is ≥400 mg/m^2.

Another interesting observation was the good median

Table 4
Univariate analysis and multivariate analysis of progression free survival and overall survival in patients with stage III or IV ovarian cancer patients who underwent IP-carboplatin-based chemotherapy (numbers represent *P* values)

Covariant (patient number)	Progression-free survival		Overall survival	
	Univariate	Multivariate	Univariate	Multivariate
Age				
<50 (30)	0.0910	0.612	0.0713	0.217
≥50 (60)				
Histology				
Clear cell (76)	0.0695	<0.001	0.0007	<0.001
Nonclear cell (14)				
Universal tumor grade				
1 (11)	0.3708	0.568	0.5002	0.774
2/3 (67)				
Size of residual tumor				
<2 cm (37)	0.1148	0.035	0.3077	0.139
≥2 cm (53)				
Dose of carboplatin				
<400 mg/m^2 (38)	0.0187	0.001	0.0063	0.002
≥400 mg/m^2 (52)				
Institution				
Kawasaki (24)	0.44924	0.290	0.2567	0.208
Hokkaido (25)				
Hiroshima (41)				

Note. Univariate analyses were performed using log-rank test. Multivariate analyses were performed using Cox regression model.

survival of stage III/IV patients with residual disease >2 cm. As Miyagi reported, IP administration of carboplatin may be a better systemic chemotherapy route than IV administration [21].

Unfortunately, survival of patients with clear cell carcinoma was significantly worse than those with nonclear cell subtypes, as indicated by another study [22]. We need to confirm this result by a prospective study, and we may have to reconsider the effective regimen for clear cell carcinoma of the ovary.

In conclusion, this study suggests that IP carboplatin-based chemotherapy is a safe and efficient approach for treatment of ovarian cancer patients. Despite the limitations of a retrospective study, we believe the results are sufficiently convincing to be a rationale for conducting a prospective randomized study to clarify the role of IP carboplatin-based chemotherapy with current combination chemotherapy agents.

References

[1] Alberts DS, Liu PY, Hannigan EV, OToole R, Williams SD, Young JA, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996;335:1950–5.

[2] Armstrong DK, Bundy BN, Baergen R, Lele SB, Walker J, Copeland LJ, Urger R. Randomized phase III study of intravenous (IV) paclitaxel and cisplatin versus IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial (GOG 172). Proc Am Soc. Clin. Oncol Abstr # 803 2002.

[3] 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.

[4] Alberts DS, Green S, Hannigan EV, OToole R, Stock-Novack D, Anderson P, et al. Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. J Clin Oncol 1992;10:706–17.

[5] Swenerton K, Jeffrey J, Stuart G, Roy M, Krepart G, Carmichael J, et al. Cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer: a randomized phase III study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1992;10:718–26.

[6] DuBois A, Lueck HJ, Meier W, Moebus V, Costa SD, Bauknecht T, Richter B, Warm M, Schroeder W, Olbricht S, Nitz U, Jackisch C. Cisplatin/paclitaxel vs carboplatin/paclitaxel in ovarian cancer: update of an Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Study Group Trial. Proc Am Soc Clin Oncol 1999.

[7] Ozols R, Bundy BN, Fowler JM, Clark-Pearson DL, Mannel R, Hartenbach E, Baergen R. Randomized phase III study of cisplatin (CIS)/paclitaxel (PAC) versus carboplatin (CARBO)/pAC in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group Trial (GOG 158) (Meeting abstract). Proc Am Soc Clin Oncol 1999.

[8] Los G, van Vugt MJ, Pinedo HM. Response of peritoneal solid tumours after intraperitoneal chemohyperthermia treatment with cisplatin or carboplatin. Br J Cancer 1994;69:235–41.

[9] Markman M, Reichman B, Hakes T, Rubin S, Lewis JL Jr, 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.

[10] Fujiwara K, Yamauchi H, Sawada S, Koike H, Mohri H, Ohishi Y, et al. The pharmacokinetics of intraperitoneal (IP) carboplatin (CBDCA) and dose-up study of intravenous (IV) cyclophosphamide (CPM) in combination with IP CBCDA for advanced ovarian cancer patients. Gan To Kagaku Ryoho 1992;19:2373–9 In Japanese.

[11] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

[12] Mantel N, Haenzel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1958;22:718–48.

[13] Cox DR. Regression models and life-tables. J R Stat Soc B 1972;34: 187–220.

[14] Barakat RR, Sabbatini P, Bhaskaran D, Revzin M, Smith A, Venkatraman E, et al. Intraperitoneal chemotherapy for ovarian carcinoma: results of long-term follow-up. J Clin Oncol 2002;20:694–8.

[15] Guastalla JP, Lhomme C, Kerbrat P, Mayer F, Namer M, Goupil P, et al. Phase II trial of intraperitoneal carboplatin in ovarian carcinoma patients with macroscopic residual disease at second-look laparotomy. A multicentre study of the French Federation Nationale des Centres de Lutte Contre le Cancer. Ann Oncol 1994;5:127–32.

[16] Malmstrom H, Simonsen E, Westberg R. A phase II study of intraperitoneal carboplatin as adjuvant treatment in early-stage ovarian cancer patients. Gynecol Oncol 1994;52:20–5.

[17] McClay EF, Braly PD, Kirmani S, Plaxe SC, Kim S, McClay ME, et al. A phase II trial of intraperitoneal high-dose carboplatin and etoposide with granulocyte macrophage-colony stimulating factor support in patients with ovarian carcinoma. Am J Clin Oncol 1995;18: 23–6.

[18] Fujiwara K, Yamauchi H, Suzuki S, Ishikawa H, Tanaka Y, Fujiwara M, Kohno I. Platelet sparing effect of paclitaxel was not related to the change of pharmacology of carboplatin. Cancer Chemother Pharmacol 2001;47:22–6.

[19] 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;23:40–7.

[20] Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000;92:699–708.

[21] Miyagi Y, Fujiwara K, Fujiwara M, Kohno I, Kigawa J, Itamochi H, Terakawa N. Intraperitoneal (IP) infusion is a pharmacologically more reasonable route for systemic hemotherapy of carboplatin—A comparative pharmacokinetic analysis of platinum using a new mathematical model after IP vs. IV infusion of carboplatin—A Sankai Gynecology Study Group (SGSG) study. Proc Am Soc Clin Oncol Abstr #2167, 2003.

[22] Sugiyama T, Kamura T, Kigawa J, Terakawa N, Kikuchi Y, Kita T, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer 2000;88:2584–9.

Int J Gynecol Cancer 2005, **15**, 426–431

ORIGINAL ARTICLE

Preliminary toxicity analysis of intraperitoneal carboplatin in combination with intravenous paclitaxel chemotherapy for patients with carcinoma of the ovary, peritoneum, or fallopian tube

K. FUJIWARA*, S. SUZUKI*, H. ISHIKAWA*, T. ODA*, E. AOTANI† & I. KOHNO*
**Department of Obstetrics and Gynecology, Kawasaki Medical School, Kurashiki City, Japan; and*
†Department of Nursing, Kawasaki University of Medical Welfare, Kurashiki City, Japan

Abstract. Fujiwara K, Suzuki S, Ishikawa H, Oda T, Aotani E, Kohno I. Preliminary toxicity analysis of intraperitoneal carboplatin in combination with intravenous paclitaxel chemotherapy for patients with carcinoma of the ovary, peritoneum, or fallopian tube. *Int J Gynecol Cancer* 2005;15:426–431.

The objective of this study was to provide preliminary toxicity data of multiple-cycle combination chemotherapy with intraperitoneal (IP) carboplatin and intravenous (IV) paclitaxel for further clinical trials. The toxicity data of 42 patients with müllerian carcinoma who underwent IP carboplatin therapy in combination with IV paclitaxel were retrospectively analyzed. Chemotherapy was repeated through the Bard IP port placed at initial surgery using IV paclitaxel at 175 mg/m^2 followed by IP carboplatin. The doses of carboplatin were either at area under the curve (AUC) = 5, 6, 6.5, 7, or 7.5. The toxicity data in a total of 237 cycles were analyzed. The median number of cycles for IP chemotherapy was 6 (range: 3–12). The incidences of maximal grade toxicities in all cycles were: grade (G)2/3 nausea/vomiting, 23.8%; G2/3 constipation, 42.9%; G2 abdominal pain, 28.6%; G2/3 sensory neuropathy, 14.3%; motor neuropathy, 4.8%; myalgia/arthralgia 33.4%; G3/4 neutrocytopenia, 85.4%; and G3/4 anemia, 35.4%. These were not related to the dose of carboplatin. The incidences of G3 thrombocytopenia in relation to the dose of carboplatin were AUC = 5, 0%; 6, 31.6%; 6.5, 44.4%; 7, 25.0%; and 7.5, 80%. G4 thrombocytopenia did not occur. A dose of carboplatin between AUC = 6 and 7 with IV paclitaxel at 175 mg/m^2 is warranted for further evaluation.

