Table 5
Clinical response according to chemotherapy-free interval ($N = 37$)

	Chemotherapy-free interval			
	<6 months[a]		≥6 months	
Total	14		23	
Response				
Complete	1	7.1%	3	13.0%
Partial	3	21.5%	10	43.5%
Stable	9	64.3%	7	30.5%
Progression	1	7.1%	3	13.0%

[a] All patients received platinum-based chemotherapy.

response rate was 56.0%, showing more than two times of response rate of patients with measurable tumor (Table 4). One (7.1%) of 14 patients with chemotherapy-free interval <6 months had complete response, while 3 (13.0%) of 23 patients with chemotherapy-free interval ≥6 months had complete response. Three patients (21.5%) with chemotherapy-free interval <6 months had partial response, while 10 patients (43.5%) with chemotherapy-free interval ≥6 months had partial response. The response rate (56.5%) of patients with chemotherapy-free interval ≥6 months was about two times higher than that (28.6%) with chemotherapy-free interval <6 months (Table 5). Clinical response rate according to number of prior regimens showed that as number of prior regimens increases, the response rate decreases (Table 6). Median TTP and overall survival were 12 months and 21 months, respectively.

A total of 468 doses (range, 6–39) of weekly paclitaxel were administered to the 37 patients. Toxicity data was available for all the 37 patients. Hematological toxicity more than grade 2 was observed in about 25%, while non-hematological toxicity was observed in 1 (2.7%) of 37 patients (Table 7). Nine patients (24.3%) had a grade 3 or 4 neutropenia. Four patients had treatment delays and two patients required granulocyte colony-stimulating factors intermittently for severe neutropenia, but there were no hospital administrations for neutropenic fever. Four patients had a grade 3 anemia, and two of them required blood transfusion. During treatment with weekly paclitaxel, one patient had a grade 3 neuropathy and the chemotherapy had to be stopped. There was no evidence for cumulative hematological and non-hematological toxicity.

Table 6
Clinical response according to number of prior regimens

	Number of prior regimens					
	1		2		3	
Total	19		14		4[a]	
Response						
Complete	4	21.2%	1	7.1%	0	
Partial	7	36.8%	4	28.6%	1	25.0%
Stable	7	36.8%	7	50.0%	2	50.0%
Progression	1	5.3%	2	14.3%	1	25.0%

[a] All patients with three prior regimens had measurable tumor.

Table 7
Toxicity profiles

Hematological toxicity	No. of patients
Neutropenia	
Grade 3	7
Grade 4	2
Leukopenia	
Grade 3	9
Grade 4	1
Thrombocytopenia	
Grade 3	0
Grade 4	0
Anemia	
Grade 3	4
Grade 4	0
Non-hematological toxicity	**No. of patients**
Peripheral neuropathy	
Grade 2	5
Grade 3	1
Alopecia	
Grade 2	11
Grade 3	0

Discussion

The treatment of recurrent and refractory cancer is a challenging problem because recurrent or refractory disease is almost never curable. The majority of patients who initially respond will develop chemotherapy-resistant disease and ultimately die. Thus, the primary treatment objectives in the salvage setting are prolonging remission and maintaining quality of life. These goals may be attainable through the evaluation of different dosing and timing regimens of standard chemotherapeutic agents.

Introduction of paclitaxel into the armamentarium of drugs to treat platinum-resistant ovarian cancer has been one of the more significant advances in the treatment of ovarian cancer in the last decade. Paclitaxel has a unique mechanism of action, is cell-cycle-specific, and acts by promoting the stability of the microtubule assembly during mitosis. In vitro data suggest that the duration of exposure plays a crucial role in the cytotoxic efficacy of paclitaxel [19,20]. Resistance to paclitaxel-mediated P-glycoprotein (Pgp) [21] has been shown to be significantly reduced by increasing the duration of exposure to paclitaxel from 3 to 96 h in Pgp-expressing paclitaxel-resistant breast cancer cell lines [22].

Weekly administration of paclitaxel has the potential to have an effect similar to that of continuous infusion while

taking advantage of the minimal hematological toxicity associated with shorter infusions. Neutropenia was the most frequent hematological adverse event observed in patients receiving once-weekly intravenous paclitaxel monotherapy. Severe neutropenia was dose-related, occurring in 3% and 15% of patients receiving 80 mg/m^2 monotherapy [23,24]. An absolute neutropenia count of 1000 has been shown to be sufficient for dosing weekly paclitaxel on any given scheduled day of treatment. In the present study, severe neutropenia and leukopenia of grade 4 were observed in 2 (5.4%) and 1 (2.7%) of 37 patients. Other hematological adverse events (grade 4 anemia or grade thrombocytopenia) were not observed. Neuropathy is experienced by most patients receiving once-weekly intravenous paclitaxel monotherapy and is usually mild or moderate [23,24]. The incidence of severe neuropathy with paclitaxel 80 mg/m^2 once weekly was approximately 10% [23,24]. Most patients experienced mild myalgia and/or arthralgia; few patients reported severe symptoms [25]. In the present study, 3/39 (7.7%) containing two patients withdrawn from this trial experienced severe neuropathy. Although alopecia of grade 2 was observed in 11/37 (29.7%), alopecia beyond grade 2 was not observed (Table 7). No patient required dose reduction was observed in this trial. Prolonged exposure to relatively low concentrations of paclitaxel has been shown to induce apoptosis [26]. In addition, prolonged low-dose paclitaxel exposure has been reported to have anti-angiogenic properties [27]. The paclitaxel dose delivered in this regimen is 24 mg/m^2 over 3 weeks as compared to 175 mg/m^2 every 3 weeks with conventional dosing. These features associated with weekly low-dose paclitaxel may explain the response seen in patients with carcinoma refractory to conventionally dosed paclitaxel.

Fennelly et al. [8] did a phase I trial with 18 patients with platinum- and paclitaxel-resistant ovarian cancer and determined that 80 mg/m^2 was the maximally tolerated dose. We also reported in the phase I study that the same dose of 80 mg/m^2 was the maximum recommended dose [13]. Thus, we performed phase II study by single weekly 80 mg/m^2 paclitaxel. Treatment with single weekly 80 mg/m^2 paclitaxel brought about an overall response rate of 45.9%, similar to that of a recent report [28]. It is noteworthy that five complete responses among 37 patients with one or more therapeutic regimens were achieved (Table 2). In addition, 3 (25.0%) of 12 patients with measurable tumor containing two complete responses had response to weekly paclitaxel (Table 3). When based on CA 125 levels, the response rate of 56.0% including a complete response of 12.0% was obtained, showing two times higher response rate compared to that in patients with measurable tumor (Table 4). These results suggest that patients with recurrence detectable only by CA 125 levels (but not morphologically measurable) are more sensible to weekly paclitaxel than those with measurable tumor. It is possible that angiogenesis of detectable tumor only by CA 125 is vulnerable to weekly paclitaxel than that of morphologically measurable tumor. Response rate (56%) of patients with chemotherapy-free interval ≥6 months showed about two times that (28.6%) of those with chemotherapy-free interval <6 months (Table 5). Similarly, a recent report demonstrated that all the responders with paclitaxel-resistant tumors were seen in patients with a paclitaxel-free interval of more than 12 months [28]. Since most of prior regimens used in patients enrolled in the present study were cisplatin-based chemotherapy, weekly paclitaxel seemed to be more effective in patients with longer platinum-free interval. In addition, we examined clinical response according to number of prior regimens. When prior regimen was 1 or 2, the clinical response rate was 58.0% or 35.7%, respectively, whereas in patients with three prior regimens, the responder was only one (25.0%) (Table 6). These results suggest that as number of prior regimens increases, the response rate decreases and therefore patients with less prior regimens may have better be treated with weekly paclitaxel. It is noteworthy that 9 of 14 patients with two prior regimens received chemotherapy containing paclitaxel while all patients with three prior regimens received chemotherapy containing paclitaxel. However, efficacy of weekly paclitaxel was not influenced by kinds of prior chemotherapy regimen.

The choice of second line drug in this present setting is dependent on toxicity and quality of life considerations, in addition to efficacy. Weekly administration of paclitaxel by 1-h infusion has been reported to have less toxicity than other schedules and primary effect in patients with pretreated gynecologic cancers [8,10,29,30]. In addition, a randomized trial comparing the weekly schedules to triweekly paclitaxel for advanced breast cancer is nearing completing in the GALGB. 'Metronomic' dosing or anti-angiogenic scheduling of cancer chemotherapeutics has been increasingly recognized to be a potential application of paclitaxel in cancer therapy [31–33].

In conclusion, weekly low-dose paclitaxel used in the present study is considered safe and effective in pretreated patients with recurrent or persistent ovarian cancer. Encouraging response rates in both platinum-sensitive and platinum-resistant patients warrant further studies.

References

[1] Silverberg E, Boring C. Cancer statistics 1990. CA Cancer J Clin 1990;40:9–26.
[2] Colombo N, Parma G, Bocciolone L, Sider M, Franchi D, Maggioni A. Role of chemotherapy in relapsed ovarian cancer. Crit Rev Oncol Hematol 1999;32:221–8.
[3] Markman M, Rothman R, Hakes T, Reichman B, Hoskins W, Rubin S, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 1991;9:389–93.
[4] Bookman M. Developmental chemotherapy in ovarian cancer: incorporation of newer cytotoxic agents in a phase III randomized trial of the Gynecologic Oncology Group (GOG-0182). Semin Oncol 2002; 29(S1):30–1.
[5] Ozols RF. Future directions in the treatment of ovarian cancer. Semin Oncol 2002;29(S1):32–42.

