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.

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