KEYWORDS: carboplatin, intraperitoneal chemotherapy, paclitaxel, toxicity.

Ovarian carcinoma spreads widely inside the peritoneal cavity at its early stage. Therefore, intraperitoneal (IP) administration of anticancer drugs would seem to be a reasonable approach. In fact, three large randomized studies investigating the role of IP cisplatin plus or minus IP paclitaxel have demonstrated a survival benefit of IP cisplatin therapy[1–3]. Nevertheless, IP cisplatin-based chemotherapy has not become a standard treatment in daily practice. This is mainly because the toxicity of cisplatin, such as severe nausea/vomiting

Address correspondence and reprint requests to: Keiichi Fujiwara, MD, PhD, Department of Obstetrics and Gynecology, Kawasaki Medical School, 577 Matsushima, Kurashiki City 701-0192, Japan.

and/or renal toxicity that requires a large amount of hydration for prevention, is now becoming unacceptable. It has been demonstrated that carboplatin, a less toxic platinum agent, has an equivalent efficacy on survival, when administered intravenously in combination with cyclophosphamide[4,5] or paclitaxel[6,7].

The reason why carboplatin has not been used as an IP chemotherapy drug is based on two studies, an animal experiment and retrospective clinical report. In the animal study, Los *et al.* showed that approximately ten times more carboplatin than cisplatin was required to obtain equivalent tissue platinum concentrations[8]. Based on this result, Markman *et al.* retrospectively analyzed their clinical data and showed that the response rate was better in cisplatin-based regimens[9]. However, in this Markman study the dose of carboplatin was too low (200–300 mg/m^2) compared to relatively a large dose of cisplatin (100 mg/m^2). For example, the dose of intravenous (IV) administration of carboplatin in the Gynecologic Oncology Group (GOG) 158 study[7] was AUC = 7.5, which is equivalent to a median dose of 471 mg/m^2[10], and the dose of cisplatin in the same study was 75 mg/m^2. In the GOG 158 study the survival was equivalent in carboplatin and cisplatin arms. Therefore, we believed that the dose of IP administration of carboplatin was critical.

In fact, as we recently reported, the dose of IP carboplatin was a significant prognostic factor in epithelial ovarian cancer patients[11]. In our retrospective study we analyzed long-term survival data for 165 ovarian cancer patients who underwent IP carboplatin-based chemotherapy. The median survival of patients with stage III/IV disease was 51 months with carboplatin doses of 400 mg/m^2 or more, but it was only 25 months with carboplatin doses smaller than 400 mg/m^2 ($P = 0.002$). Although the majority of the patients in the study did not receive current standard combination therapy with paclitaxel, the survival data was excellent when appropriate dose of carboplatin was administered. Therefore, we believe that it is of great interest and very important to examine if IP administration of carboplatin is better than IV administration of carboplatin in combination with paclitaxel by a prospective randomized phase III study, but first a determination of the optimal dose of IP carboplatin is necessary. The GOG is now planning a phase I and feasibility study for IP carboplatin with IV paclitaxel.

In order to provide preliminary toxicity data to the Phase I Committee of GOG for the future phase I study, we decided to analyze the toxicity of multiple-cycle combination chemotherapy with IP carboplatin and IV paclitaxel at 175 mg/m^2, particularly focusing on thrombocytopenia.

Materials and methods

The toxicity data of 42 patients with carcinoma of the ovary ($n = 36$), peritoneum ($n = 4$), or fallopian tube ($n = 2$) who underwent IP carboplatin therapy in combination with IV paclitaxel were analyzed retrospectively. Based on our pharmacological study showing that approximately 67% of IP-administered carboplatin was absorbed and entered into systemic circulation[12], IP carboplatin chemotherapy has been considered to be a route of systemic chemotherapy, and its role has been explored in the Kawasaki Medical School. Therefore, eligible patients were those with high-risk stage I through stage IV carcinoma of ovary, peritoneum, or fallopian tube regardless the size of residual disease. The patients in this study were treated either as subjects of a dose-finding study[13], phase II study (unpublished data), or out of protocol. For the patients in the dose-finding study or phase II study, the protocols were approved by the ethical committee of the Kawasaki Medical School and written informed consent was obtained from each patient. The patients treated in the out of protocol setting ($n = 4$) were those who did not meet the entry criteria of the protocol, such as a history of treatment for other malignancies within 5 years, but they have never received chemotherapy or radiation therapy. The doses of chemotherapeutic drugs for the patients treated out of protocol were calculated and controlled according to the study protocol. All patients had normal bone marrow, liver, renal, respiratory, and cardiac functions. Patients with impaired function of at least one of those organs were excluded from this analysis.

All patients received initial laparotomy, and the Bard IP port was placed before the abdomen was closed. Chemotherapy was repeated using IV administration of paclitaxel at 175 mg/m^2, followed by IP administration of carboplatin through the IP port. Paclitaxel was dissolved in 500 mL saline and administered intravenously as a 3-h drip infusion. For IP carboplatin administration, 500 mL of 5% glucose was infused through the IP port during paclitaxel administration, and then the calculated dose of carboplatin was administered as a bolus infusion. The IP port and catheter were flushed by 5 mL of heparin after carboplatin infusion. The position of the patient was rotated to diffuse the fluid inside the entire peritoneal cavity. The infused carboplatin was not drained afterward.

The dose of carboplatin was calculated using the Calvert formula[14]. The glomerular filtration rate was substituted by the estimated creatinine clearance rate calculated by the Cockcroft–Gault formula[15]. The target AUC of the patients in this study was either at AUC = 5 ($n = 5$), 6 (19), 6.5 (9), 7 (4), or 7.5 (5).

 International Journal of Gynecological Cancer **15**, 426–431

The blood counts were checked at least twice weekly. NCI-CTC version 2 grading system was applied. When hematological toxicities greater than grade 2 occurred, blood counts were checked more frequently. The dose of carboplatin was reduced by a target AUC of −0.5 for the next cycle when a grade 2 thrombocytopenia occurred. When grade 3 thrombocytopenia occurred, the dose of carboplatin was reduced by a target AUC of −1 for the subsequent cycle. The dose of paclitaxel was not changed when grade 3/4 neutropenia was observed, but prophylactic use of granulocyte colony-stimulating factor for the following courses was allowed in these cases.

When grade 3 neurotoxicity was observed, the use of paclitaxel was terminated. All the IP catheter-related toxicity data were analyzed as long as the IP carboplatin therapy was continued. However, other toxicity data were not collected when administration of paclitaxel was terminated because the purpose of this study is to analyze toxicities of the combination chemotherapy with IP carboplatin and IV paclitaxel.

The number of chemotherapeutic cycles was determined based on the patients' condition. Basically patients with stage I disease were scheduled to receive three to six cycles of treatment, and patients with advanced stage disease were scheduled to receive six or more cycles.

Results

The mean age of the 42 patients was 56 ± 14 years. The distribution of stages was I, 8; II, 5; III, 24; and IV, 5. Toxicity data were available in a total of 237 cycles. The median number of cycles for IP chemotherapy was 6 (range: 3–12). The indicated toxicity data are the worst grades recorded during all the cycles unless otherwise indicated.