[6] McGuire WP, Rowinsky EK, Rosenshein NB, et al. Taxol: a unique antineoplastic agent with significant activity in advanced epithelial ovarian neoplasms. Ann Intern Med 1989;111:273–9.
[7] Sarosy G, Kohn E, Link C, et al. Taxol dose intensification in patients with recurrent ovarian cancer. Proc Am Soc Clin Oncol [abstr.] 1992;11:226.
[8] Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, McKenzie M, O'Connor C, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 1997;15:187–92.
[9] Seidman AD, Hudis CA, Albanel J, et al. Dose dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 1998;16:3353–61.
[10] Anderson H, Boman K, Ridderheim M, et al. Updated analysis of a randomized study of single agent paclitaxel given weekly vs 3 weeks to patients with ovarian cancer treated with prior platinum therapy. Proc Am Soc Clin Oncol [abstr 1505] 2000;19:380a.
[11] Kohn EC, Sarosy G, Bicher A, et al. Dose-intense Taxol: high response rate in patients with platinum-resistant recurrent ovarian cancer. J Natl Cancer Inst 1994;86:18–24.
[12] Kohn EC, Sarosy GA, Davis P, et al. A phase I/II study of dose-intense paclitaxel with cisplatin and cyclophosphamide as initial therapy of poor-prognosis advanced-stage epithelial ovarian cancer. Gynecol Oncol 1996;62:181–91.
[13] Takano M, Kikuchi Y, Kita T, Suzuki M, Ohwada M, Yamamoto T, et al. Phase I and pharmacological study of single paclitaxel administered weekly for heavily pretreated patients with epithelial ovarian cancer. Anticancer Res 2002;22:1833–8.
[14] Miller KD, Sweeney CJ, Sledge Jr GW. Redefining the target: chemotherapeutics as antiangiogenics. J Clin Oncol 2001;19:1195–206.
[15] Kerbel RS, Klement G, Pritchard KI, Kamen B. Continuous low-dose anti-angiogenic/metronomic chemotherapy: from the research laboratory into the oncology clinic. Ann Oncol 2002;13:12–5.
[16] Blessing A. Design, analysis and interpretation of chemotherapy trials in gynecologic cancer. In: Deppe G, editors. Chemotherapy of Gynecologic Cancer, second ed. New York, NY: Alan R. Liss, Inc., Scientific and Medical Publications; 1990. p. 63–97.
[17] Rustin GJS, Nelstrop AE, McClean P, Brady MF, McGuire WP, Hoskins WJ, et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. J Clin Oncol 1996; 14:1545–51.
[18] Markman M, Hoskins W. Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated populations. J Clin Oncol 1992;10:513–4.
[19] Lopes NM, Adams EF, Pitts TW, Bhuyan BK. Cell kill kinetics and cell cycles effects of Taxol on human and hamster ovarian cell lines. Cancer Chemother Pharmacol 1993;432:235–42.
[20] Georgiadis MS, Russell E, Gazdar AF, Johnson BE. Paclitaxel cytotoxicity against human lung cancer cell lines increases with prolonged exposure duration. Clin Cancer Res 1997;3:449–54.
[21] Yamamoto K, Kikuchi Y, Kudoh K, Nagata I. Modulation of cisplatin sensitivity by Taxol in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. J Cancer Res Clin Oncol 2000;126:168–72.
[22] Zhan Z, Scala S, Monks A, Hose C, Bates S, Fojo T. Resistance to paclitaxel mediated by P-glycoprotein can be modulated by changes with schedule of administration. Cancer Chemother Pharmacol 1997;40:245–50.
[23] Perez EA, Vogel CL, Irwin DH, et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol. 2001;19:4216–23.
[24] Socinski MA, Schell MJ, Bakri K, et al. Second-line, low-dose, weekly paclitaxel in patients with stage IIIB/IV non-small cell ling carcinoma who fail first-line chemotherapy with carboplatin plus paclitaxel. Cancer 2002;95:1265–73.
[25] Kikuchi Y, Hiramatsu H, Seto H, Kita T. A rare case of advanced ovarian carcinoma who developed difficulty walking 25 days after treatment with weekly paclitaxel. Anti-Cancer Drugs 2001;12:631–3.
[26] Saunders DE, Lawrence WD, Christensen C, Wappler NL, Ruan H, Deppe G. Paclitaxel induced apoptosis in MCF-7 breast cancer cells. Int J Cancer 1997;70:214–20.
[27] Klanber N, Parangi S, Flynn E, Hamel E, D'Anato RJ. Inhibition of angiogenesis and breast cancer in mice by the microtubule inhibitors 2-methylestradiol and Taxol. Cancer Res 1997;57:81–6.
[28] Ghamande S, Lele S, Marchetti D, Baker T, Odunsi K. Weekly paclitaxel in patients with recurrent or persistent advanced ovarian cancer. Int J Gynecol Cancer 2003;13:142–7.
[29] Abu-rustum N, Aghajanian C, Barakat RR, et al. Salvage weekly paclitaxel in recurrent ovarian cancer. Semin Oncol 1997;24(S15):62–7.
[30] Klaasen V, Wilhe H, Strumberg D, et al. Phase I study with a weekly 1 h infusion of paclitaxel in heavily pretreated patients with metastatic breast and ovarian cancer. Eur J Cancer 1996;32A:547–9.
[31] Kerbel RS. Tumor angiogenesis: past, present, and the near future. Carcinogenesis 2000;21:505–15.
[32] Schimer M. Angiogenic chemotherapeutic agents. Cancer Metast Rev 2000;19:67–73.
[33] Wang J, Lou P, Lesniewski R, Henkin J. Paclitaxel at ultra low concentrations inhibits angiogenesis without affecting cellular microtubule assembly. Anti-Cancer Drugs 2000;14:13–9.

A Phase I Study and Pharmacologic Evaluation of Irinotecan and Carboplatin for Patients with Advanced Ovarian Carcinoma who Previously Received Platinum-Containing Chemotherapy

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BACKGROUND. The objectives of the current study were to determine the maximum tolerated dose (MTD) of irinotecan and carboplatin in combination, to evaluate the efficacy and toxicity of the combination in patients with advanced ovarian carcinoma who previously received platinum-containing chemotherapy, and to examine the pharmacokinetics and pharmacodynamics of both drugs by using the Chatelut formula.

METHODS. Patients with advanced ovarian carcinoma who previously received platinum-containing chemotherapy were treated with a combination of irinotecan and carboplatin. Carboplatin was administered as a 60-minute intravenous infusion on Day 1 and was followed by irinotecan, which was administered as a 90-minute intravenous infusion on Days 1, 8, and 15. Six dose levels of irinotecan (in mg/m^2)/carboplatin (mg · mL/min) were planned: 50 mg/m^2/4 mg · mL/minute, 60 mg/m^2/4 mg · mL/minute, 50 mg/m^2/5 mg · mL/minute, 60 mg/m^2/5 mg · mL/minute, 50 mg/m^2/6 mg · mL/minute, and 60 mg/m^2/6 mg · mL/minute. The carboplatin dosage was calculated by using the Chatelut formula. Treatment was repeated at 28-day intervals.

RESULTS. In total, 19 patients in cohorts of 3 to 5 patients received irinotecan and carboplatin at 5 dose levels. The dose-limiting toxicities were Grade 4 neutropenia and Grade 4 thrombocytopenia. The MTD of the irinotecan/carboplatin combination was 60 mg/m^2/5 · mg mL/minute. Partial responses were observed at higher dose levels. Pharmacologic studies demonstrated that administration of the dosage estimated with the Chatelut formula instead of the Chatelut formula with adjustment for serum creatinine resulted in a slightly excessive dose of carboplatin.

CONCLUSIONS. The recommended dose for the Phase II study was irinotecan 60 mg/m^2 on Days 1, 8, and 15 with carboplatin 5 mg/mL · minute on Day 1 repeated every 4 weeks. *Cancer* **2005;104:1204–12.** © *2005 American Cancer Society.*

KEYWORDS: irinotecan, carboplatin, ovarian carcinoma, pharmacokinetics, Chatelut formula.

An objective response is achieved in approximately 60–80% of women with advanced ovarian carcinoma who are treated with platinum plus taxane combination chemotherapy.[1,2] Nonetheless, recurrence rates remain high even with current treatments, and most women with advanced ovarian carcinoma ultimately die of their disease. Thus, it is important not only to establish effective second-line chemotherapies but to use new drugs with no cross-resistance in first-line chemotherapy to avoid expression of drug-resistant clones in the early treatment period.

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Irinotecan (CPT-11) is a plant alkaloid extract from *Camptotheca acuminate* and a potent inhibitor of DNA topoisomerase I. It exhibits excellent antitumor activity not only against experimental models of a broad spectrum of tumors but against drug-resistant tumor cell lines. No cross-resistance has been found between CPT-11 and carboplatin, and a synergistic effect has been observed when CPT-11 has been used in combination with carboplatin in preclinical studies.[3–5] Moreover, it was demonstrated recently that CPT-11 is an active agent in patients with platinum-resistant ovarian carcinoma.[6]

Carboplatin is an analogue of cisplatin with less nonhematologic toxicity, and leukopenia and thrombocytopenia are its dose-limiting toxicities (DLTs).[7,8] The area under the plasma concentration-versus-time curve (AUC) of carboplatin correlates well with the extent of myelosuppression as well as with the response rate in patients with ovarian carcinoma,[9] and the dose of carboplatin can be individualized to achieve a particular AUC by using several formulae.[10,11] The most widely accepted is the Calvert formula, which is based on the linear correlation between carboplatin clearance and the glomerular filtration rate.[10] However, because the effect of the possible pharmacokinetic interaction with coadministered drugs on carboplatin clearance is unknown, the most practical formula for routine clinical use remains a matter of controversy.[12–17] The objectives of the current study were: 1) to determine the maximum tolerated dose (MTD) and the recommended dose of CPT-11 and carboplatin in combination for patients with advanced ovarian carcinoma who previously received platinum-containing chemotherapy, 2) to investigate the pharmacokinetics and pharmacodynamics of the combination, and 3) to evaluate the utility of the serum creatinine adjustment model for the Chatelut formula by using the creatinine peroxidase-antiperoxidase (PAP) method developed in a previous study in Japanese patients.[18]

MATERIALS AND METHODS

Patient Selection

Patients were enrolled in the study if they fulfilled the following eligibility criteria: 1) histologically proven ovarian carcinoma; 2) prior platinum-containing chemotherapy, whether in platinum-sensitive or platinum-resistant patients[19]; 3) life expectancy $\geq$ 3 months; 4) age 15 years or older but younger than 75 years; 5) an Eastern Cooperative Oncology Group performance status $<$ 2; 6) adequate bone marrow and organ function (leukocytes $\geq$ 4000/μL, neutrophils $\geq$ 2000/μL, platelets $\geq$ 100,000/μL, total bilirubin $\geq$ 1.5 mg/dL, serum transaminase levels not more than 2.5 times the upper limit of normal, serum creatinine $\geq$ 1.5 mg/dL); 7) having measurable lesions was not required; and 8) written informed consent. This study was approved by the Institutional Review Board of the National Cancer Center Hospital.

Patients who had active infection, bowel obstruction, interstitial pneumonitis, severe heart disease, or a past history of hypersensitivity to antitumor drugs were excluded from the study. Patients who had pleural effusion or ascites that required drainage, brain metastasis, or active concomitant malignancy also were excluded.

Treatment Plan and Dose-Escalation Procedure

Carboplatin dissolved in 250 mL of saline or 5% glucose solution was infused over 60 minutes; subsequently, CPT-11 dissolved in 500 mL saline or 5% glucose solution was given as a 90-minute intravenous infusion. Administration of CPT-11 was planned for Days 1, 8, and 15, and administration of carboplatin was planned on Day 1 at a dose targeting a specific AUC, as determined by the Chatelut formula: dose (mg) = AUC $\cdot$ [0.134 $\cdot$ weight + (218 $\cdot$ weight $\cdot$ (1-0.00457 $\cdot$ age) $\cdot$ (1-0.314 $\cdot$ gender)/serum creatinine expressed in micromolar concentration)], with weight expressed in kilograms, age in years, and gender equal to 0 for male and 1 for female.[11] Serum creatinine was measured by the PAP method with the Serotec CRE-L kit (Serotec Company, Sapporo, Japan). CPT-11 was withdrawn on Days 8 and 15 if the leukocyte count was $<$ 3000/μL, the platelet count was $<$ 100,000/μL, or diarrhea was $\geq$ Grade 1. This chemotherapy regimen was repeated every 4 weeks. Granisetron was used routinely as an antiemetic on Days 1, 8, and 15. Prophylactic granulocyte-colony stimulating factors were not used routinely.

The starting dose of CPT-11 and carboplatin was 50 mg/m^2 and AUC 4. Dose escalation with six different dose levels was planned, and at least three patients were entered at each dose level. No interpatient dose escalation was performed.

DLT and MTD

Severe or life-threatening (Grade 3 or 4) nonhematologic toxicity, with the exception of nausea and emesis, was considered dose limiting. A leukocyte count $<$ 1000/μL or a neutrophil count $<$ 500/μL that lasted $>$ 3 days or a platelet count $<$ 25,000/μL of any duration also were considered dose limiting. The dose was escalated to the next level when none of the three patients experienced DLT in the first cycle. If one of the three patients experienced DLT in the first cycle, then three additional patients were entered at that dose level. The MTD was defined as one dose level

below the dose that induced DLT in three of six patients during the first cycle.

Assessment of Treatment

We used World Health Organization (WHO) criteria to assess the response to treatment of patients who had measurable lesions.[20] Measurable lesions were evaluated radiographically. Pleural effusion, ascites, and bone metastases were not considered measurable sites. Patients without measurable lesions were classified as not evaluable.

