endometrial cancer was published in 2006 and revised in 2009. Both surgery and adjuvant chemotherapy play an important role in the treatment of advanced endometrial cancer patients. Postoperative adjuvant chemotherapy is recommended for high-risk patients with residual tumor smaller than 2 cm.[3] And postoperative adjuvant chemotherapy may improve the prognosis for intermediate-risk patients.[4,5] At present, the combination of doxorubicin plus cisplatin (AP) is considered to be the standard chemotherapy for advanced or recurrent endometrial cancer.[6] However, chemotherapy with better efficacy and tolerability is needed.

The efficacy of taxanes in advanced or recurrent endometrial cancer has been studied. The response rate for paclitaxel is reported to be 30–35% (35.7%,[7] 30.4%[8]). Paclitaxel is considered to be one of the key drugs for the treatment of endometrial cancer. Paclitaxel plus carboplatin (TC) has attracted the attention of investigators for use in patients with endometrial cancer because of its success in ovarian cancers. This study was a multicenter phase II clinical study to evaluate the feasibility of TC for postoperative chemotherapy in patients with endometrial cancer.

Material and Method

Patient eligibility

To be enrolled, patients needed to have the following criteria: (i) primary endometrial cancer histologically confirmed; (ii) operation including hysterectomy as the initial treatment; (iii) International Federation of Gynecology and Obstetrics (FIGO 1988) stage Ic to IV or stage Ib with grade 3 (including all histological types); (iv) no prior chemotherapy, radiation therapy, or hormone therapy; (v) with or without the existence of measurable disease; (vi) aged 20–74 years; (vii) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or less; (viii) adequate organ function (neutrophil count $\geq 2000/mm^3$, platelet count $\geq 100\,000/mm^3$, hemoglobin ≥ 8.0 g/dL, aspartate amino transferase and alanine amino transferase ≤ 100 IU or less than or equal to 2.5 times as high as the normal limit, serum total bilirubin ≤ 1.5 mg/dL, and serum creatinine ≤ 1.5 mg/dL); (ix) written informed consent. This study was conducted according to the Declaration of Helsinki and was approved by the Japan Kanto Tumor Board (JKTB) and the institutional review boards of each participating institution. Written informed consent was obtained from all of the patients.

Treatment schedule

Patients received paclitaxel 180 mg/m^2 and carboplatin area under the curve (AUC) 6 mg/mL/min on day 1 of a 21-day cycle. Paclitaxel was infused intravenously in 500 mL of 5% glucose or normal saline for 3 h using non-polyvinyl chloride equipment with in-line filtering. This was followed by carboplatin in 250 mL of 5% glucose for 1 h at the dose of AUC 6 mg/mL/min calculated using the Calvert formula[9] and estimating glomerular filtration rate (GFR) using the Jelliffe equation.[10] A serotonin antagonist and dexamethasone were used as antiemetics for the acute phase, followed by dexamethasone alone for the delayed phase. Dexamethasone, diphenhydramine, and ranitidine were given as standard paclitaxel anaphylaxis premedication. If a hypersensitive reaction did not occur in the first cycle, it was permitted to reduce the dexamethasone dose to 8 mg at the next cycle. Patients were treated for six cycles unless they dropped out due to unacceptable toxicities and/or tumor progression. Toxicities were evaluated every cycle according to NCI-CTCAE version 3.0.