Nonhematological toxicities

IP catheter-related complications occurred in two patients (4.8%), one infection and one intestinal perforation probably due to catheter infection. The patient with intestinal perforation died because of severe peritonitis. There was no inflow IP catheter obstruction in this series. The incidences of the maximal grade of adverse events in all cycles were as follows: grade (G)2/3 nausea/vomiting, 23.8%; G2/3 constipation, 42.9%; G2 abdominal pain, 28.6%; G2/3 sensory neuropathy, 14.3%; G3 motor neuropathy, 4.8%; and G3

Table 1. Nonhematological toxicity of patients who underwent administration of IP carboplatin at various doses in combination with IV paclitaxel at 175 mg/m^2

Carboplatin AUC		5	6	6.5	7	7.5
Number of patients		5	19	9	4	5
Fatigue	G1	3 (60%)	8 (42.1%)	3 (33.3%)	1 (25%)	5 (100%)
	G2	0	4 (21.1%)	1 (11.1%)	1 (25%)	0
	G3	0	0	1 (11.1%)	0	0
Nausea	G1	3 (60%)	10 (52.6%)	6 (66.7%)	2 (50%)	2 (40%)
	G2	1 (20%)	4 (21.1%)	2 (22.2%)	1 (25%)	1 (20%)
	G3	0	1 (5.2%)	0	0	0
Vomiting	G1	1 (20%)	3 (15.8%)	3 (33.3%)	0	3 (60%)
	G2	1 (20%)	5 (26.3%)	1 (11.1%)	0	1 (20%)
	G3	0	0	0	0	0
Constipation	G1	2 (40%)	6 (31.6%)	0	0	2 (40%)
	G2	2 (40%)	6 (31.6%)	5 (55.6%)	2 (50%)	1 (20%)
	G3	0	0	2 (22.2%)	0	0
Abdominal pain	G1	0	8 (42.1%)	2 (22.2%)	0	4 (80%)
	G2	1 (20%)	3 (17.8%)	5 (55.6%)	2 (50%)	1 (20%)
	G3	0	0	0	0	0
Sensory neuropathy	G1	0	12 (52.6%)	2 (22.2%)	2 (50%)	3 (60%)
	G2	0	0	4 (44.4%)	0	1 (20%)
	G3	0	0	1 (11.1%)	0	0
Motor neuropathy	G1	0	2 (10.5%)	1 (11.1%)	0	0
	G2	0	1 (5.2%)	0	0	0
	G3	0	1 (5.2%)	0	00	
Myalgia/arthralgia	G1	2 (40%)	5 (26.3%)	2 (22.2%)	0	1 (20%)
	G2	0	5 (26.3%)	5 (55.6%)	1 (25%)	1 (20%)
	G3	0	1 (5.3%)	1 (11.1%)	0	0

Table 2. Relationship between the doses of IP carboplatin, incidences of grade 3/4 neutropenia and thrombocytopenia, and percentages of patients who required dose reduction of carboplatin because of grade 2 or 3 thrombocytopenia

Initial dose of carboplatin (AUC)	5	6	6.5	7	7.5
Number of patients	5	19	9	4	5
G3 Neutrocytopenia	20%	31.6%	22.2%	50.0%	20%
G4 Neutrocytopenia	20%	57.9%	77.8%	50.0%	80%
G2 Thrombocytopenia	40%	21.1%	11.1%	25.0%	20%
G3 Thrombocytopenia	0%	31.6%	44.4%	25.0%	80%
Carboplatin dose reduction	40%	42.1%	44.4%	50.0%	100%

G4 thrombocytopenia was not observed.

myalgia/arthralgia 33.4%. As shown in Table 1 these toxicities were not related to the dose of carboplatin.

Hematological toxicities

Grade 3/4 anemia occurred in 35.4% of patients. The relationship of the initial dose of carboplatin to incidences of G3/4 neutrocytopenia and G2/3 thrombocytopenia is summarized in Table 2.

Neutrocytopenia

The incidence of G4 neutropenia was 20% in the cohort of AUC = 5, and it increased as the dose of carboplatin increased to AUC = 6.5, where it then seemed to reach a plateau, although this is not certain because the number of patients in the cohort of AUC = 7 was too small. Febrile neutropenia was observed in two patients at the level of AUC = 7.5, and these patients were treated with granulocyte colony-stimulating factor and antibiotics.

Thrombocytopenia

The relationship between the initial dose of carboplatin and incidences of G2 and G3 thrombocytopenia is summarized in Table 2. The incidence of G3 thrombocytopenia seemed to increase as the dose of carboplatin escalated, but, again, this was uncertain because the number of patients in the cohort of AUC = 7 was only four. G4 thrombocytopenia did not occur in this series. No platelet infusion was given to the patients in this study.

The distribution of patients who experienced dose reduction of carboplatin in terms of the treatment cycle, when dose reduction was necessary, is summarized in Table 3. Eighty percent of patients in the cohort of AUC = 7.5 required dose reduction at the second cycle because of grade 3 thrombocytopenia. The distribution of patients who required dose reduction due to grade 3 thrombocytopenia appears to be similar in the cohorts of AUC = 6 and 6.5, but it is not clear in the cohort of AUC = 7 because of the small number of patients.

Discussion

IP administration of carboplatin for ovarian cancer treatment is now becoming of greater interest because it is easy to administer and less toxic than cisplatin. Carboplatin is as efficacious as cisplatin in ovarian cancer patients when administered intravenously[4–7]. IP administration of cisplatin has been shown to have a survival advantage compared to IV administration[1–3]. However, IP carboplatin has never been extensively studied because of two studies, one preclinical[8] and another clinical[9], that have shown that carboplatin is less efficacious than cisplatin as an IP chemotherapy agent. However, these studies must be challenged. The former study showed that approximately ten times carboplatin than cisplatin was required to obtain equivalent tissue concentration of platinum, but it did not discuss the difference of bioactivities between cisplatin and carboplatin. The dose of carboplatin used in the latter clinical study was significantly lower than the dose of cisplatin. A recent

Table 3. Relationship between the initial dose of IP carboplatin and time of dose reduction because of grade 2 or 3 thrombocytopenia

Carboplatin dose (AUC)		5		6		6.5		7		7.5	
Patients treated (*n*)		5		19		9		4		5	
Patients dose reduced (*n*)		2		8		4		2		5	
Time of dose reduction due to G2 or G3 thrombocytopenia		Thrombocytopenia									
		G2	G3	G2	G3	G2	G3	G2	G3	G2	G3
Second cycle	Patients (*n*)	0	0	1	1	0	1	0	0	0	4
Third cycle	Patients (*n*)	1	0	0	2	0	1	0	2	0	0
Fourth cycle	Patients (*n*)	0	0	0	2	0	2	0	0	0	0
Fifth cycle	Patients (*n*)	0	0	1	0	0	0	0	0	0	1
>Sixth cycle	Patients (*n*)	1	0	0	1	0	0	0	0	0	0

pharmacological study suggested that serum AUC of free platinum after IP carboplatin infusion was exactly the same as the serum AUC after IV administration[16], while IP AUC was significantly higher when carboplatin was administered in the IP cavity. Therefore, it seems likely that IP carboplatin administration is more efficacious than IV administration. This hypothesis must be tested by a prospective randomized study, but toxicities of IP carboplatin infusion have not been well defined. In this study we collected retrospective toxicity data to be used as a basis for conducting a phase I study.

Thrombocytopenia is the major toxicity concern in the combination chemotherapy with carboplatin. Since grade 3 thrombocytopenia occurred in four of five patients in the cohort of AUC = 7.5, this AUC seems to be too toxic for further evaluation. The incidence of dose reduction in the present analysis was approximately 50% when the initial dose of carboplatin was between AUCs of 5 and 7. This is because patients had dose reductions when grade 2 thrombocytopenia occurred. It is possible that the incidence of dose reduction may be less if the criteria for dose reduction were restricted to the occurrence of grade 3 thrombocytopenia. However, it is also possible that more cases of grade 3 thrombocytopenia would occur in the subsequent cycles. There was no clear relationship between the carboplatin dose and incidence of grade 3 thrombocytopenia (Table 2). This may be because the number of patients in the AUC = 7 were only four. Therefore, it is necessary to determine the most appropriate dose for IP administration of carboplatin between AUC = 6 and 7 in combination with IV paclitaxel at 175 mg/m^2.

It was not clear if the incidence of grade 4 neutropenia might be related to the dose of carboplatin because neutrocytopenia is common when paclitaxel is combined.

The incidence of nonhematological toxicities appeared to be reasonable (Table 1). IP catheter-related toxicity was rare. There was one catheter infection and one intestinal perforation probably due to infection. It is difficult to make a direct comparison between the occurrence of infection and carboplatin itself because the incidence was very low in the present study and in our previous retrospective analysis[11]. These infectious complications, however, must be prevented by a careful manipulation at the time of needle puncture into the IP port system by applying strict sterilization guidelines.