CA-125 response was defined as a 50% reduction in the CA-125 level below the baseline value that persisted for ≥ 4 weeks. The CA-125 response was assessed and reported separately from the response of patients with measurable disease.[21] Toxicity was evaluated according to the Japan Clinical Oncology Group Grading system.[22]

Pharmacologic Analysis

CPT and carboplatin were infused in 1 arm of each patient, and blood samples for the pharmacokinetic study were taken from each patient's other arm on Day 1 of the first course. Blood samples (1 mL) for pharmacokinetic analysis of CPT-11 were obtained before the chemotherapy; at the end of the CPT-11 infusion; and 5 minutes, 15 minutes, and 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours after the end of the infusion. The concentrations of CPT-11 and its metabolites (SN-38 and SN-38 glucuronide [SN-38G]) were measured by a modified, reverse-phase, high-performance liquid chromatography method.[23] Blood samples (2 mL) for measurement of carboplatin were obtained before chemotherapy; at the end of the infusion; and 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 10 hours, and 24 hours after the end of the infusion. After immediate centrifugation, the plasma was transferred to an Amicon Centrifree tube (Amicon, Inc., Beverly, MA), and the ultrafiltrates of the plasma were stored at − 20 °C until measurement of the plasma-free platinum concentration by flameless atomic absorption spectrometry.[24] The carboplatin level was calculated based on the platinum/carboplatin molar ratio. The AUC was obtained by the trapezoidal method with extrapolation to infinity using WINNONLIN version 1.1 software (Scientific Consulting, Apex, NC). The biliary index was calculated based on the method described in a previous report.[25]

In the pharmacodynamic study, we evaluated the correlations between pharmacokinetic parameters and observed hematologic toxicities in the first course. Hematologic toxicity was calculated according to the following formula: percentage decrease = 100 × (count before treatment − nadir count)/(count before treatment), and it was related to the AUC according to a sigmoid E_{max} model as follows: Effect (%) = $100 \times E_{max}(AUC)^{\kappa}/(AUC_{50})^{\kappa} + AUC^{\kappa}$. Nonlinear least-squares regression performed with WINNONLIN was used to estimate the AUC that produce 50% of the maximum effect (AUC_{50}) and the sigmoidicity coefficient (κ).

To evaluate for adjustment serum creatinine by adding 0.2 mg/dL,[18] we compared the observed carboplatin clearance with carboplatin clearance calculated with the Chatelut formula using PAP methods with or without the adjustment model. The accuracy of the estimate was measured by calculating the mean predictive error (MPE) and the root mean square error (RMSE).[26]

TABLE 1
Patient Characteristics

Characteristic	No. of patients
No. of patients entered	19
Median age in yrs (range)	58 (40–63)
Performance status	
0	6
1	13
Histology	
Serous	15
Mucinous	1
Endometrioid	1
Clear cell	1
Unclassified	1
No. of previous regimens	
1	10
2	6
3	2
4	1
Platinum-free interval	
< 3 mos	10
3–6 mos	3
≥ 6 mos	6
Disease sites	
Pelvic tumor	7
Liver metastasis	3
Lymph node metastasis	3
Ascites	5
Pleural effusion	3
Other	2
Median 24-hr creatinine clearance mL/min (range)	65.9 (16.9–98.8)

RESULTS

Patient Characteristics

In total, 19 patients were enrolled on this trial between August 1996 and July 1999, and all patients previously has received platinum-containing chemotherapy. The patient characteristics are listed in Table 1. Their median age was 58 years (range, 40–63 yrs), and the performance status was 0 in 6 patients and 1 in 13

TABLE 2
Dose-Escalation Schedule and Actual Doses Given to Patients

Level	Dose		No. of patients	Total no. of courses	CPT-11 dose intensity (mg/m^2/wk) delivered/projected	CPT-11 percentage dose delivered[a]
	CBDCA (AUC)	CPT-11 (mg/m^2)				
1	4	50	3	7	30/38	81
2	4	60	3	8	26/45	64
3	5	50	3	7	29/38	80
4	5	60	5	23	25/45	60
5	6	50	5	25	21/38	58

CBDCA: the observed area under the concentration curve (AUC) for carboplatin; CPT-11: irinotecan.
[a] Actually delivered CPT-11 dose as a percentage of the planned dose.

TABLE 3
Major Toxicities Stratified by Dose Levels (70 courses)

	Toxicity grade															
	Leukopenia		Neutropenia		Anemia		Platelets		Nausea/emesis				Diarrhea			
Level	3	4	3	4	3	4	3	4	1	2	3	4	1	2	3	4
1	0	0	1	0	1	0	0	0	2	1	0	0	0	0	0	0
2	0	0	0	0	1	0	0	0	2	0	0	0	0	0	0	0
3	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0
4	1	0	0	1	3	0	4	0	0	2	0	0	0	1	0	0
5	1	1	2	2[a]	2	0	1	3	2	1	1	0	2	1	0	0

Platelets: thrombocytopenia.
[a] Two patients experienced Grade 3 febrile neutropenia.

patients. Nine patients had received one or more chemotherapy regimens before this study. In total, 70 courses of the regimen used in this study were administered through 5 dose levels, and all patients were assessable for toxicity (Table 2). The median number of courses was 4 (range, 1–7 courses). One-half of the patients (58.2%) in this study actually received CPT-11 on Day 8, but only 31.3% of patients received CPT-11 on Day 15. CPT-11 was withdrawn on Day 8 or Day 15 on 72 occasions, because of thrombocytopenia in 49% of episodes and because of leukopenia in 31% of episodes. However, on 9 occasions, the thrombocyte count was $> 75{,}000/\mu L$; and, on 17 occasions, the leukocyte count was $> 2000/\mu L$. Dose intensity and the percentage of the CPT-11 dose administered that was delivered at each dose level are shown in Table 2.

Recommended Dose Level

None of the 3 patients at Dose Levels 1, 2, 3, and 4 experienced DLTs. Because 1 of the 3 patients at Dose Level 5 experienced DLT (neutropenia and thrombocytopenia), an additional 3 patients were enrolled. Two of those patients developed DLT (neutropenia and thrombocytopenia); therefore, it was concluded that Dose Level 4 was the MTD and the recommended dose.

Toxicity

Leukopenia and neutropenia were the DLTs associated with this combination chemotherapy. Major toxicities stratified by dose levels are shown in Table 3. At Dose Level 5, 2 patients required platelet infusion and developed febrile neutropenia that required intravenous antibiotics. No anemia that required blood transfusion was observed in any treatment cycle at any level. Gastrointestinal toxicities, such as nausea, emesis, diarrhea, and appetite loss, were prominent. CPT-11 caused diarrhea, but it was mild (Grade 1–2). No treatment-related deaths occurred in the current study.

Responses

Ten patients had measurable lesions, and they were assessed for responses according to WHO criteria (2 patients at Dose Level 1, 2 patients at Dose Level 2, 1 patient at Dose Level 3, 3 patients at Dose Level 4, and

TABLE 4
Objective Response and CA-125 Response

Level	No. of patients	Response				No. of CA-125 responses[a]
		PR	NC	PD	NE	
1	3	0	2	0	1	1
2	3	0	2	0	1	0
3	3	0	0	1	2	0
4	5	3	0	0	2	2
5	5	2	1	0	2	3

PR: partial response; NC: no change; PD: progressive disease; NE: not evaluable.
[a] The number of CA-125 responses means number of patients who achieved a 50% reduction in CA-125 level compared with the baseline level, which that must have persisted for ≥ 4 weeks.

3 patients at Dose Level 5). An objective response was observed in 5 patients: a partial response was seen at Dose Level 4 in 3 patients, and a partial response was seen at Dose Level 5 in 2 patients. The platinum-free interval was < 3 months in 2 of the 3 patients who achieved a partial response at Dose Level 4. CA-125 responses were observed in 6 patients (Table 4). The median time to disease progression in this study was 6.1 months (range, 0.93–19.4 mos), and the median survival was 16.2 months (range, 2.5–51.9 mos).

Pharmacologic Study of CPT-11 and CBDCA

The pharmacokinetic study was performed in only 13 patients, because the other 6 patients refused blood sampling for the pharmacokinetic analysis. A summary of the pharmacokinetic parameters of CPT-11, SN-38, and SN-38G is shown in Table 5. The concentrations of CPT-11 and SN-38 versus the time curve at each dose are shown in Figures 1 and 2, respectively. The metabolic ratios of SN-38 and the biliary indexes calculated as the AUC of CPT-11 and the AUC of SN-38/AUC of SN-38G[25] were similar at both dose levels.

A summary of the pharmacokinetic parameters of carboplatin is shown in Table 5. The measured AUCs of carboplatin were higher than the estimated AUCs (Fig. 3). The observed carboplatin clearance and the carboplatin clearance calculated using the Chatelut formula were 74.1 ± 24.6 mL/minute (range, 31.8–120.0 mL/min) and 93.7 ± 29.2 mL/minute (range 37.0–138.9 mL/min), respectively. The accuracy of the estimation evaluated on the basis of the MPE and the RMSE was 22.8% and 31.3%, respectively, using the Chatelut formula without the adjustment model and − 1.1% and 17%, respectively, on the basis of calculations with the adjustment model (Fig. 4).

The pharmacodynamic analysis was undertaken to evaluate the correlations between pharmacokinetic parameters and hematologic toxicity in the first course. The correlation between the SN-38 AUC and the percentage decrease in neutrophil count is shown in Figure 5 (r = 0.292), and the AUC_{50} of SN-38 was 36.0 ng/hour/mL, with κ estimated at 0.38. The correlation between the carboplatin AUC and the percentage decrease in thrombocyte is shown in Figure 6 (r = 0.514), and the AUC_{50} of carboplatin was 2.76 mg · min/mL, with κ estimated at 2.80.

DISCUSSION

Based on the results of the current study, the combination of CPT-11 and carboplatin was feasible for patients who previously received platinum-containing chemotherapy, and it was concluded that the recommended dose for the Phase II study in patients with advanced ovarian carcinoma was CPT-11 60 mg/m^2 on Days 1, 8, and 15 combined with carboplatin AUC 5 on Day 1. To our knowledge, this is the first report of combination therapy with carboplatin and CPT-11 in patients with ovarian carcinoma.

In Phase I trials in previously untreated patients with lung carcinoma, the recommended dose of this regimen was CPT-11 50 mg/m^2 on Days 1, 8, and 15 and carboplatin AUC 5 mg/mL · minute on Day 1, and the DLTs were neutropenia, thrombocytopenia, and diarrhea.[27,28] Although the recommended CPT-11 dose in the current study was higher than in those studies, the main DLTs were neutropenia and thrombocytopenia, as expected, and no severe nonhematologic toxicities, such as diarrhea, were observed. We believe that the reasons for this may be that the dose intensity of CPT-11 (mg/m^2 per week) and the percentage of the dose delivered in our study were lower than in the other studies. The difference of the dose intensity is attributable to the fact that our criteria for administration on Days 8 and 15 were stricter than those used in the previous studies[17,27,28] and to the difference in the number of patients in a previously untreated or heavily treated setting.

Although the sequence of administration of CPT-11 and carboplatin in the current study was different from the sequence used in the patients with lung carcinoma, the pharmacokinetic parameters of CPT-11 and SN-38 were almost the same as those in the patients with lung carcinoma who were treated with CPT-11 (50 mg/m^2 on Days 1, 8, and 15) followed by a fixed dose of carboplatin (300 mg/m^2 on Day 1).[28] The sequence of the drug administration in a previous study did not affect the pharmacodynamics or kinetics in the combination of CPT-11 and cisplatin.[29] Therefore, the drug sequence administration may have no major influence on the pharmacokinetic parameters in the combination of CPT-11 and carboplatin.