Between cycles, chemotherapy was delayed one week if an absolute leukocyte count $< 2000/mm^3$, neutrophil count $< 1000/mm^3$, platelet count $< 75\,000/mm^3$, hemoglobin < 8.0 g/dL, and/or grade 3 or more non-hematologic toxicity were observed according to the blood counts and symptoms on the day of the scheduled chemotherapy. Chemotherapy was resumed after confirmation of an absolute leukocyte count $\geq 2000/mm^3$, neutrophil count $\geq 1000/mm^3$, platelet count $\geq 75\,000/mm^3$, hemoglobin ≥ 8.0 g/dL, and grade 2 or less non-hematologic toxicity. The paclitaxel and carboplatin doses were reduced to minus 1 level (Table 1) if chemotherapy was delayed two weeks due to hematologic toxicity, or an absolute leukocyte count $< 1000/mm^3$, neutrophil count $< 500/mm^3$, platelet count $< 50\,000/mm^3$, and/or hemoglobin level < 8.0 g/dL were observed. If chemotherapy was delayed two weeks due to grade 3 or more non-hematologic toxicity, only the paclitaxel dose was reduced to minus 1 level. Patients experiencing delays of three weeks or more due to hematologic and/or

Table 1 Dose levels of paclitaxel and carboplatin

Dose level	Level 0	Level −1	Level −2
Paclitaxel (mg/m^2)	180	150	135
Carboplatin (mg/mL/min)	AUC6	AUC5	AUC4

non-hematologic toxicity dropped out from the study. Drugs to treat complications and/or toxicities were allowed, but prophylactic use of granulocyte colony stimulating factor (G-CSF) was abstained.

Endpoints and statistical analyses

Among all of the patients who were registered following the protocol, a group of patients who were not repetitively registered or falsely registered was defined as all registered cases. In the all registered cases, a group of patients who met the eligibility criteria and received a part or all of the six cycles of chemotherapy according to the protocol were defined as the full analysis set (FAS). The feasibility was mainly evaluated in the FAS. We also defined the per-protocol set (PPS) for the purpose of robustness of the results. The PPS is defined as a group of patients who met the eligibility criteria and received a part or all of the six cycles of chemotherapy according to the protocol without serious violation of the protocol.

The endpoint of this study was feasibility, defined by a treatment successful execution ratio, relative dose intensity, and the incidence of hematologic and non-hematologic toxicity. It was decided that this feasibility study did not calculate the proper necessary number of cases for statistical evaluation and the planned number of registered was set cases as 60. The treatment successful execution ratio is the ratio of successfully executed cycles of the planned six cycles. The relative dose intensity of paclitaxel was calculated from the actual doses given to the patients, number of cycles, and treatment duration. The numerator was the total given dose of paclitaxel per m^2 divided by the treatment duration (week), and the denominator was the total planned dose of paclitaxel per m^2 per week ($180\ mg/m^2 \times 6$ cycles $= 1080\ mg/m^2$; $1080\ mg/m^2 \div 18$ weeks $= 60\ mg/m^2$/week). The relative dose intensity of carboplatin was calculated as the actual AUC given to the patients per week divided by the planned AUC per week (AUC 6×6 cycles $\div$ 18 weeks). The incidences of hematologic and non-hematologic toxicity were evaluated in the FAS by counting the worst grades of each patient in all cycles.

Results

Patient characteristics

Sixty patients with endometrial cancer were registered in this clinical study from December 2005 through November 2006. All of the 60 patients were judged eligible for the feasibility evaluation. The median age of the patient population was 57 years (range: 31–74). Patient and disease characteristics are shown in Table 2. Most patients had a performance status of 0 or 1, and 44 (73.3%) of the patients were with stage III/IV disease at presentation.

Table 2 Patient and disease characteristics (patients $n = 60$)

Patient characteristics	
Age (years, median [range])	57 (31–74)
Performance status (ECOG) (n [%])	
0	53 (88.3)
1	6 (10.0)
2	1 (1.7)
Histology (n [%])	
Endometrioid adenocarcinoma	40 (66.7)
Endometrioid adenocarcinoma with squamous differentiation	6 (10.0)
Serous adenocarcinoma	2 (3.3)
Clear cell adenocarcinoma	7 (11.7)
Mucinous adenocarcinoma	2 (3.3)
Mixed adenocarcinoma	3 (5.0)
Stage (n [%])	
Stage I	13 (21.7)
Ib (G3)/Ic	3 (5.0)/10 (16.7)
Stage II	3 (5.0)
IIa/IIb/IIc	1 (1.7)/2 (3.3)/ 0 (0.0)
Stage III	42 (70.0)
IIIa/IIIb/IIIc	23 (38.3)/2 (3.3)/ 17 (28.3)
Stage IV	2 (3.3)
IVb	2 (3.3)

ECOG, Eastern Cooperative Oncology Group.