We understand that the results of this study have problems as a nature of retrospective analysis, such as a wide variety in the number of courses of treatment. Also, the number of patients was too small for statistical analysis. Nevertheless, we believe that the results of this study have provided useful information for designing a phase I study in the future. As a summary, evaluation of IP carboplatin administration using a target AUC between 6 and 7 is warranted to determine the dose of IP carboplatin for a phase III study targeting thrombocytopenia.

References

1 Markman M, Bundy BN, Alberts DS *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 BN, Baergen R *et al.* Randomized phase III study of intravenous (IV) paclitaxel and cisplatin versus IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial (GOG 172). *Proc Am Soc Clin Oncol* 2002; Abstract 803.

3 Alberts DS, Liu PY, Hannigan EV *et al.* Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;**335:**1950–5.

4 Swenerton K, Jeffrey J, Stuart G *et al.* Cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer: a randomized phase III study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1992;**10:**718–26.

5 Alberts DS, Green S, Hannigan EV *et al.* Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. *J Clin Oncol* 1992;**10:**706–17.

6 DuBois A, Lueck HJ, Meier W *et al.* A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) study group trial. *J Natl Cancer Inst* 2003;**95:**1320–9.

7 Ozols RF, Bundy BN, Greer BE *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:**3194–200.

8 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.

9 Markman M, Reichman B, Hakes T *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.

10 Bookman MA, McGuire WP III, Kilpatrick D *et al.* Carboplatin and paclitaxel in ovarian carcinoma: a phase I study of the Gynecologic Oncology Group. *J Clin Oncol* 1996;**14**:1895–902.
11 Fujiwara K, Sakuragi N, Yoshida N *et al.* First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up. *Gynecol Oncol* 2003;**90**:637–43.
12 Fujiwara K, Yamauchi H, Sawada S *et al.* The pharmacokinetics of intraperitoneal (IP) carboplatin (CBDCA) and dose-up study of intravenous (IV) cyclophosphamide (CPM) in combination with IP CBCDA for advanced ovarian cancer patients. *Gan To Kagaku Ryoho* 1992;**19**:2373–9.
13 Fujiwara K, Suzuki S, Ishikawa H *et al.* Dose-escalation of intraperitoneal (IP) carboplatin in combination with 3-hour intravenous (IV) infusion of paclitaxel at 175 mg/m? as a first-line chemotherapy for patients with epithelial ovarian cancer. *Proc Am Soc Clin Oncol* 2001; Abstract 2147.
14 Calvert AH, Newell DR, Gumbrell LA *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;**7**:1748–56.
15 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.
16 Miyagi Y, Fujiwara K, Fujiwara M, *et al.* Intraperitoneal (IP) infusion is a pharmacologically more reasonable route for systemic chemotherapy of carboplatin—a comparative pharmacokinetic analysis of platinum using a new mathematical model after IP vs. IV infusion of carboplatin. A Sankai Gynecology Study Group (SGSG) study. *Proc Am Soc Clin Oncol* 2003; Abstract 2167.

Accepted for publication February 18, 2004

Int J Gynecol Cancer 2008

Combination chemotherapy of intraperitoneal carboplatin and intravenous paclitaxel in suboptimally debulked epithelial ovarian cancer

S. NAGAO*, K. FUJIWARA*, R. OHISHI*, Y. NAKANISHI*, N. IWASA*, M. SHIMIZU*, T. GOTO* & K. SHIMOYA†

**Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Yamane, Hidaka City, Japan; and †Department of Obstetrics and Gynecology, Kawasaki Medical School, Kurashiki City, Japan*

Abstract. Nagao S, Fujiwara K, Ohishi R, Nakanishi Y, Iwasa N, Shimizu M, Goto T, Shimoya K. Combination chemotherapy of intraperitoneal carboplatin and intravenous paclitaxel in suboptimally debulked epithelial ovarian cancer. *Int J Gynecol Cancer* 2008.

The objective of this study was to retrospectively assess the efficacy and safety of combination chemotherapy of intraperitoneal (IP) carboplatin and intravenous (IV) paclitaxel in suboptimally debulked ovarian cancer. Between March 1998 and March 2006, 44 patients with histologically confirmed epithelial ovarian carcinoma or peritoneal carcinoma with a residual mass greater than 1 cm received combination chemotherapy of IV paclitaxel and IP carboplatin. Administration of IV paclitaxel at 175 mg/m^2 immediately followed by IP carboplatin at an area under the curve of 6 was scheduled every 3 weeks for at least six cycles. The diagnosis and stage were ovarian carcinoma stage II in 8, III in 25, and IV in 6 cases, and peritoneal carcinoma stage III in 5 cases. Eighty-three percent of patients completed more than six cycles of chemotherapy. The incidences of grade 3/4 hematologic toxicities were 41 (93%) for neutrocytopenia, 10 (41%) for thrombocytopenia, and 18 (23%) for anemia. Observed grade 3/4 nonhematologic toxicities were 1 (2%) for allergy, 1 (2%) for fatigue, 1 (2%) for vomiting, 1 (2%) for liver dysfunction, and 4 (9%) for peripheral neuropathy. Two patients (5%) encountered catheter problems (one obstruction and one infection). Overall response rate was 80% (16 complete response, 19 partial response, 3 stable disease, and 6 progressive disease). Median progression-free survival and overall survival were 24 and 31 months, respectively. Combination chemotherapy of IP carboplatin and IV paclitaxel is effective and safe in suboptimally debulked ovarian cancer, and further evaluation is warranted.

KEYWORDS: carboplatin, intraperitoneal chemotherapy, suboptimally debulked epithelial ovarian cancer.

A characteristic feature of ovarian cancer is intraperitoneal (IP) spread of disease even in the early stages. IP delivery of chemotherapy has been considered a reasonable therapeutic approach in patients with ovarian cancer. Recently, three large randomized phase III clinical trials conducted by the Gynecologic Oncology Group (GOG) have shown that IP chemotherapy is clearly superior to intravenous (IV) cisplatin-based chemotherapy in terms of survival[1–3]. Based on the results of these trials, the National Cancer Institute (NCI) recommended that strong consideration should be given to a regimen containing IP cisplatin combined with IV only or IV plus IP taxane in women with optimally debulked epithelial ovarian cancer[4]. However, this treatment has not achieved broad acceptance because of toxicity concerns. More safe and convenient therapy is now needed.

Carboplatin and cisplatin have equivalent efficacy against epithelial ovarian cancer, and carboplatin is less toxic and more convenient than cisplatin. As a consequence, carboplatin has become a standard platinum compound in epithelial ovarian cancer when given IV[5,6]. It has also been shown to achieve objective responses when delivered by the IP route in previous

Address correspondence and reprint requests to: Keiichi Fujiwara, MD, PhD, Department of Gynecologic Oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka City 350-1241, Japan. Email: fujiwara@saitama-med.ac.jp

doi:10.1111/j.1525-1438.2008.01192.x

retrospective studies[7–9]. Replacing cisplatin with carboplatin is a reasonable way to reduce IP cisplatin-related toxicity, although a phase III trial is needed to confirm the advantages of IP carboplatin.

The target patient population for IP chemotherapy has been those with small residual disease. The reason for this is the poor direct penetration of anticancer drugs into the tumors[10]. However, several pharmacologic studies have suggested that the area under the curve (AUC) of platinum in the serum after administration of cisplatin or carboplatin is similar regardless of the route of administration[11].

Recently, Miyagi *et al.*[12] reported a comparative pharmacokinetic study of IP and IV carboplatin using the three-compartment mathematical model in patients who received paclitaxel simultaneously. Using this model, 24-h free platinum AUC in the serum was identical regardless of whether carboplatin was administered IP or IV. However, the 24-h platinum AUC in the peritoneal cavity was approximately 17 times higher when carboplatin was administered by the IP route. The results of this study imply that IP infusion of carboplatin is feasible not only as a regional therapy but also as a more reasonable route for systemic chemotherapy. In other words, IP infusion of carboplatin may produce an additional effect to peritoneal tumors by exposing high concentration of anticancer drug without systemic effect of carboplatin compromising.

IP carboplatin may thus be valuable not only in patients with optimal tumors but also in those with suboptimal tumors. We conducted a retrospective study to assess the efficacy and safety of combination chemotherapy of IV paclitaxel and IP carboplatin in suboptimally debulked ovarian cancer, for a future trial.