TABLE 5
Summary of Pharmacokinetic Parameters[a]

Pharmacokinetic parameter	No. of patients	Cmax	$AUC^{0-\infty}$	CL	$T_{1/2}$	Biliary index[b]
CPT-11		μ/mL	μg·hr/ml	L/m² hr	Hr	
50 mg/m²	8	0.69 ± 0.06	3.32 ± 0.25	13.21 ± 1.32	8.03 ± 0.75	—
60 mg/m²	5	1.14 ± 0.10	4.79 ± 0.44	13.00 ± 1.32	8.35 ± 1.05	—
SN-38		ng/mL	ng·hr/ml		Hr	
50 mg/m²	8	22.86 ± 2.6	225.6 ± 40.3	—	10.51 ± 1.98	—
60 mg/m²	5	28.27 ± 4.5	283.9 ± 62.7	—	11.67 ± 2.41	—
SN-38G		ng/mL	ng·hr/ml		Hr	ng·hr/ml
50 mg/m²	8	29.8 ± 3.1	464.7 ± 70.4	—	12.06 ± 1.50	1692.8 ± 843.7
60 mg/m²	5	45.6 ± 12.5	1040.2 ± 416.8	—	16.05 ± 1.41	1652.2 ± 511.4
CBDCA		mg/mL	mg·min/ml	mL/min	Hr	
AUC 4	6	13.97 ± 4.1	4.95 ± 0.99	77.7 ± 27.53	4.25 ± 0.74	—
AUC 5	4	16.4 ± 3.3	5.59 ± 0.48	77.99 ± 30.73	4.17 ± 1.23	—
AUC 6	3	21.7 ± 2.5	7.94 ± 1.88	80.69 ± 24.83	4.18 ± 0.37	—

Cmax: maximum plasma concentrations; AUC: area under the concentration curve; CL: clearance; $T_{1/2}$: elimination half-life; CPT-11: irinotecan; SN-38: 7-ethyl-10-hydroxycamptothecin; SN38G: SN-38-glucuronide; CBDCA: the observed AUC of carboplatin.

[a] Data shown are the mean ± standard deviation in 13 patients.

[b] "Biliary index (ng·hr/ml)" was calculated as $AUC_{CPT-11} \times AUC_{SN-38}/AUC_{SN-38G}$.

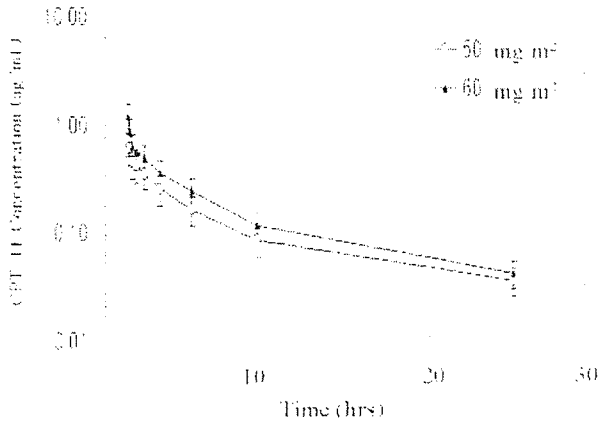

FIGURE 1. The concentrations of irinotecan (CPT-11) versus the time curve are illustrated for patients who received doses of 50 mg/m² and 60 mg/m² (n = 13 patients).

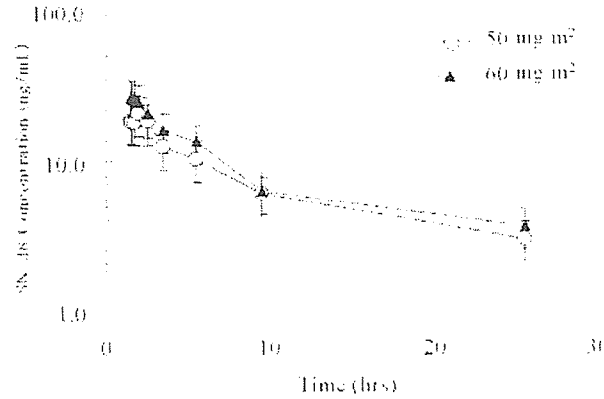

FIGURE 2. The concentrations of SN-38 versus the time curve are illustrated for patients who received in doses of 50 mg/m² and 60 mg/m² (n = 13 patients).

Although we used the Chatelut formula in the current study, several formulas are available to calculate the dose of carboplatin. The Calvert formula requires measurement of the glomerular filtration rate with a radioisotope, but creatinine clearance rates estimated by the Cockcroft–Gault or Jelliffe formula or actually measured, 24-hour creatinine clearance have been used widely instead. Several studies have compared the performance of the Chatelut formula and the Calvert formula by using several methods,[14–16] but the performance of each formula remains a matter of controversy, because previous studies have reported differences according to race, gender, method of calculating creatinine clearance, and unknown pharmacokinetic interactions between drugs in combination.[12–17] Fukuda et al. reported that a Phase I study of CPT-11 and carboplatin in 11 previously untreated Japanese patients with solid malignancies showed a significant correlation between measured carboplatin clearance and carboplatin clearance estimated by the Chatelut formula, and those authors recommended using the formula.[18] However, several clinical pharmacologic studies have shown that carboplatin clearance calculated by the Chatelut formula was higher than measured clearance and clearance calculated by the Calvert formula.[12–14] Furthermore, it has been reported that the adjusted serum creatinine value is

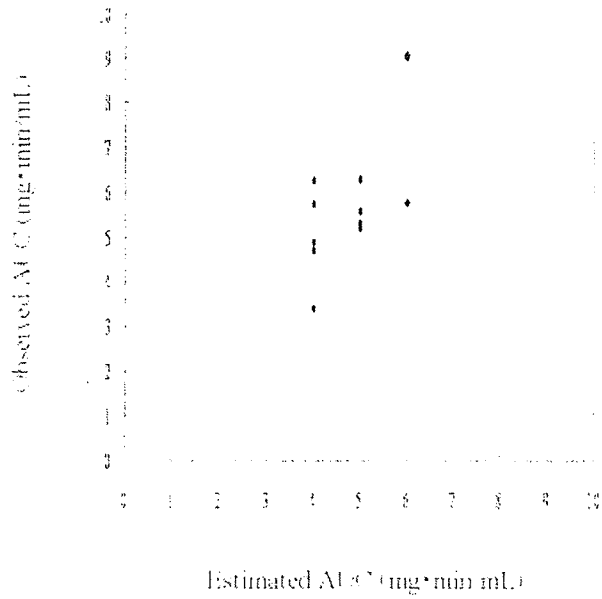

FIGURE 3. This chart illustrates the correlation between the observed area under the plasma concentration-versus-time curve (AUCs) of carboplatin (CBDCA) and the estimated AUC.

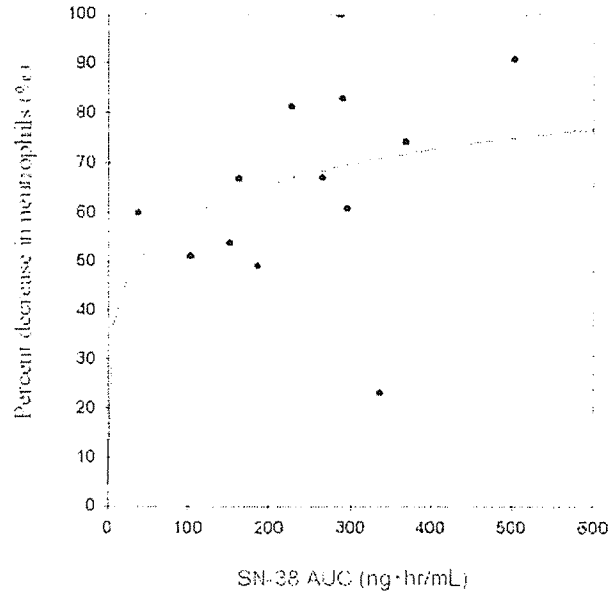

FIGURE 5. This chart illustrates the correlation between the SN-38 area under the plasma concentration-versus-time curve (AUC) and the percentage decrease in neutrophil count in Course 1 based on the sigmoid E_{max} model.

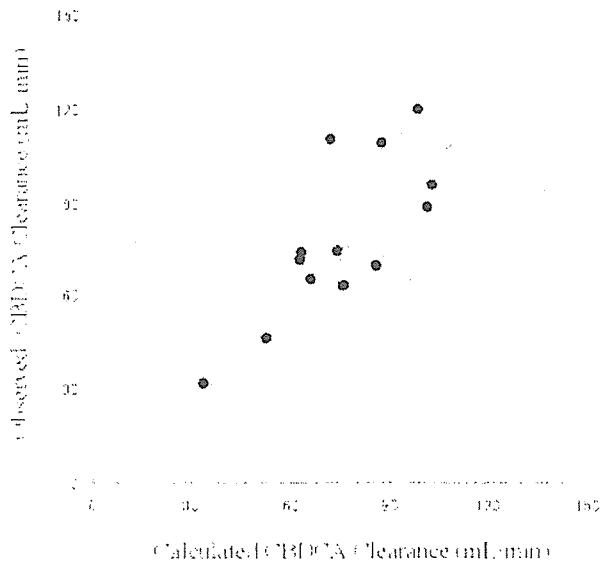

FIGURE 4. This chart illustrates the correlation between observed carboplatin (CBDCA) clearance and CBDCA clearance calculated with the Chatelut formula (open circles) and with the Chatelut formula adjusted for serum creatinine (solid circle) (see Dooley et al., 2002[17]). The line of identity (solid line) is shown. The bias and precision of each formula are expressed by the mean prediction error and the root mean square error (see Kaneda et al., 1990[24]).

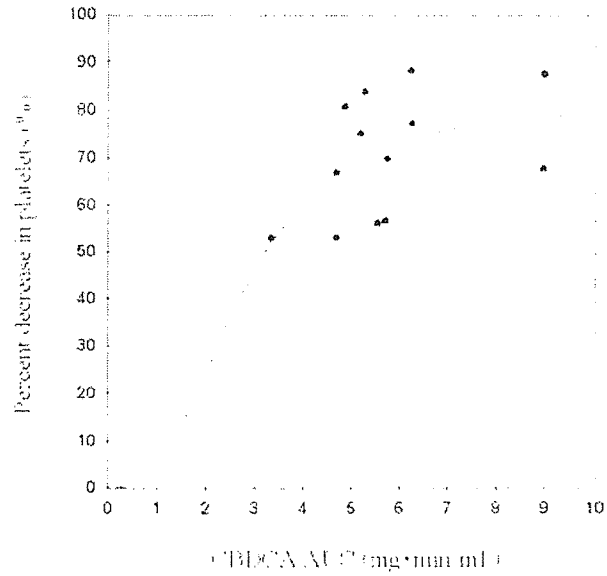

FIGURE 6. This chart illustrates the correlation between the carboplatin (CBDCA) area under the plasma concentration-versus-time curve (AUC) and the percentage decrease in platelet count in Course 1 based on the sigmoid E_{max} model.

appropriate for calculating the proper carboplatin clearance in Japanese patients.[18] Similar to previous reports, our study showed that the calculated carboplatin clearance values were higher than the measured values, and the accuracy of estimation by using the Chatelut formula improved when adjusted serum creatinine values were used.