Feasibility

Forty-four of 60 (73.3%) patients completed the planned six cycles of chemotherapy (Table 3). The relative dose intensity of paclitaxel was 86.3% (dose intensity: median [range] 51.8 [33.0–59.9] mg/m^2/week). The relative dose intensity of carboplatin was 87.5% (dose intensity: median [range] 1.75 (0.97–2.0) AUC/week). The incidences of hematologic and non-hematologic toxicity are summarized in Tables 4 and 5. Grades 3 and 4 hematologic toxicities were observed as follows: leukopenia (61.7%), neutropenia (95.0%), anemia (21.7%), and thrombocytopenia (5.0%). Grade 3 non-hematologic toxicities were observed as follows: nausea (3.3%), vomiting (1.7%), neuropathy (5.0%), myalgia (6.7%), and constipation (1.7%). Liver dysfunction was observed in two patients (3.3%), and both of

Table 3 Treatment successful execution ratio

Cycle	1st	2nd	3rd	4th	5th	6th
No. patients treated (%)	60 (100)	58 (96.7)	58 (96.7)	54 (90.0)	53 (83.3)	44 (73.3)

Table 4 Number of patients with hematologic toxicities in each grade (patients $n = 58$)

Hematologic toxicity	G1	G2	G3	G4	G3/4 (%)
Leukopenia	0	21	33	4	37 (61.7)
Neutropenia	0	1	15	42	57 (95.0)
Anemia	14	28	11	2	13 (21.7)
Thrombocytopenia	13	12	2	1	3 (5.0)
Infection	0	1	3	1	4 (6.9)

Toxicities were evaluated every course according to NCI-CTCAE version 3.0.

Table 5 Number of patients with non-hematologic toxicities (patients $n = 58$)

Non-hematologic toxicity	G1	G2	G3	G4	G3/4 (%)
Nausea	34	12	2	0	2 (3.3)
Vomiting	13	1	1	0	1 (1.7)
Neuropathy	25	3	3	0	3 (5.0)
Myalgia	17	6	4	0	4 (6.7)
Constipation	15	19	1	0	1 (1.7)
Alopecia	15	39	0	0	0 (0.0)

Toxicities were evaluated every course according to NCI-CTCAE version 3.0.

them had grade 1 liver dysfunction. No grade 4 non-hematologic toxicity was observed.

There were six patients who dropped out from the protocol due to neutropenia. Other reasons of dropout were tumor progression (1 case), dyspnea (1 case) and arrhythmia (1 case) immediately after instillation of paclitaxel, grade 3 neuropathy under the dose reduction (1 case), infection without neutropenia (1 case), request of patient (3 cases), and request of physician (2 cases). The two patients who had paclitaxel-associated hypersensitive reactions (3.3%) developing during the first cycle subsided with rapid discontinuation of the infusion. There were no patients who had hypersensitive reactions to carboplatin. The two patients who discontinued the protocol by physicians' request have received five cycles of chemotherapy.

There were two cases with measurable diseases. One case with stage IIIa disease had progressive disease (PD). The other had stage IVb disease, dropped out from the protocol because of a hypersensitive reaction at the first cycle, and died of the disease. There were two patients who died of the disease during the follow-up period (range: 4–13 months). One of them was the patient with stage IVb disease mentioned above, and the other had stage IIIa disease.