Materials and methods

Patients

The study population comprised patients with pathologically proven epithelial ovarian carcinoma or peritoneal carcinoma with a residual mass greater than 1 cm. All patients received combination chemotherapy of IP carboplatin and IV paclitaxel at Kawasaki Medical School Hospital between March 1998 and March 2006. We reviewed the medical records and extracted pertinent information on age, performance status according to World Health Organization criteria at the beginning of chemotherapy, tumor site, stage and histology, surgical procedure, size and site of residual tumor, number of courses of chemotherapy completed, grade of hematologic and nonhematologic toxicity, clinical response, progression-free survival (PFS), and overall survival (OS). Chemotherapy-induced toxicity was graded according to the NCI common toxicity criteria version 2. Tumor size was measured using computed tomography or magnetic resonance imaging every two or three cycles. The response was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients received secondary debulking surgery if a sufficient response was achieved. Thus, confirmation of an objective response no less than 4 weeks after the criteria for response were first met was not required. PFS was defined as the date from primary surgery to the date of the appearance of disease progression. OS was defined as the observed length of life from primary surgery to death or, for living patients, the date of last contact. PFS and OS were calculated using the Kaplan–Meier method.

Operative procedure

All patients received debulking or staging surgery primarily. We did not perform radical surgery in patients in whom completion of optimal debulking surgery was judged impossible. In some patients, a laparoscopic staging procedure was performed. Patients who responded to chemotherapy received interval or secondary debulking surgery after three to six cycles of chemotherapy. A Bard IP port system was placed within the subcutaneous fat before the abdomen was closed. The IP port was placed laparoscopically in patients who underwent a laparoscopic staging procedure. The site of port placement was usually at the right upper abdomen.

Chemotherapy

Chemotherapy comprised IV paclitaxel at 175 mg/m^2 diluted in 500 mL of 5% glucose administered over 3 h, followed by carboplatin at a dose based on AUC = 6, which is administered through the IP port. For IP carboplatin diffusion, 500–1000 mL of 5% glucose was infused through the IP port during paclitaxel administration, and then the calculated dose of carboplatin was administered as a bolus infusion. The carboplatin dose was calculated using the method of Calvert *et al.*, and the glomerular filtration rate was estimated using the Cockcroft formula[13,14]. Chemotherapy was scheduled to be repeated every 21 days for at least six cycles. Standard antiemetic therapy with ondansetron or granisetron and dexamethasone were administered to all patients. Granulocyte colony-stimulating factor was administered daily at a dose of 2 μg/kg

subcutaneously to patients who experienced grade 4 neutropenia or febrile neutropenia. Treatment was delayed when the granulocyte count was under 1500/μL or the platelet count was less than 100,000/μL. In cases of febrile neutropenia, the dose of paclitaxel was reduced to 135 mg/m^2 and the dose of carboplatin was reduced by a target AUC = 1 for the subsequent cycle. If the platelet count was less than 50,000/μL, the dose of carboplatin was reduced by AUC = 1 in the next cycle. When grade 3 or 4 neuropathy was observed, paclitaxel was replaced by docetaxel at 60 mg/m^2. In the patients who experienced grade 3 or 4 nonhematologic toxicity, except neuropathy, vomiting, or allergy, the dose of paclitaxel was reduced to 135 mg/m^2, and the dose of carboplatin was reduced by AUC = 1 in the next cycle.

Results

We identified 44 patients. Their clinical characteristics are listed in Table 1. The mean age was 59.5 years (range 33–80 years). Clinical diagnosis and FIGO stage were as follows: ovarian cancer stage II, 8 patients; stage III, 25 patients; stage IV, 6 patients; and peritoneal cancer stage III, 5 patients. The histology was 29 serous adenocarcinomas, 3 endometrioid adenocarcinomas, 3 mucinous adenocarcinomas, 3 clear cell adenocarcinomas, and 6 other types (5 adenocarcinoma otherwise not specified and 1 poorly differentiated carcinoma). Seven patients underwent a laparoscopic staging procedure including biopsy. No patient underwent colon or small bowel resection. About half of the patients had a large residual tumor greater than 5 cm, and most patients had residual tumor in the abdominal cavity.

Table 2 shows hematologic toxicity after combination chemotherapy of IP carboplatin and IV paclitaxel. Grade 3/4 neutropenia, thrombocytopenia, and anemia were observed in 93%, 23%, and 41% of the patients, respectively. The most common hematologic toxicity was neutropenia. There was no case of febrile neutropenia. As shown in Table 3, nonhematologic toxicity was mild, and grade 3/4 toxicity was rare. The observed grade 3/4 nonhematologic toxicities were one allergy, one fatigue, one vomiting, one liver dysfunction, and four peripheral neuropathy. One patient experienced IP catheter obstruction during the 11th course and another experienced IP catheter infection during the 6th course. The incidence of catheter-related toxicity was low (5%). There were no cases of ileus or perforation of the intestine. Among the 44 patients, 37 (84%) completed six or more cycles. Reasons for discontinuing therapy before the six planned cycles included allergy to paclitaxel ($n = 1$), liver dysfunction ($n = 1$), neuropathy ($n = 2$), disease progression ($n = 2$), and patient refusal ($n = 1$).

Of the 44 patients, all had residual tumors that could be evaluated for clinical response by computed tomography or magnetic resonance imaging. There were 16 (36%) complete responses and 19 (43%) partial responses, and the clinical response rate was 80%. On the other hand, there were three (7%) stable disease and six (14%) disease progression. The median follow-up time was 18 months (range 7–80 months). There were 26 recurrences and 20 deaths, and the estimated median PFS and OS were 24 and 31 months, respectively (Fig. 1).

Table 1. Clinical characteristics of patients

Total number of patients	44		
Mean age (years)	59.5 (range 33–80)		
PS			
0–1	37		
2–3	7		
Clinical diagnosis and stage		Histology	
Ovarian cancer		Serous	29
Stage II	8	Endometrioid	3
Stage III	25	Mucinous	3
Stage IV	6	Clear cell	3
Peritoneal cancer		Others	6
Stage III	5		
Maximum size of residual tumor (cm)		Site of residual tumor	
1–2	15	Peritoneal cavity	42
3–4	8	Lymph node	14
5–6	9	Distant	4
7–10	10		
>10	2		

PS, performance status.

Discussion

In this retrospective study, we demonstrated a significant response to the IP administration of carboplatin with IV paclitaxel in patients with suboptimally debulked epithelial ovarian or peritoneal cancer.

Table 2. Hematologic toxicity at first course ($n = 44$)

	G3, *n* (%)	G4, *n* (%)	G3/4, *n* (%)
Neutropenia	11 (25)	30 (68)	41 (93)
Thrombocytopenia	10 (23)	0	10 (23)
Anemia	15 (34)	3 (7)	18 (41)
Febrile neutropenia	0	0	0

Table 3. Nonhematologic toxicity ($n = 44$)

	G3	G4
Allergy	0	1
Fatigue	1	0
Vomiting	1	0
Diarrhea	0	0
Constipation	0	0
Liver dysfunction	1	0
Neurosensory	2	1
Neuromotor	1	0
Arthralgia/myoralgia	0	0
Ileus	0	0
IP tube infection	1	—
IP tube obstruction	1	—

Limitations to this study include (1) the use of carboplatin as an IP agent and (2) the use of IP therapy for suboptimal disease.

Carboplatin and cisplatin have equivalent efficacy against epithelial ovarian cancer, and carboplatin is less toxic and more convenient than cisplatin. As a consequence, carboplatin has become a standard platinum compound in epithelial ovarian cancer when given IV[5,6]. It has also been shown to achieve objective responses when delivered by the IP route in previous retrospective studies[7–9]. Replacing cisplatin with carboplatin is a reasonable way to reduce IP cisplatin-related toxicity, although a phase III trial is needed to confirm the advantages of IP carboplatin.