In recent years, it has been demonstrated that paclitaxel is highly effective for ovarian carcinoma, and paclitaxel plus platinum combination chemotherapy now is accepted widely as a standard regimen for the first-line treatment for advanced ovarian carcinoma.[1,2] CPT-11 is a topoisomerase I inhibitor that has unique antitumor action. In a Phase II trial, CPT-11 and cisplatin combination chemotherapy yielded a high response rate of 76% in previously untreated patients with advanced ovarian carcinoma.[30] CPT-11 and cisplatin also yielded an overall response rate of 40% in patients who were treated previously with platinum-containing chemotherapy and a response rate of 30% in platinum-resistant patients.[31] Kigawa et al. reported a high response rate (60%) to second-line CPT-11 and cisplatin combination chemotherapy among patients who were treated previously cisplatin, and there was no difference in the proportion of patients who had platinum-sensitive or platinum-resistant tumors between responders and nonresponders.[32] Although the current study was performed in a Phase I trial setting, it is noteworthy that half of the patients with measurable lesions achieved responses. A previous study reported that the CPT-11 response rate was 17%, even among patients with platinum-resistant tumors.[7] Thus, our regimen may be effective both in patients with platinum-sensitive disease and in patients with platinum-resistant disease who previously received paclitaxel plus platinum combination chemotherapy.

In conclusion, the recommended doses of CPT-11 and carboplatin in combination are 60 mg/m^2 and an AUC of 5 mg/mL · minute according to the Chatelut formula, respectively, and this regimen may be effective in patients with ovarian carcinoma who previously received platinum-containing chemotherapy. The results of the pharmacologic analysis in this study suggest that the carboplatin clearance rates calculated with the Chatelut formula are higher than the actually measured carboplatin clearance and that adjustment for serum creatinine may be useful in calculating the proper dose.

REFERENCES

1. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with Stage III and IV ovarian cancer. *N Engl J Med.* 1996;334:1–6.
2. 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;21:3194–3200.
3. Misawa T, Kikkawa F, Maeda O, et al. Establishment and characterization of acquired resistance to platinum anticancer drugs in human ovarian carcinoma cells. *Jpn J Cancer Res.* 1995;86:88–94.
4. Kano Y, Akutsu M, Suzuki K, Yoshida M. Effects of carboplatin in combination with other anticancer agents on human leukemia cell lines. *Leukemia Res.* 1993;17:113–119.
5. Kano Y, Suzuki K, Akutsu M, et al. Effects of CPT-11 in combination with other anticancer agents in culture. *Int J Cancer.* 1992;50:604–610.
6. Bodurka DC, Levenback C, Wolf JK, et al. Phase II trial of irinotecan in patient with metastatic epithelial ovarian cancer or peritoneal cancer. *J Clin Oncol.* 2003;21,291–297.
7. Evans BD, Raju KS, Calvert AH, Harland SJ, Wiltshaw E. Phase II study of JM8, a new platinum analog, in advanced ovarian carcinoma. *Cancer Treat Rep.* 1983;67:997–1000.
8. Leyvraz S, Ohnuma T, Lassus M, Holland JF. Phase I study of carboplatin in patients with advanced cancer, intermittent intravenous bolus, and 24-hour infusion. *J Clin Oncol.* 1985;3:1385–1392.
9. Jordrell DI, Egorin MJ, Canetta RM, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol.* 1992;10: 520–528.
10. Calvert AH, Harland SJ, Newell DR, et al. Early clinical studies with cisdiammine-1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol.* 1982;9:140–147.
11. Chatelut E, Canal P, Brunner V, et al. Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst.* 1995;87:573–580.
12. Fujiwara Y, Takahashi T, Yamakido M, Ohune T, Tsuya T, Egorin MJ. Re: prediction of carboplatin clearance from standard morphological and biological patients characteristics. *J Natl Cancer Inst.* 1997;89:260–261.
13. Minami H, Ando Y, Saka H, Shimokata K. Re: prediction of carboplatin clearance from standard morphological and biological patients characteristics. *J Natl Cancer Inst.* 1997;89: 968–969.
14. Okamoto H, Nagamoto A, Kunitoh H, Kunikane H, Watanabe K. Prediction of carboplatin clearance calculated by patient characteristics or 24-hour creatinine clearance: a comparison of the performance of three formulae. *Cancer Chemother Pharmacol.* 1998;42:307–312.
15. Donahue A, McCune JS, Faucette S, et al. Measured versus estimated glomerular filtration rate in the Carver equation: influence on carboplatin dosing. *Cancer Chemother Pharmacol.* 2001;47:373–379.
16. Dooley MJ, Poole SG, Rishchin D, Webster LK. Carboplatin dosing: gender bias and inaccurate estimates of glomerular filtration rate. *Eur J Cancer.* 2002;38:44–51.
17. Fukuda M, Oka M, Soda H, et al. Phase I study of irinotecan combined with carboplatin in previously untreated solid cancers. *Clin Cancer Res.* 1999;5:3963–3969.
18. Ando Y, Minami H, Saka H, Ando M, Sugiura S, Sakai S, Shimokata K. Adjustment of creatinine clearance of improves accuracy of Calvert's formula for carboplatin dosing. *Br J Cancer.* 1997;76:1067–1071.
19. Ozols RF. Treatment of recurrent ovarian cancer: increasing option-recurrent results. *J Clin Oncol.* 1997;15:2177–2180.
20. Miller AB, Hoogstraten B, Staquet M. Reporting results of cancer treatment. *Cancer.* 1981;147:207–214.

21. Rustin GJ, Nelstrop AE, McClean P, et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. *J Clin Oncol.* 1996;14:1547–1551.
22. Tobinai K, Kohno A, Shimada Y, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. *Jpn J Clin Oncol.* 1993;23:250–257.
23. Kaneda N, Nagata H, Furuta T, YokokuraT. Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in the mouse. *Cancer Res.* 1990;50:1715–1720.
24. Le Roy AF, Wehling ML, Sponseller HL, et al. Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. *Biochem Med.* 1977;18:184–191.
25. Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. *Cancer Res.* 1994;54:3723–3725.
26. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm.* 1981;9:503–512.
27. Takeda K, Negoro S, Takefuji N, et al. Dose escalation study of irinotecan combined with carboplatin for advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol.* 2001;48:104–108.
28. Sato M, Ando M, Minami H, et al. Phase I/II and pharmacologic study of irinotecan and carboplatin for patients with lung cancer. *Cancer Chemother Pharmacol.* 2001;48:481–487.
29. de Jonge MJA, Verweij J, Planting AST, et al. Drug-administration sequence does not change pharmacodynamics and kinetics of irinotecan and cisplatin. *Clin Cancer Res.* 1999;5:2012–2017.
30. Sugiyama T, Yakusiji M, Kamura T, et al. Irinotecan and cisplatin as first line chemotherapy for advanced ovarian cancer. *Oncology.* 2002;63:16–22.
31. Sugiyama T, Yakushiji M, Nishida T, et al. Irinotecan combined with cisplatin in patients with refractory or recurrent ovarian cancer. *Cancer Lett.* 1998;128:211–218.
32. Kigawa J, Takahashi M, Minagawa Y, et al. Topoisomerase-I activity and response to second-line chemotherapy consisting of camptothecin-11 and cisplatin in patients with ovarian cancer. *Int J Cancer.* 1999;84:521–524.

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Secondary cytoreductive surgery for recurrent epithelial ovarian carcinoma: proposal for patients selection

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The value of secondary cytoreductive surgery (SCS) for recurrent ovarian cancer is still controversial. The aim of this study was to clarify candidates for SCS. Between January 1987 and September 2000, we performed SCS in 44 patients with recurrent ovarian cancer, according to our selection criteria, disease-free interval (DFI) >6 months, performance status <3, no apparent multiple diseases, age <75years and no progressive disease during preoperative chemotherapy, if undertaken. The variables were investigated by univariate and multivariate analyses. Of 44 patients, 26 (59.1%) achieved complete removal of all visible tumours at SCS. Secondary cytoreductive surgery outcome, complete or incomplete resection, was significantly related to overall survival ($P=0.0019$). As for variables determined before SCS, DFI >12 months, no liver metastasis, solitary tumour and tumour size <6 cm were independently associated with favourable overall survival after recurrence in the multivariate analysis. Patients with three or all four variables ($n=31$) had significantly better survival compared with the other patients ($n=13$) (47 *vs* 20 months in median survival, $P<0.0001$). In these patients, fairly good median survival (40 months) was obtained even in patients with incomplete resection. Secondary cytoreductive surgery had a large impact on survival of patients with recurrent ovarian cancer when they had three or all of the above-mentioned four factors at recurrence. These patients should be considered as ideal candidates for SCS.
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Since Griffiths (Griffiths, 1975) first demonstrated the inverse relationship between residual tumour size after primary debulking and survival of ovarian cancer patients in 1975, many investigators have reproduced and confirmed this observation (Hacker *et al*, 1983; Vogl *et al*, 1983; Delgado *et al*, 1984; Conte *et al*, 1985; Louie *et al*, 1986; Neijt *et al*, 1987; Hainsworth *et al*, 1988; Sutton *et al*, 1989). Thus, the value of debulking of large tumour masses in the primary surgery of ovarian cancer has been generally accepted, and primary cytoreductive surgery followed by chemotherapy is considered to be a standard treatment procedure for patients with advanced ovarian cancer.

The cytoreduction contributes to removal of the tumour burden and relief of symptoms caused by tumours or massive ascites. In addition, the cytoreduction has another important effect on the sensitivity to postsurgical chemotherapy. By removing bulky tumours, the decreased growth fractions should increase (Norton and Simon, 1977) and poorly perfused anoxic cells should decrease. By reducing the number of cancer cells, the chance for cancer cells to undergo spontaneous mutations resulting in drug resistance should decrease (Goldie and Coldman, 1979). All these effects are believed to enhance the sensitivity to chemotherapy.

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Theoretically, the favourable effects of cytoreduction may also be expected in patients with recurrent ovarian cancer. Recently, several investigators have reported the significant value of secondary cytoreductive surgery (SCS) in a subset of patients with recurrent ovarian cancer (Jänicke *et al*, 1992; Eisenkop *et al*, 1995, 2000; Vaccarello *et al*, 1995; Cormio *et al*, 1999; Zang *et al*, 2000, 2004; Munkarah *et al*, 2001; Scarabelli *et al*, 2001; Tay *et al*, 2002). The value of complete resection at the time of SCS for highly selected patients is in consensus in these recent reports. They reported a considerable number of factors related to good prognosis including longer disease-free interval (DFI), smaller size of residual tumour at primary cytoreductive surgery, good response to first-line chemotherapy, younger age at recurrence and smaller size of maximum tumour at recurrence. However, there is limited information regarding the ideal candidates for SCS. Although only preoperative or intraoperative variables before starting SCS should be analysed for selection of the candidate, these variables have been analysed together with SCS outcome in most previous studies. In addition, the follow-up periods of living patients were rather short (the median or average follow-up periods were between 1 and 4 years) (Jänicke *et al*, 1992; Vaccarello *et al*, 1995; Cormio *et al*, 1999; Zang *et al*, 2000, 2004; Munkarah *et al*, 2001; Scarabelli *et al*, 2001) in most of the previous reports.

Since 1987, we have performed SCS according to our criteria of patient selection in 44 out of 70 ovarian cancer patients who had recurrence after DFI. In the present study, the median follow-up

period of living patients is 60 months after the initiation of treatment, SCS or chemotherapy before SCS, for recurrence. Using univariate and multivariate analyses of variables before starting SCS, we planned to clarify the ideal candidates for SCS among patients with recurrent ovarian cancer.

PATIENTS AND METHODS

Patient selection

Between January 1984 and December 1999, we treated 236 patients with stage I to IV epithelial ovarian cancer at the Department of Obstetrics and Gynecology, University of Tokyo Hospital. Our standard surgical procedures for ovarian cancer consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic or total omentectomy, and in advanced cases, debulking of tumour masses with maximum efforts. Patients with no or small intraperitoneal residual tumours (less than 2 cm in diameter) also underwent systematic retroperitoneal lymphadenectomy. The extent of retroperitoneal lymphadenectomy is pelvic lymph nodes only (1984–1986) or both pelvic and aortic lymph nodes (1987–1999). All but stage Ia patients underwent at least six cycles of cisplatin-based chemotherapies following surgery as described previously (Onda *et al*, 1998). Of the 236 patients, 204 (86%) achieved complete clinical remission after primary treatment.