Discussion

In general, combination therapies have higher response rates in patients with advanced or recurrent endometrial cancer compared to therapies with single agent. Gynecologic Oncology Group compared doxorubicin to AP (GOG107); the response rate and the progression-free survival were superior in the combination chemotherapy (42% vs 25%, $P = 0.004$; 5.7 months vs 3.8 months, $P = 0.014$). However, there was no difference in the overall survival, and AP was associated with higher grade and more frequent hematologic and non-hematologic toxicity.[6] A randomized GOG trial (GOG177) compared the survival benefits of the combination of paclitaxel/doxorubicin/cisplatin (TAP) with G-CSF and AP in patients with advanced or recurrent endometrial cancer.[11] Although TAP is being compared with TC in GOG randomized trial (GOG209), TAP has not been accepted as the standard chemotherapy in Japan due to concerns of toxicity.

Watanabe *et al.* reported the current status of postoperative management of endometrial cancer in Japan by surveying members of the Japanese Gynecologic Oncology Group (JGOG).[12] As adjuvant therapy, chemotherapy (79.9%) was significantly ($P < 0.01$) preferred over radiotherapy (13.0%) or hormonal therapy (7.1%). In evidence-based guidelines for treatment of uterine body neoplasm in Japan, regimens including anthracyclines and platinum-based drugs are recommended for postoperative adjuvant chemotherapy. Contrary to those guidelines, Watanabe *et al.* reported that a combination of paclitaxel and carboplatin was the most preferred first-line regimen for adjuvant chemotherapy followed by combination regimens consisting of anthracycline and platinum.

The combination of paclitaxel and carboplatin has made a significant impact in the field of gynecologic oncology as the current first-line chemotherapy for

epithelial ovarian cancer.[13] Although currently there is not sufficient evidence to recommend TC over AP, taxane plus platinum combination therapies are considered to be very promising as postoperative chemotherapy for patients with endometrial cancer.[14,15] JGOG randomized phase II study (JGOG2041) comparing docetaxel plus cisplatin (DP), docetaxel plus carboplatin (DC), and TC in patients with advanced or recurrent endometrial cancer concluded that taxane plus platinum regimens could be the candidates of future phase III trials.[16]

In this study, we have examined the feasibility of TC for postoperative chemotherapy in patients with endometrial cancer in a local clinical study group. Forty-four of 60 (73.3%) patients completed the planned six cycles of chemotherapy. The relative dose intensities of paclitaxel and carboplatin were 86.3% and 87.5%, respectively. We have assessed the feasibility of TC based on the description regarding the dose limiting toxicity in Combined Antineoplastic Agents Guidelines – Guidelines for Clinical Trials I/II written by Japan Society of Clinical Oncology's Clinical Trial Committee,[17] and the incidences of hematologic and non-hematologic toxicity were considered to be acceptable. In comparison with the toxicity of AP which is currently considered to be standard chemotherapy for endometrial cancer,[6] the toxicity of TC seemed to be acceptable. The frequency of hypersensitive reactions at the first administration of paclitaxel is reported to be 5–8%,[18] and was 3.3% (two cases) in the present study. Those two patients rapidly recovered from grade 3 dyspnea and grade 2 arrhythmia by termination of paclitaxel infusion. Although there was a report which stated that paclitaxel could be administered even after hypersensitive reactions,[18] those two patients dropped out from the study according to the protocol. There was no patient who experienced hypersensitive reactions against carboplatin. This is consistent with the report that hypersensitive reactions do not occur with carboplatin less than or equal to five cycles.[19] These data will be useful for further phase III trials of chemotherapy in patients with endometrial cancer.