We used IP carboplatin in patients with suboptimally debulked ovarian cancer based on the concept that IP infusion of carboplatin is valuable not only as an IP regional therapy but also as a more reasonable route for systemic chemotherapy[10]. The advantage of IP chemotherapy has been described in terms of a regional therapy that could maintain an extremely high IP cavity/plasma drug ratio and expose tumors to a high concentration of drugs. Early clinical studies have shown that the peak peritoneum/plasma ratio of AUC is 24 for IP carboplatin[15]. However, penetration of anticancer drugs from the tumor surface is limited to a few millimeters[11]. Therefore, IP chemotherapy is thought to be indicated only in patients with a very small residual tumor. There are many published comparative studies of IP versus IV administration for ovarian cancer. These studies aimed exclusively at patients with optimally debulked ovarian cancer. NCI and GOG have conducted a meta-analysis of these trials and concluded that IP chemotherapy is beneficial for "optimally debulked" stage III ovarian cancer patients. Recently, Miyagi *et al.* showed that carboplatin administrated by the IP route is rapidly absorbed into the systemic circulation, and the 24-h platinum AUC in the serum was equivalent regardless of whether carboplatin was administered by the IP or IV route. In contrast, the 24-h platinum AUC in the peritoneal cavity when carboplatin was administered by the IP route was approximately 17 times higher than that by the IV route[12]. This result implies that IP administration of carboplatin is probably not inferior to IV administration of carboplatin in terms of efficacy, even in patients with a large residual tumor. Indeed, we demonstrated that a combination of IP carboplatin and IV paclitaxel produced reasonable response.

The occurrence of toxicity was low and catheter problems were rare in our patients. Among the 44 patients, 37 (84%) completed six or more cycles of chemotherapy. We presume that the good compliance with IP therapy in our study may be attributed to three factors. First, we replaced cisplatin with carboplatin to reduce IP cisplatin-related toxicity. Second, we administered paclitaxel by the IV route alone to reduce IP paclitaxel-related toxicity. It is known that IP paclitaxel often causes severe abdominal pain[3,16]. Third, we did not perform radical surgery, including bowel resection in patients in whom optimal debulking surgery was judged to be impossible. This approach may be reasonable in reducing catheter-related problems. Walker *et al.*[17] demonstrated the relationship between bowel resection and catheter problems. These authors reported that IP therapy was not initiated in 16% of patients who underwent left colon or rectosigmoid colon resection versus 5% of those who did not in GOG 172.

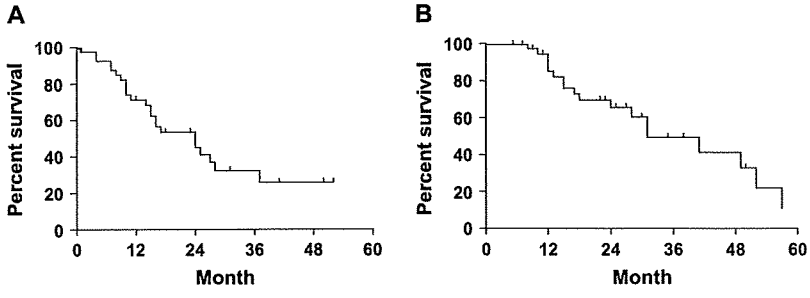

Figure 1. A) PFS and B) OS. Median follow-up time was 18 months (range 7–80 months). There were 26 recurrences and 20 deaths, and the estimated median PFS and OS were 24 and 31 months, respectively.

Catheter materials may be an important factor. We used the Bard port system exclusively. In the Memorial Sloan Kettering study, catheter-related complications were studied in two different periods. These investigators used a Port-A-Cath system in the earlier period and a multiple fenestrated Bard port system in the later period. They also avoided catheter placement when bowel surgery was performed in the later period. The complication rate decreased from 36.8% in the earlier period to 9.9% in the later period[18,19].

The results of GOG 172 indicate a possible contribution of the addition of day 8 IP paclitaxel[3]. Paclitaxel is a favorable drug for IP infusion. The peak peritoneal/plasma concentration ratio of paclitaxel after IP paclitaxel infusion is approximately 1000[15]. This high concentration is due to its large molecular weight and water insolubility. Penetration of the peritoneum is difficult, and drugs are not expected to enter the inner core of the tumor tissue through the systemic circulation. Therefore, IP paclitaxel is at a disadvantage in patients with a large tumor or metastasis outside the abdominal cavity, although it may be vital in optimally debulked epithelial ovarian cancer.

Combination chemotherapy of IP carboplatin and IV paclitaxel is effective and safe in suboptimally debulked ovarian cancer. The results of a prospective phase II study of IV paclitaxel and IP carboplatin in suboptimally debulked ovarian cancer conducted by our study group will be reported soon.

References

1 Alberts DS, Liu PY, Hannigan EV *et al.* Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 1996;**335**:1950–5.

2 Markman M, Bundy BN, Alberts DS *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.

3 Armstrong D, Bundy B, Wenzel L *et al.* Phase III randomized trial of intravenous cisplatin and paclitaxel versus an intensive regimen of intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel in stage III ovarian cancer: a Gynecologic Oncology Group study. *N Engl J Med* 2006;**354**:34–43.

4 National Cancer Institute. NCI issues clinical announcement for preferred method of treatment for advanced ovarian cancer. Available at: http://www.cancer.gov/newscenter/pressreleases/IPchemotherapyrelease. Accessed November 6, 2006.

5 Ozols RF, Bundy BN, Greer BE *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**:3194–200.

6 du Bois A, Luck HJ, Meier W *et al.* A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;**95**:1320–9.

7 Speyer JL, Beller U, Colombo N *et al.* Intraperitoneal carboplatin: favorable results in women with minimal residual ovarian cancer after cisplatin therapy. *J Clin Oncol* 1990;**8**:1335–41.

8 Pfeiffer P, Bennedbaek O, Bertelsen K. Intraperitoneal carboplatin in the treatment of minimal residual ovarian cancer. *Gynecol Oncol* 1990; **36**:306–11.

9 Fujiwara K, Markman M, Morgan M *et al.* Intraperitoneal carboplatin-based chemotherapy for epithelial ovarian cancer. *Gynecol Oncol* 2005; **97**:10–5.

10 Fujiwara K, Armstrong DK, Morgan M *et al.* Principles and practice of intraperitoneal chemotherapy for ovarian cancer. *Int J Gynecol Cancer* 2007;**17**:1–20.

11 Los G, Mutsaers PH, van der Vijgh WJ *et al.* Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. *Cancer Res* 1989;**49**:3380–4.

12 Miyagi Y, Fujiwara K, Kigawa J *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.

13 Calvert AH, Newell DR, Gumbrell LA *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;**7**:1748–56.

14 Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.

15 Markman M. Intraperitoneal chemotherapy. *Semin Oncol* 1991;**18**: 248–54.

16 Markman M, Rowinsky E, Hakes T *et al.* Phase I trial of intraperitoneal taxol: a Gynecologic Oncology Group Study. *J Clin Oncol* 1992; **10**:1485–91.

17 Walker JL, Armstrong DK, Huang HQ *et al.* Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006; **100**:27–32.

18 Makhija JL, Leitao M, Sabbatini P *et al.* Complications associated with intraperitoneal chemotherapy catheters. *Gynecol Oncol* 2001;**81**:77–81.

19 Davidson SA, Rubin SC, Markman M *et al.* Intraperitoneal chemotherapy: analysis of complications with an implanted subcutaneous port and catheter system. *Gynecol Oncol* 1991;**41**:101–6.

Accepted for publication October 30, 2007

ORIGINAL ARTICLE

Phase II Study of Intraperitoneal Carboplatin With Intravenous Paclitaxel in Patients With Suboptimal Residual Epithelial Ovarian or Primary Peritoneal Cancer

A Sankai Gynecology Cancer Study Group Study

Keiichi Fujiwara, MD, PhD, Shoji Nagao, MD, PhD,* Junzo Kigawa, MD, PhD,† Jun Noma, MD, PhD,‡ Nobuo Akamatsu, MD, PhD,§ Yasunari Miyagi, MD, PhD,|| Fumitaka Numa, MD, PhD,¶ Makoto Okada, MD, PhD,** and Eriko Aotani, RN, MSN,††*

Purpose: To assess the antitumor efficacy and safety of 2 treatment modalities: intraperitoneal carboplatin combined with intravenous (IV) paclitaxel.

Patients and Methods: Eligible patients were those with epithelial ovarian carcinoma or primary peritoneal carcinoma stages II to IV who underwent initial surgery and had a residual tumor size of 2 cm or larger. Patients received IV paclitaxel 175 mg/m^2 followed by intraperitoneal carboplatin AUC6. The primary end point was a response. Secondary end points were toxicity, progression-free survival, and overall survival.