By September 2000, 70 of the 204 (34%) patients had recurrence and, from January 1987 to September 2000, 44 of the 70 (63%) patients underwent SCS prior to or following chemotherapy. Administration of chemotherapy before SCS was decided based on various clinical factors including short DFI (DFI <12 months) and poor performance status (PS 3) defined by ECOG (Eastern Cooperative Oncology Group). Our selection criteria for SCS were as follows: (1) DFI >6 months, (2) age at recurrence <75 years, (3) PS 0–2 just before the surgery, (4) absence of apparent extensive intraperitoneal dissemination or multiple distant metastases and (5) no progressive disease during presurgical chemotherapy, if undertaken. There were three exceptions to the above-mentioned criteria for SCS. One patient with DFI <6 months (5 months) underwent SCS, because the recurrent site was expected to be limited to a solitary aortic lymph node by CT. The other two patients had PS 3 at surgery. One patient with three metastatic brain tumours underwent emergent brain surgery followed by γ-knife radiosurgery to one residual tumour (Kawana *et al*, 1997), and one patient underwent ileocaecal resection because of acute bowel obstruction. Before the treatment, informed consent was obtained from all of the patients.

Chemotherapy

Of 44 patients, 21 (47.7%) received chemotherapy before SCS and all of 44 patients were treated with chemotherapy after SCS. In all, one to eight (median: 2) cycles of presurgical chemotherapy were performed in eight of 13 (61.5%) patients with DFI <12 months and 13 of 31 (41.9%) patients with DFI >12 months. In total, 44 patients received two to nine (median: 4) cycles of postsurgical chemotherapy.

In all, two to four cycles of presurgical chemotherapy were generally administered until beneficial response (partial or minor response) was observed. In two patients, second-line chemotherapy showed no beneficial response, and SCS was performed after successful third-line chemotherapy (seven and eight cycles in total). One patient received only a cycle of presurgical chemotherapy, because SCS could not be scheduled immediately after diagnosis of recurrence.

The number of postsurgical chemotherapy given was determined by SCS outcome and response to chemotherapy, evaluated by CT scan and serum level of CA125. Generally, three to four cycles of chemotherapy were planned for patients with no residual tumour and five to six cycles of chemotherapy were planned for patients with any residual disease. In principle, we gave at least two cycles of chemotherapy after the serum level of CA125 was normalised. Thus, three patients were treated with more than six cycles of chemotherapy after SCS. On the contrary, chemotherapy was discontinued before accomplishment of the planned cycles in five patients because rapid disease progression or severe adverse effects were observed during the planned cycles.

In presurgical and postsurgical chemotherapies, a platinum-based combination, CAP, EP or TJ, was used. The CAP regimen consisted of 600 mg m^{-2} of cyclophosphamide, 30 mg m^{-2} of doxorubicin and 50–75 mg m^{-2} of cisplatin. The EP regimen consisted of 80 mg m^{-2} of etoposide during days 1–5 and 75 mg m^{-2} of cisplatin. Paclitaxel was introduced in Japan in 1998 and, thereafter, a TJ regimen consisting of paclitaxel (175 mg m^{-2} over 3-h infusion) and AUC 5 of carboplatin was used as second-line chemotherapy.

Statistical methods

Survival was measured from the day of starting treatment for recurrence, that is, the day of starting presurgical chemotherapy or the day of performing SCS. The survival curves were determined by the Kaplan–Meier product limit method (Kaplan and Meier, 1958). Factors influencing survival were analysed using the log-rank test (univariate) and Cox's proportional-hazards regression analysis (multivariate). These analyses were performed using a JMP program (SAS Institute Inc., USA). Contingency table analysis was performed using the χ^2 test or χ^2 test for trend.

RESULTS

Patient characteristics

The number of patients was three in stage I, two in stage II, 36 in stage III and three in stage IV according to the International Federation of Gynecology and Obstetrics (FIGO). Histology was serous type in 35, clear-cell type in three, endometrioid type in three, transitional cell type in two and mixed epithelial type in one. Median DFI was 18.5 months with a range of 5–58 months: one patient (2.3%) had 5 months, 12 (27.3%) had 6–12 months and 31 (70.5%) had >12 months. Median age at recurrence was 52 years with a range of 37–74 years. Median follow-up period of patients, excluding those who died, was 60 months with a range of 17–199 months from the initiation of treatment for recurrence.

Surgery

Our attempt to perform SCS resulted in exploratory laparotomy in four patients (9.1%) due to the presence of unexpected extensive peritoneal tumours. Various debulking surgeries classified into four categories such as (1) gastrointestinal resection, (2) resection of other organs, (3) lymph node dissection and (4) other tumour debulking was performed with maximum efforts in the remaining 40 patients (90.9%). Among these patients, gastrointestinal resection (category 1) was required in 11 patients (25.0%), large bowel resection in nine patients (20.5%), small bowel resection in three patients (6.8%), partial gastrectomy in one patient and ileocaecal resection in one patient (2.3%), and one of the patients (2.3%) underwent sigmoid colostomy. Three patients had category 1 surgeries at two sites. Resection of other organs (category 2) was required in six patients (13.6%), splenectomy in three patients (6.8%), distal pancreatectomy in two patients (4.5%), partial liver resection in one patient, hysterectomy in one patient and brain tumour resection in one patient (2.3%). Two patients had category 2 surgeries at two sites. Regional or distant lymph node dissection (category 3) was performed in 12 patients (27.3%). Five patients

(11.4%) underwent systematic aortic lymphadenectomy and one (2.3%) underwent both systematic pelvic and aortic lymphadenectomies. Selective dissections of the following lymph nodes were performed in six patients: aortic nodes in one patient, pelvic nodes in one patient, axillary nodes in one patient, portal nodes in one patient, inguinal nodes in one patient and mesenteric nodes in one patient (2.3%). Other tumour debulking (category 4) including removal of tumours in the remnant omentum, the diaphragmatic muscles and vaginal stump, and tumours on the visceral or parietal peritoneum including the under surface of the diaphragm, was performed in 22 patients (50.0%); omentectomy in seven patients; partial full-thickness diaphragm resection in one patient; resection of tumours around the vaginal stump in four patients (9.1%); peritoneum resection of disseminated tumours on the under surface of the diaphragm; and other peritoneal surfaces in 16 patients (36.4%). Six patients were counted twice because they underwent two types of category 4 surgeries. In all, 10 patients underwent two or three out of the above four categories of debulking surgery. No patients died within a month following SCS.

Cytoreductive outcome and survival of patients

Among a total of 44 patients, complete resection of visible tumours was achieved in 26 patients (59.1%), largest residual tumours <1 cm in diameter were left in 11 patients (25.0%) and largest residual tumours $\geqslant 1$ cm in diameter were left in seven patients (15.9%). The median survival and 5-year survival of all patients who underwent cytoreductive surgery were 32 months and 33.2% (Figure 1), whereas the median survival and 5-year survival of 26 patients who had recurrence after complete remission achieved by primary treatment and did not undergo the surgery were 11 months and 3.9%. Figure 2 shows the survival of patients after the initiation of treatment for recurrence according to the outcome of SCS (SCS outcome). The median survival and 5-year survival after recurrence of the patients with largest residual tumours 0, <1 and $\geqslant 1$ cm were 52 months and 47.6%, 23 months and 18.2% and 20 months and 0%, respectively ($P=0.0007$, log rank). The overall survival of patients with no residual tumour was much better than that of patients with residual tumours (22 months in median survival and 12.0% in 5-year survival, figure not shown) with statistical significance ($P=0.0019$). There was no statistical difference in overall survival between patients with residual tumours <1 and $\geqslant 1$ cm ($P=0.1314$).

Factors influencing survival in univariate analyses

Factors influencing overall survival after recurrence were analysed using univariate analyses. Factors analysed and the results of univariate analyses are listed in Tables 1 and 2. As for prognostic factors determined during primary therapy, univariate analyses revealed that peritoneal tumour spread ($P=0.039$), FIGO stage ($P=0.045$) and aortic lymph node metastasis ($P=0.009$) were significantly associated with overall survival after recurrence. Regarding prognostic factors determined at recurrence, univariate analyses revealed that DFI ($P=0.002$), presence of liver metastasis ($P=0.005$), number of recurrent tumours ($P=0.007$), size of maximum tumour ($P<0.001$) and SCS outcome ($P=0.002$) had significant associations with overall survival after recurrence.

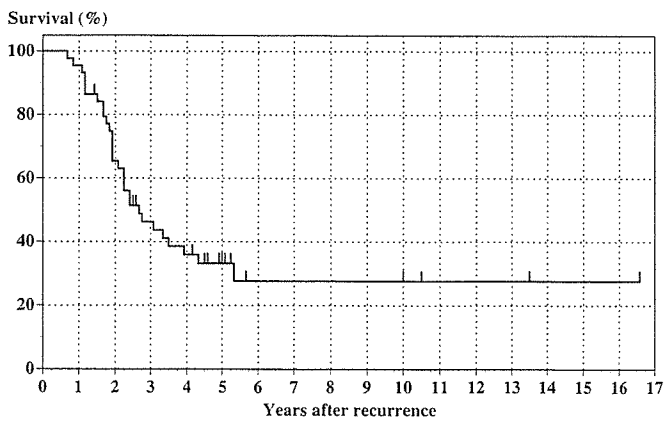

Figure 1 Survival of all 44 patients who underwent SCS.

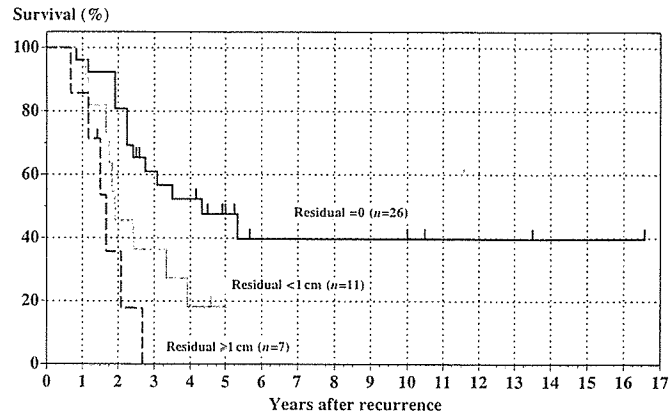

Figure 2 Outcome of SCS and survival. Survival of the patients with largest residual tumours 0, <1 and $\geqslant 1$ cm is shown in solid black, solid grey and dotted black line, respectively. The difference of survival is statistically significant ($P=0.0007$, log rank). There is no statistical difference in survival between patients with residual tumours <1 and $\geqslant 1$ cm ($P=0.1314$, log rank).

Table 1 Univariate analyses for variables during primary treatment

Variables	Number	Median survival (months)	P-value
Peritoneal tumour spread			
Localised to the pelvis	10	NA	
Extended beyond the pelvis	34	29	0.039
Stage			
I/II	5	NA	
III/IV	39	29	0.045
Aortic lymph node metastases			
Absent	25	64	
Present	14	27	
Not assessed	5	25	0.009
Pelvic lymph node metastases			
Absent	20	47	
Present	21	32	
Not assessed	3	25	0.126
Systematic lymphadenectomy			
Not performed	3	25	
Pelvic only	7	29	
Pelvic and aortic	34	33	0.296
Histology			
Serous	35	37	
Others	9	23	0.197
Residual tumour at PCS			
0	34	32	
Any	10	40	0.961

PCS = primary cytoreductive surgery; NA = not applicable.