Results: Twenty-six patients were enrolled, and 24 patients were eligible for assessment. The response rate was 83.3% (95% CI, 62.6%–95.3%; Table 4). The median progression-free survival was 25 months. The median overall survival had not been reached. Incidences of grade (G) 3/4 hematological toxicities were absolute neutrophil count, 96%; hemoglobin, 29%; and thrombocytopenia, 16%. Nonhematological toxicities included G2 liver function, 4%; G3 sensory neuropathy, 8%; and G3 myalgia and arthralgia, 4%.

Conclusions: Intraperitoneal administration of carboplatin combined with IV paclitaxel was well tolerated and showed satisfactory response in the patients with bulky residual tumor. Large-scale phase III trial comparing with IV carboplatin is warranted in this patient population.

Key Words: Intraperitoneal chemotherapy, Carboplatin, Ovarian cancer, Suboptimal residual disease, Phase II study

(*Int J Gynecol Cancer* 2009;19: 834–837)

*Department of Gynecologic Oncology, Saitama Medical University, International Medical Center, Hidaka, Saitama, Japan; †Tottori University, Koyama-Minami, Tottori, Japan; ‡Hiroshima City Hospital; §Himeji Red Cross Hospital, Tatsunomachi, Himejishi, Japan; ||Okayama Ofuku Clinic, ¶Tokuyama Central Hospital, Tokuyama, Japan; **Yamaguchi Red Cross Hospital, Yahatababa, Yamaguchi-shi, Yamaguchi, Japan; ††Kitasato University, Minato, Tokyo, Japan.

Received January 22, 2009, and in revised form January 29, 2009.
Accepted for publication February 24, 2009.

Address correspondence and reprint requests to Keiichi Fujiwara, MD, PhD, Department of Gynecologic Oncology, Saitama Medical University, International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298 Japan. E-mail: fujiwara@saitama-med.ac.jp.

Conflict of Interest Statement: The authors declare that there are no conflicts of interest.

ISSN: 1048-891X
DOI: 10.1111/IGC.0b013e3181a29dfe

Despite the development of new anticancer agents such as platinum and taxane, ovarian cancer remains the most lethal of gynecologic malignancies. One strategy to treat ovarian cancer is intraperitoneal (IP) chemotherapy, and because the most distinct characteristic of ovarian or peritoneal cancer is early intra-abdominal dissemination of the disease, this seems to be a reasonable approach. The IP modality has been investigated for years, including several phase I and II studies using various anticancer agents.[1] Intraperitoneal cisplatin and IP paclitaxel are now considered the choice of treatments based on a series of randomized phase III trials conducted in the United States that evaluated the survival benefit of IP over intravenous (IV) administration of these agents. Three randomized trials[2–4] showed that IP cisplatin-based chemotherapy significantly improved survival compared with cisplatin chemotherapy administered intravenously. A meta-analysis showed a 22% reduction of hazards ratio to death, prompting the US National Cancer Institute to

recommend IP chemotherapy for patients with small residual tumors.

Rationale for Using Intraperitoneal Carboplatin

Intraperitoneal chemotherapy has not been accepted in the international gynecologic oncology community despite these positive reports. One reason is that IP cisplatin-based chemotherapy has not been tested against the current standard chemotherapy, IV paclitaxel plus IV carboplatin. In addition, significant toxicity occurred in one study that demonstrated the best survival rate using IP cisplatin plus IV paclitaxel.[4] Investigators are developing protocols for an optimal IP regimen that are superior to the current standard regimen but are less toxic than previous regimens. Carboplatin is the most feasible platinum agent to reduce cisplatin-based toxicities. A relatively large retrospective study showed the efficacy and toxicity of IP carboplatin-based chemotherapy in patients with ovarian cancer.[5]

Rationale for Investigating IP Chemotherapy in Patients With Suboptimal Residual Tumors

Usually, IP chemotherapy is given to patients with optimally debulked tumors (usually ≤1 cm) because direct penetration of the anticancer agents is limited to a few millimeters.[6–9] However, when platinum agents were administered intraperitoneally, the area under the curve (AUC) of these agents in the serum is known to be equal to the AUC after IV administration.[10,11] Therefore, IP platinum therapy is hypothesized to be a systemic chemotherapy route that should have a heightened regional effect because it can deliver an extremely high concentration of anticancer agents. An interesting clinical observation supports this hypothesis. In the Gynecologic Oncology Group (GOG) 104 trial, the hazard ratio for the risk of death in the IP group compared with the intravenous group was 0.76 (95% CI, 0.61–0.96; $P = 0.02$) in patients with residual tumors of 2 cm or less.[2] When the hazard ratio was calculated only for patients with tumors of 0.5 cm or less, the hazard ratio was 0.8. Therefore, the therapeutic gain of IP therapy in reducing death hazard was slightly greater in patients with residual tumors between 0.5 and 2 cm than in patients with smaller residual tumors (<0.5 cm). This observation implies that IP therapy in patients with larger residual tumors may be more effective than, or as effective as, in patients with smaller residual disease tumors. Two retrospective studies showed that IP carboplatin-based chemotherapy was considerably efficacious in suboptimally debulked ovarian cancer patients.[5,15]

Based on these observations, we conducted a phase II trial to evaluate the therapeutic response of IP carboplatin-based chemotherapy in patients with suboptimally debulked disease.

TABLE 1. Characteristics of patients enrolled in the study

	n = 26 (%)
Diagnosis	
Ovarian	23 (89)
Primary peritoneum	3 (11)
Histology	
Serous	18 (69)
Mucinous	1 (4)
Endometrioid	4 (15)
Undifferentiated	0
Others	3 (12)
Performance status	
0	16 (62)
1	8 (29)
2	2 (9)
FIGO stage	
II	3 (12)
III	17 (65)
IV	6 (23)
Residual disease	
<5 mm	0
5–10 mm	0
10–20 mm	0
<20 mm	26 (100)
Second or interval debulking	
Yes	16 (62)
No	10 (38)

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 2. Toxicity of IP carboplatin plus IV paclitaxel combination chemotherapy

	n = 26
Ineligible for assessment of combination chemotherapy	2
Paclitaxel anaphylaxis	1
Catheter obstruction at the first cycle	1
No. patients eligible for assessment of combination chemotherapy	n = 24 (%)
ANC	
G3	6 (25)
G4	17 (71)
Febrile neutropenia	0
Hemoglobin	
G3	6 (25)
G4	1 (4)
Platelet	
G3	2 (8)
G4	2 (8)
GOT	
G2	1 (4)
GPT	
G2	1 (4)
ALP	
G2	1 (4)
Bilirubin	0
Creatinine	0
Neurotoxicity	
Sensory G3	2 (8)
Motor	0
Myalgia/arthralgia	
G2	1 (4)
Gastrointestinal	
G2	1 (4)

ALP, alkaline phosphatase; ANC, absolute neutrophil count; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase.

PATIENTS AND METHODS

This is a phase II study to assess the efficacy and safety of carboplatin administered intraperitoneally in combination with IV paclitaxel in patients with epithelial ovarian cancer or primary peritoneal cancer who had suboptimal residual tumor after initial debulking surgery.

Patients

Patient inclusion criteria included histologically confirmed epithelial ovarian or peritoneal cancer, stages II, III, and IV, with radiographically measurable residual tumor 2 cm or larger and adequate hematological (absolute neutrophil count $\geq 2000/mm^3$, and platelet count $\geq 100{,}000/mm^3$), renal (serum creatinine $\leq 1.5 \times$ the institutional upper limit of normal), and hepatic (serum bilirubin ≤ 1.5 mg/dL and both aspartate aminotransferase and alkaline phosphatase $\leq 2 \times$ the institutional upper limit of normal) laboratory values.

Exclusion criteria consisted of a history of invasive carcinoma of any other organs, excluding nonmelanoma skin cancer, and concomitant severe heart disease, cerebrovascular disease, uncontrollable diabetes, hypertension, severe infection, pulmonary fibrosis, interstitial pulmonitis, and symptomatic brain metastasis.

The study protocol was reviewed by the institutional review board, and written informed consent was obtained from the patients before registration.

Treatment

Patients had IP ports placed immediately before the abdomen was closed at the initial surgery. Chemotherapy was started by IV administration of paclitaxel at 175 mg/m^2 for 3 hours followed by IP administration of carboplatin at AUC6. During the IV paclitaxel administration, approximately 1000 mL of 5% glucose or normal saline was infused through the IP port, and then the designated dose of carboplatin was infused as a bolus immediately after IV paclitaxel administration was completed. These treatments were repeated every 3 weeks for 6 to 8 cycles. Interval debulking surgery was allowed after 3 to 5 cycles and then followed by chemotherapy, using the same regimen.

END POINTS

The primary end point was the response rate, and secondary end points were safety, progression-free survival, and overall survival.

Evaluation

Response was assessed using the Response Evaluation Criteria in Solid Tumors, and toxicity was assessed using National Cancer Institute Common Toxicity Criteria version 2.

TABLE 3. Completion of protocol treatment

No. Protocol Treatment Received	n = 26
0	2
1	0
2	0
3	0
4	1
5	1
6	13
7	2
8	7

TABLE 4. Clinical response

Clinical Response	n = 24
Complete response	6
Partial response	14
Response rate	83.3%
95% CI	62.6%–95.3%
No change	4
Progressive disease	0

Sample Size

The sample size was calculated to be 37, so that the response rate was expected to be 75%; threshold response, 55%; and alpha error, 0.05 with a power of 80%.

RESULTS

From December 2001 to January 2005, 26 patients were enrolled. The study was closed early because of slow accrual due to conflicting clinical trials.

Characteristics of patients enrolled in the study are summarized in Table 1. Of 26 patients, 2 patients were excluded from toxicity analysis because one had paclitaxel anaphylaxis at the first cycle and the other had IP port obstruction at the first cycle. Therefore, 24 patients were eligible for toxicity analysis. All 24 patients were eligible for evaluation of response and survival.

Toxicity

Table 2 lists grades 3 to 4 hematological and grade 2/3 nonhematological toxicities after the protocol treatment. The data showed that there were no specific toxicities related to the IP chemotherapy.

Completion of Protocol Treatment

The total number of protocol therapy cycles and the number of patients are shown in Table 3. Scheduled protocol treatment was completed in 22 (85%) patients. Reasons for terminating the protocol treatment in 4 patients were: disease progression (2), catheter complication (1), and paclitaxel anaphylaxis (1). There was no discontinuation of IP chemotherapy because of excessive toxicity or patient refusal.

Clinical Efficacy

Clinical response for 24 patients is described in Table 4. The response rate was 83.3% (95% CI, 62.6%–95.3%). As of the median follow-up of 31 months, median progression-free survival was 25 months. Median overall survival was not reached.

DISCUSSION

The basic concept of IP chemotherapy is that it is regional therapy. Ideally, anticancer drugs should stay in the intraperitoneal cavity for a long time and not enter systemic circulation, thus minimizing systemic toxicity. Unfortunately, however, because anticancer drugs do not penetrate more than a few millimeters, the optimal patient for IP chemotherapy is presumed to have minimal residual tumor after surgery. This study challenges that hypothesis.

The response rate, which was the primary objective of this study, was satisfactory in patients who received IP carboplatin-based chemotherapy. In addition, the median progression-free survival and overall survival seemed long enough after IP chemotherapy. Although it is not shown that IP carboplatin therapy is superior to

IV carboplatin or IP cisplatin therapy, these observations highly warrant using IP carboplatin-based chemotherapy and justify the inclusion of suboptimally debulked patients in future trials of IP chemotherapy, although current inclusion criteria for the IP trial was only for optimally debulked patients.

Because the IP cisplatin-based chemotherapy regimen used in GOG172 was too toxic,[4] the expectation for using IP carboplatin now has become increasingly of interest. However, the use of carboplatin-based IP chemotherapy has been ignored, and the problem with the hypothesis has been discussed in previous literature.[12] One animal study[13] and one small retrospective clinical study[14] suggested that IP carboplatin-based therapy was inferior to IP cisplatin-based chemotherapy. An animal study showed that tissue platinum concentration after IP carboplatin administration was considerably lower than that after IP cisplatin administration.[13] The antitumor response in the clinical study was shown to be less effective after IP carboplatin-based chemotherapy than after IP cisplatin-based chemotherapy.[14] However, in the animal study, the author did not take into consideration the difference in the doses of these 2 platinum agents in determining the difference in biological activity. Usually, carboplatin needs to be administered in higher doses (6-8 times more milligrams per patient body) compared with cisplatin. A similar problem was found in the clinical study in which a higher dose of cisplatin (100 mg/m^2) was given, but the dose of carboplatin was considerably lower (200 mg/m^2) than the standard. The present study clearly showed that IP carboplatin-based chemotherapy, administered in sufficient dose, was efficacious and well tolerated, and a phase III trial comparing IP cisplatin and IP carboplatin is warranted to elucidate whether IP carboplatin is less toxic without compromising antitumor efficacy.

A pharmacological study[11] and 2 retrospective studies[5,15] suggested that IP carboplatin-based chemotherapy would be feasible for ovarian cancer patients with bulky residual disease. Although the size is small and the study was closed prematurely, this prospective phase II study confirmed those results. Because IP carboplatin-based chemotherapy has the ability to expose a high concentration of the drug to the tumor surface while it provides the similar AUC of platinum in the systemic blood circulation, it may provide better clinical outcome in the ovarian cancer patients.

In conclusion, our study clearly indicates that a large-scale randomized phase III trial to test the value of IP carboplatin compared with current standard IV carboplatin chemotherapy or IP cisplatin-based chemotherapy is warranted. Including patients with suboptimal residual disease is also justified in a future trial using IP carboplatin.

ACKNOWLEDGMENTS

The authors thank all the patients and investigators of the following participating institutions: Fukuyama Medical Center, Himeji Red Cross Hospital, Hiroshima City Hospital, JA Onomichi Hospital, Kawasaki Hospital, Kawasaki Medical School, Mazda Hospital, Okayama Red Cross Hospital, Okayama University, Saiseikai Suita Hospital, Tokushima University, Tokuyama Central Hospital, Tottori University, and Yamaguchi Red Cross Hospital.

REFERENCES

1. Fujiwara K, Armstrong D, Morgan M, et al. Principles and practice of intraperitoneal chemotherapy for ovarian cancer. *Int J Gynecol Cancer.* 2007;17:1–20.
2. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med.* 1996;335:1950–1955.
3. Markman M, Bundy BN, Alberts DS, 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;19:1001–1007.
4. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;354:34–43.
5. Fujiwara K, Sakuragi N, Suzuki S, et al. First-line intraperitoneal carboplatin-based chemotherapy for 165 patients with epithelial ovarian carcinoma: results of long-term follow-up. *Gynecol Oncol.* 2003;90:637–643.
6. Ozols RF, Young RC, Speyer JL, et al. Phase I and pharmacological studies of adriamycin administered intraperitoneally to patients with ovarian cancer. *Cancer Res.* 1982;42:4265–4269.
7. Durand RE. Flow cytometry studies of intracellular adriamycin in multicell spheroids in vitro. *Cancer Res.* 1981;41:3495–3498.
8. West GW, Weichselbaum R, Little JB. Limited penetration of methotrexate into human osteosarcoma spheroids as a proposed model for solid tumor resistance to adjuvant chemotherapy. *Cancer Res.* 1980;40:3665–3668.
9. Nederman T, Carlsson J. Penetration and binding of vinblastine and 5-fluorouracil in cellular spheroids. *Cancer Chemother Pharmacol.* 1984;13:131–135.
10. Howell SB, Pfeifle CL, Wung WE, et al. Intraperitoneal cisplatin with systemic thiosulfate protection. *Ann Intern Med.* 1982;97:845–851.
11. Miyagi Y, Fujiwara K, Kigawa J, 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 versus intravenous infusion of carboplatin—a Sankai Gynecology Study Group (SGSG) study. *Gynecol Oncol.* 2005;99:591–596.
12. Fujiwara K, Markman M, Morgan M, et al. Intraperitoneal carboplatin-based chemotherapy for epithelial ovarian cancer. *Gynecol Oncol.* 2005;97:10–15.
13. Los G, Verdegaal EM, Mutsaers PH, et al. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. *Cancer Chemother Pharmacol.* 1991;28:159–165.
14. Markman M, Reichman B, Hakes T, 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;50:100–104.
15. Nagao S, Fujiwara K, Ohishi R, et al. Combination chemotherapy of intraperitoneal carboplatin and intravenous paclitaxel in suboptimally debulked epithelial ovarian cancer. *Int J Gynecol Cancer.* 2008; 18:1210–1214.