Table 2 Univariate analyses for variables at recurrence

Variables	Number	Median survival (months)	*P*-value
Age at recurrence (years)			
<50	17	29	
⩾50	27	40	0.860
Disease-free interval (months)			
⩾12	31	47	
<12	13	23	0.002
Intraperitoneal tumour			
Absent	12	64	
Present	32	27	0.117
Pelvic or aortic lymph node metastases			
Absent	34	32	
Present	10	37	0.419
Distant metastasis			
Absent	38	32	
Present	6	40	0.496
Liver metastasis			
Absent	42	33	
Present	2	20	0.005
No. of recurrent tumours			
Solitary	16	64	
Multiple	28	27	0.007
Size of maximum tumour (cm)			
<6	38	40	
⩾6	6	14	<0.001
Massive ascites (>500 ml)			
Absent	41	33	
Present	3	32	0.318
PS			
0–2	42	29	
3	2	42	0.746
Presurgical chemotherapy			
Not done	23	33	
Done	21	29	0.677
Bowel resection			
Not done	33	33	
Done	11	27	0.650
Residual tumour at SCS			
0	26	52	
Any	18	22	0.002

PS = performance status; SCS = secondary cytoreductive surgery.

Factors influencing survival in multivariate analysis

To determine patient selection for the surgery, we performed multivariate analysis using statistically significant prognostic factors in univariate analyses. Out of eight significant factors, SCS outcome was omitted in the multivariate analysis because SCS outcome is not yet known on considering indications for the surgery, although SCS outcome had a statistically significant correlation with the number of recurrent tumours ($P<0.001$, χ^2 test). The multivariate analysis using the remaining seven factors revealed that four factors determined at recurrence, specifically DFI, presence of liver metastasis, number of recurrent tumour and size of maximum tumour, were independently and significantly associated with survival after recurrence (Table 3). Additionally, the multivariate analysis using only these four factors confirmed

Table 3 Multivariate analysis using the seven prognostic variables in the univariate analyses

	Multivariate analysis	
Variables	**Risk ratio (95% CI)**	***P*-value**
Peritoneal tumour spread at PCS		
Localised to the pelvis	1.00	
Extended beyond the pelvis	0.80 (0.42–1.76)	0.540
Stage		
I/II	1.00	
III/IV	0.90 (0.22–5.60)	0.893
Aortic lymph node metastases at PCS		
Absent	1.00	
Present	1.23 (0.56–2.64)	
Not assessed	1.78 (0.61–5.33)	0.088
Disease-free interval (months)		
⩾12	1.00	
<12	2.45 (1.11–5.39)	0.027
Liver metastasis		
Absent	1.00	
Present	4.00 (1.40–10.03)	0.013
No. of recurrent tumours		
Solitary	1.00	
Multiple	3.73 (1.79–9.58)	<0.001
Size of maximum tumour (cm)		
<6	1.00	
⩾6	7.43 (3.12–18.92)	<0.001

PCS = primary cytoreductive surgery.

that all four factors were independently and significantly associated with survival after recurrence. The relative risk (95% confidence interval) was 0.37 (0.20–0.68) for DFI >12 months, 0.23 (0.10–0.65) for absence of liver metastasis, 0.26 (0.12–0.48) for a solitary tumour and 0.20 (0.09–0.42) for size of maximum tumour <6 cm.

Grouping of patients determined by the number of favourable prognostic factors

According to the number of favourable statuses among the above-mentioned four prognostic factors, that is, DFI >12 months, no liver metastasis, solitary tumour and tumour size <6 cm, patients were divided into four groups as follows: patients with all four favourable factors (Group 4, $n=10$), patients with three favourable factors (Group 3, $n=21$), patients with two favourable factors (Group 2, $n=11$) and patients with only one favourable factor (Group 1, $n=2$). There were no patients with zero favourable factors. Complete resection of visible tumours was achieved in 100% (10 of 10), 62% (13 of 21), 18% (two of 11) and 50% (one of two) of patients in Group 4, Group 3, Group 2 and Group 1, respectively. Apparently, a higher rate of complete surgical resection was achieved in patients with a larger number of favourable factors, and the distribution was statistically significant by contingency table analysis ($P<0.001$, χ^2 test for trend). The 5-year survival of Group 4 was 88.9% and median survival was not reached. The 5-year survivals and median survivals of Group 3, Group 2 and Group 1 were 26.0, 0 and 0%, and 37, 20 and 10 months, respectively (figure not shown). The differences of overall survival were also statistically significant among the four groups ($P<0.001$, log rank) and between them (e.g. $P<0.007$ in Group 1 *vs* Group 2, $P<0.001$ in Group 2 *vs* Group 3 and $P<0.001$ in Group

3 *vs* Group 4, log rank). Figure 3 shows the combined survival of Group 4 and Group 3 and that of Group 2 and Group 1. Patients with three or all four favourable factors (Group 3/4) ($n=31$) had significantly better survival compared with those with less than three favourable factors (Group 1/2) ($n=13$) (median and 5-year survival; 47 months and 45.9% *vs* 20 months and 0%, $P<0.001$).

Survival of patients determined by the number of favourable prognostic factors and SCS outcome

Patients with three or all four favourable prognostic factors (Group 3/4) had better survival when complete surgical resection was achieved at the time of SCS ($n=23$) (64 months in median survival, 53.8% in 5-year survival). However, even when SCS left residual tumours, survival of the Group 3/4 patients ($n=8$) was fairly good (40 months in median survival, 25% in 5-year survival). On the other hand, Group 1/2 patients had poorer survival both in completely resected cases ($n=3$) and in incompletely resected cases ($n=10$) (23 and 18 months in median survival, and 0 and 0% in 5-year survival) (Figure 4).

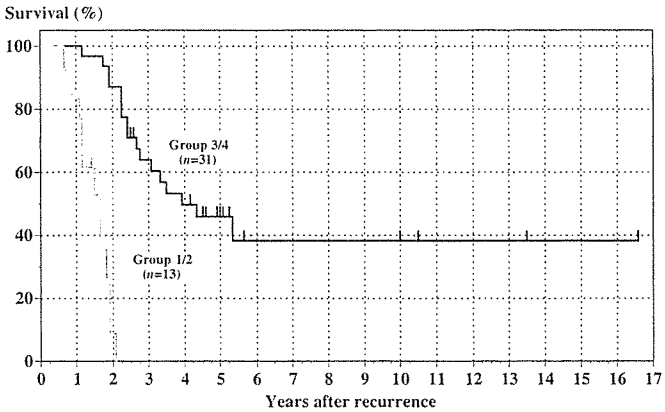

Figure 3 Comparison in survival between patients having one or two favourable prognostic factors (Group 1/2) and three or four favourable factors (Group 3/4). Survival of patients in Group 3/4 and Group 1/2 is shown as a solid black or solid grey line, respectively. Patients in Group 3/4 had significantly better survival compared with patients in Group 1/2 ($P<0.001$, log rank).

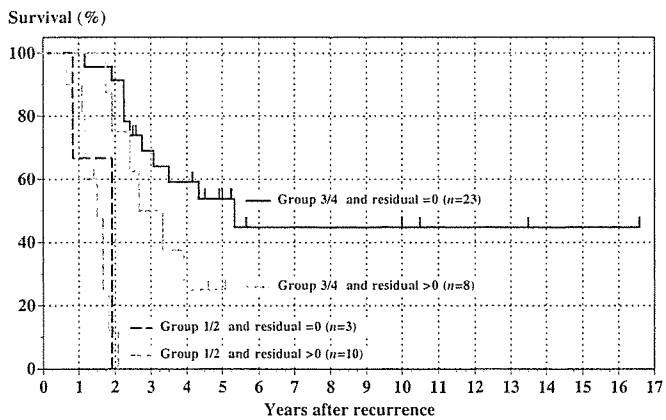

Figure 4 Survival in relation to SCS outcome and number of favourable prognostic factors. Survival of patients in Group 3/4 are shown as solid lines. Solid black line and solid grey line show the survival of patients with no residual tumour and residual tumour at SCS, respectively. Survival of patients in Group 1/2 are shown as dotted lines. Dotted black line and dotted grey line show the survival of patients with no residual tumour and any residual tumour at SCS, respectively.

DISCUSSION

We achieved surgical removal of all visible tumours in 59.1% of patients at the time of SCS. Residual tumours <1 or $\geqslant 1$ cm in diameter were present in 25.0 and 15.9%, respectively. In line with previous reports, removal of all visible tumours at SCS contributed to long-term survival (Figure 2). The rate of complete resection (59.1%) in our series was a little lower than the rates reported by Eisenkop *et al* (2000), Landoni *et al* (1998) and Cormio *et al* (1999). However, in Landoni's study, the subjects were restricted to those patients who were sensitive to first-line chemotherapy and chemotherapy before SCS. Cormio *et al* also restricted the subjects to patients with apparently isolated and resectable tumours and without ascites. Our criteria for patient selection were similar to those of Eisenkop *et al*, and their subjects were patients with DFI >6 months and without liver metastases. They achieved an 82% complete resection rate by using argon beam laser to remove disseminated cancer foci and reported 44 months in median survival and approximately 35% in 5-year survival in the completely resected cases. In our experience, median survival and 5-year survival in completely resected cases were 52 months and 47.6%, respectively, being much better than previous reports. Our rate of optimal cytoreduction, 84.1% (if defined as residual tumour <1 cm), was similar to the rate of complete resection in Eisenkop's report. In our series, optimally resected cases had 40 months in median survival and 38.6% in 5-year survival (figure not shown), in keeping with the survival of completely resected cases in Eisenkop's study. These findings suggest that the debulking efforts performed at SCS in our cases are comparable to those of previous reports.

Univariate analyses revealed that three factors during primary treatment (peritoneal spread, aortic lymph node metastasis, FIGO stage) and five factors at recurrence (DFI, liver metastasis, number of tumours, size of maximum tumour, SCS outcome) were significantly related to overall survival after recurrence. In the multivariate analysis excluding SCS outcome, the significance of all the three factors during primary treatment disappeared. Four factors determined at recurrence, that is, DFI, presence of liver metastasis, number of tumours and size of maximum tumour, were revealed to be independent prognostic factors.

DFI is the most important prognostic factor after recurrence, as described in many previous reports. In most studies, the cutoff period of DFI was set to 12 months. Two cutoff periods were set in Eisenkop's study (Eisenkop *et al*, 2000) (12 and 36 months) and in Tay's study (Tay *et al*, 2002) (12 and 24 months), and patients were divided into three groups. Although we also analysed our patients with DFI >12 months using cutoff periods such as 24 and 36 months, there were no significant differences between patients with and without DFI >24 or 36 months (data not shown). Recently, Zang *et al* (2004) performed SCS even in patients with DFI of 3 months and reported negative influence of DFI on overall survival. However, their follow-up period was only 16 months. This might be too short to detect a statistical difference.

Size of maximum tumour was also identified by Eisenkop *et al* (2000) as an independent prognostic factor. Eisenkop *et al* used 10 cm as the cutoff size, whereas we used 6 cm. The difference may be due to our earlier detection of recurrent tumours by using ultrasonography or CT scan within a 3-month interval. In our cases, there were only two patients in whom maximum tumour size exceeded 10 cm in diameter. At all events, tumour size seems to be an important factor reflecting biological aggressiveness of recurrent tumours.

The number of recurrent tumours has not been previously highlighted as a prognostic determinant. One reason is that some studies restricted the subjects for SCS to patients with isolated tumours or a solitary tumour (Cormio *et al*, 1999; Munkarah *et al*, 2001; Scarabelli *et al*, 2001). Another possible reason is that Eisenkop *et al* (2000) and Tay *et al* (2002) did not analyse the

number of recurrent tumours as a factor influencing survival, although they pointed out that this factor may influence SCS outcome. In concordance with our results, Zang *et al* (2004) reported that the number of recurrent tumours influenced both overall survival and SCS outcome.

The current study revealed that liver metastasis is another important prognostic determinant. Vaccarello *et al* (1995) examined the relationship between site of recurrence and survival, and reported that liver metastasis had a negative influence on survival. In most studies, patients with liver metastasis were excluded from subjects for SCS. In our series, two patients with solitary liver metastasis were included: one patient underwent hepatic resection and the other patient did not undergo hepatic resection because of the presence of unresectable metastatic portal lymph nodes. They did not achieve good survival (20 and 14 months, respectively).

From the results of the multivariate analysis, we propose the following criteria for patient selection for SCS. Patients with recurrent ovarian cancer should be considered as ideal candidates for SCS when they have three or all of the following four factors at recurrence: (1) DFI >12 months, (2) no liver metastasis, (3) a solitary tumour and (4) tumour size <6 cm. Considering our original patient selection, we should propose exclusion criteria including (1) age at recurrence $\geqslant 75$ years, (2) PS 3 or 4 just before SCS and (3) progressive disease during presurgical chemotherapy, if undertaken. Although we used intraoperative findings for the number and size of tumours, size of maximum tumour was consistent between intraoperative findings and imaging in available cases. Therefore, we can accurately evaluate all these factors, except the number of tumours, before SCS. As for the number of tumours, ultrasonography or CT scan before SCS cannot always identify multiple peritoneal disseminated tumours. When the patient meets the criteria for SCS preoperatively, it is recommended to decide whether SCS should be accomplished after reconfirming the criteria at the time of laparotomy.

In the previous studies, several prognostic factors were shown to have significant correlation with overall survival of the patients. However, these factors were obtained from SCS in selected patients in most of the previous studies. In addition, how to use several significant prognostic factors to select good candidates for SCS was not fully analysed. To our knowledge, generally accepted or recommended selection criteria are 'patients with longer DFI' (Bristow *et al*, 1996; Roberts, 1996; Rose, 2000; Sijmons and Heintz, 2000). Thus, it was sometimes difficult to decide whether or not SCS should be performed in patients who have some favourable factors and a few unfavourable factors. We believe that our selection criteria for SCS should be helpful in deciding whether SCS should be performed.

In conclusion, our data suggest that patients with three or all four of the above-mentioned favourable factors are ideal candidates for SCS, and that the final decision should be made at laparotomy in borderline cases. It seems that SCS has a large impact on survival of patients with recurrent ovarian cancer when the patients are selected by the new criteria (47 months in median survival and 45.9% in 5-year survival). However, these patients were likely to have good sensitivity to chemotherapy, because they had DFI >6 months. In a recent trial of recurrent ovarian cancer with DFI >6 months, patients who received platinum-based chemotherapy with or without paclitaxel had a favourable prognosis: 29 and 24 months in median survival and around 20% in 5-year survival, respectively (Parmar *et al*, 2003). Although patients undergoing SCS using the new criteria of patient selection seem to have much better survival than patients receiving chemotherapy alone, our study was retrospective and noncomparative, and our data were based on a relatively small number of strictly selected patients. To provide solid evidence for the therapeutic benefit of SCS and to find better selection criteria for the surgery, further studies including randomised controlled studies are required.

REFERENCES

Bristow RE, Lagasse LD, Karlan BY (1996) Secondary surgical cytoreduction for advanced epithelial ovarian cancer – patient selection and review of the literature. *Cancer* **78:** 2049–2062

Conte PF, Sertoli MR, Bruzzone M, Rubagotti A, Rosso R, Bentivoglio G, Conio A, Pescetto G (1985) Cisplatin, methotrexate, and 5-fluorouracil combination chemotherapy for advanced ovarian cancer. *Gynecol Oncol* **20:** 290–297

Cormio G, di Vagno G, Cazzolla A, Bettocchi S, di Gesu G, Loverro G, Selvaggi L (1999) Surgical treatment of recurrent ovarian cancer: report of 21 cases and a review of the literature. *Eur J Obstet Gynecol Reprod Biol* **86:** 185–188

Delgado G, Oram DH, Petrilli ES (1984) Stage III epithelial ovarian cancer: the role of maximal surgical reduction. *Gynecol Oncol* **18:** 293–298

Eisenkop SM, Friedman RL, Spirtos NM (2000) The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer* **88:** 144–153

Eisenkop SM, Friedman RL, Wang HJ (1995) Secondary cytoreductive surgery for recurrent ovarian cancer. A prospective study. *Cancer* **76:** 1606–1614

Goldie JH, Coldman AJ (1979) A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* **63:** 1727–1733

Griffiths CT (1975) Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr* **42:** 101–104

Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM (1983) Primary cytoreductive surgery for epithelial ovarian cancer. *Obstet Gynecol* **61:** 413–420

Hainsworth JD, Grosh WW, Burnett LS, Jones III HW, Wolff SN, Greco FA (1988) Advanced ovarian cancer: long-term results of treatment with intensive cisplatin-based chemotherapy of brief duration. *Ann Intern Med* **108:** 165–170

Jänicke F, Holscher M, Kuhn W, von Hugo R, Pache L, Siewert JR, Graeff H (1992) Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. *Cancer* **70:** 2129–2136

Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. *J Am Stat Assoc* **53:** 457–481

Kawana K, Yoshikawa H, Yokota H, Onda T, Nakagawa K, Tsutsumi O, Taketani Y (1997) Successful treatment of brain metastases from ovarian cancer using gamma-knife radiosurgery. *Gynecol Oncol* **65:** 357–359

Landoni F, Pellegrino A, Cormio G, Milani R, Maggioni A, Mangioni C (1998) Platin-based chemotherapy and salvage surgery in recurrent ovarian cancer following negative second-look laparotomy. *Acta Obstet Gynecol Scand* **77:** 233–237

Louie KG, Ozols RF, Myers CE, Ostchega Y, Jenkins J, Howser D, Young RC (1986) Long-term results of a cisplatin-containing combination chemotherapy regimen for the treatment of advanced ovarian carcinoma. *J Clin Oncol* **4:** 1579–1585

Munkarah A, Levenback C, Wolf JK, Bodurka Bevers D, Tortolero Luna G, Morris RT, Gershenson DM (2001) Secondary cytoreductive surgery for localized intra-abdominal recurrences in epithelial ovarian cancer. *Gynecol Oncol* **81:** 237–241

Neijt JP, ten Bokkel Huinink WW, van der Burg ME, van Oosterom AT, Willemse PH, Heintz AP, van Lent M, Trimbos JB, Bouma J, Vermorken JB, van Hauwelingen JC (1987) Randomized trial comparing two combination chemotherapy regimens (CHAP-5 v CP) in advanced ovarian carcinoma. *J Clin Oncol* **5:** 1157–1168

Norton L, Simon R (1977) Tumor size, sensitivity to therapy, and design of treatment schedules. *Cancer Treat Rep* **61:** 1307–1317

Onda T, Yoshikawa H, Yasugi T, Mishima M, Nakagawa S, Yamada M, Matsumoto K, Taketani Y (1998) Patients with ovarian carcinoma upstaged to stage III after systematic lymphadenectomy have similar

survival to stage I/II patients and superior survival to other stage III patients. *Cancer* **83:** 1555–1560

Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, Wheeler S, Swart AM, Qian W, Torri V, Floriani I, Jayson G, Lamont A, Trope C (2003) Paclitaxel plus platinum-based chemotherapy *versus* conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* **361:** 2099–2106

Roberts WS (1996) Cytoreductive Surgery in Ovarian Cancer: Why, When, and How? *Cancer Control* **3:** 130–136

Rose PG (2000) Surgery for recurrent ovarian cancer. *Semin Oncol* **27**(3, Suppl 7): 17–23

Scarabelli C, Gallo A, Carbone A (2001) Secondary cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. *Gynecol Oncol* **83:** 504–512

Sijmons EA, Heintz AP (2000) Second-look and second surgery: second chance or second best? *Semin Surg Oncol* **19:** 54–61

Sutton GP, Stehman FB, Einhorn LH, Roth LM, Blessing JA, Ehrlich CE (1989) Ten-year follow-up of patients receiving cisplatin, doxorubicin, and cyclophosphamide chemotherapy for advanced epithelial ovarian carcinoma. *J Clin Oncol* **7:** 223–229

Tay EH, Grant PT, Gebski V, Hacker NF (2002) Secondary cytoreductive surgery for recurrent epithelial ovarian cancer. *Obstet Gynecol* **99:** 1008–1013

Vaccarello L, Rubin SC, Vlamis V, Wong G, Jones WB, Lewis JL, Hoskins WJ (1995) Cytoreductive surgery in ovarian carcinoma patients with a documented previously complete surgical response. *Gynecol Oncol* **57:** 61–65

Vogl SE, Pagano M, Kaplan BH, Greenwald E, Arseneau J, Bennett B (1983) Cisplatin based combination chemotherapy for advanced ovarian cancer. High overall response rate with curative potential only in women with small tumor burdens. *Cancer* **51:** 2024–2030

Zang RY, Li ZT, Tang J, Cheng X, Cai SM, Zhang ZY, Teng NN (2004) Secondary cytoreductive surgery for patients with relapsed epithelial ovarian carcinoma: who benefits? *Cancer* **100:** 1152–1161

Zang RY, Zhang ZY, Li ZT, Chen J, Tang MQ, Liu Q, Cai SM (2000) Effect of cytoreductive surgery on survival of patients with recurrent epithelial ovarian cancer. *J Surg Oncol* **75:** 24–30

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Treatment options in the management of ovarian cancer

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The standard regimen used as primary chemotherapy of ovarian cancer is combination chemotherapy using paclitaxel and carboplatin. The main objective of first-line chemotherapy is to induce complete response. Although most cases respond to the initial chemotherapy, many cases relapse within 3 years. Such relapsed and persistent cases become resistant to first-line chemotherapy and require second-line chemotherapy. Objectives of such a second-line chemotherapy are to obtain disease palliation to cease disease progression. Meanwhile, consolidation or maintenance chemotherapy may be added to prevent or inhibit disease relapse for patients with advanced disease after induction of complete remission by a primary chemotherapy. When the unresectable tumour is presumed by primary surgery, neoadjuvant chemotherapy may be selected. Recently, conventional cytotoxic anticancer drugs containing paclitaxel have been shown to be capable of inhibiting angiogenesis. The notion of 'redefining' chemotherapeutic drugs has been recognised; thus, continuous low-dose chemotherapy – so-called metronomic chemotherapy – has been approved as a new concept. Many new molecular-targeted therapies became available for clinical cancer therapy. The explosion of new molecular targets and the development and application of many powerful technologies should accelerate the discovery of innovative molecular therapeutics. Understanding the molecular mechanisms will help to clarify the pathways in ovarian cancer development and help to identify new therapeutic and diagnostic targets. These are exciting times for new drug development and the treatment of cancer. Cautious optimism should prevail for all investigators involved in translating these exciting new biological findings into new pharmacological agents for treatment of cancer.

Keywords: chemotherapy, ovarian cancer

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1. Introduction

For centuries, surgery was considered the only curative treatment for cancer. Likewise, radiation therapy offered some patients a possible cure for localised cancers. However, once the disease had spread from its original site of origin, the patient was deemed inoperable and, therefore, incurable. The first drug used for cancer treatment was a derivative of mustard gas [1]. In 1948, Farber and associates [2] reported on the use of folate antagonists for the treatment of childhood leukaemia. Since that time, > 100 pharmacological agents have been introduced for that treatment of cancer. Combining agents with different mechanisms of action and nonoverlapping toxicities is now considered the most acceptable approach to the eradication of disseminated cancers.

Ovarian cancer is the fifth leading cause of cancer death in women in the US, with an estimated 23,300 cases diagnosed and 13,900 deaths in 2002 [3]. Improvements in the management of ovarian cancer have resulted in increased 5-year

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