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Disclosure

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Docetaxel/irinotecan combination chemotherapy in platinum/taxane-refractory and -resistant ovarian cancer: JGOG/WJGOG Intergroup Study

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Abstract
Background The aim of this phase II study was to evaluate the efficacy and toxicity of docetaxel and irinotecan combination chemotherapy in patients with ovarian cancer refractory and resistant to both platinum and taxan treatment.
Patients and methods Patients who had been treated with platinum and paclitaxel but whose ovarian cancer progressed or recurred within 6 months of treatment ($n = 41$) received docetaxel 60 mg/m^2 (day 1) and irinotecan 60 mg/m^2 (days 1, 8), repeated every 21 days [Japan Gynecologic Oncology Group (JGOG) study 3015] or every 28 days [West Japan Gynecologic Oncology Group (WJGOG) study 002] until disease progression was observed or unacceptable toxicity. Sixteen patients had platinum/paclitaxel-refractory disease, and 25 patients had platinum/paclitaxel-resistant disease.
Results Thirty-two patients were available for determination of the clinical response. The overall response rate [complete response (CR) + partial response (PR)] was 6.3%, and the disease control rate (CR + PR + stable disease) was 34.4%. Among the 23 patients with resistant tumor, the disease control rate was 47.8%. Ten patients with refractory tumor showed a 10% disease control rate. The median progression-free interval was 12.1 weeks and the median overall survival time was 45.3 weeks. The major toxic adverse effect was neutropenia (grade 4, 56.1%), but the incidence of neutropenic fever was less frequent (4.9%). Neurotoxicity and gastro-intestinal toxicity were mild.
Conclusion Among our patients, a combination of docetaxel and irinotecan was well tolerated. However, this combination may not be a beneficial option for patients with platinum-refractory and -resistant ovarian cancer in terms of response rate and survival.

Keywords Ovarian cancer · Recurrence · Platinum refractory · Platinum resistance · Docetaxel · Irinotecan

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Introduction

Cytoreductive surgery and adjuvant chemotherapy by paclitaxel/carboplatin is the standard of care for epithelial ovarian cancer (EOC). However, over 70% of patients with an advanced stage of EOC are reported to relapse. The

therapeutic strategy involving chemotherapy for recurrent ovarian cancer is planned on the basis of the platinum-free interval. Markman et al. [1] found that patients with longer than a 24-month platinum-free interval showed a superior response to chemotherapy than those with an interval of between 5 and 12 months. This phenomenon has been observed by many researchers [2, 3]. Despite recent advances in the treatment of EOC, many phase II trials with a single agent have achieved only a 10–20% response rate in patients with platinum-refractory or -resistant disease [4–6].

Docetaxel is an alternative taxane which demonstrates a similar antitumor effect as paclitaxel but has a different toxicity profile [7]. Docetaxel has also shown some effect on platinum-resistant tumors. Two phase II studies showed a 35 and 40% response, respectively, in platinum-refractory ovarian cancer, with the accompanying adverse effect of rather severe toxicity [8, 9]. Irinotecan hydrochloride, one of the topoisomerase-1 inhibitors, achieved a 40% response rate in patients with refractory and recurrent ovarian cancer when used in combination with cisplatin [10].

The development of a new chemotherapeutic regimen for platinum/taxane-refractory or -resistant ovarian cancer is a matter of great urgency. Docetaxel and irinotecan each show promising antitumor effects in ovarian cancer. Moreover, the toxicity profile of these two drugs differs. As such, an investigation of the efficacy of these two drugs would provide valuable information. In this context, a phase II clinical trial was conducted to assess both the antitumor effect and the toxicity of the docetaxel/irinotecan combination for patients with platinum-refractory and -resistant ovarian cancer. This clinical trial was conducted in two groups [Japan Gynecologic Oncology Group (JGOG) and West Japan Gynecologic Oncology Group (WJGOG)] at the same time. Here, we have combined and analyzed the data from these two studies because both had the same eligibility criteria and used the same dosage of docetaxel and irinotecan.

Patients and methods

Eligibility

This phase II trial was conducted by the JGOG (study 3015) and the WJGOG (study 002). Patients were eligible if they satisfied the following criteria (note: throughout all subsequent text, the asterisk following a value presented in parenthesis indicates criteria/values for the WJGOG002 study only): (1) histologically confirmed EOC; (2) recurrent disease after previous treatment with a treatment-free interval of <6 months (resistant disease) or failure to respond to first-line chemotherapy with at least two cycles of platinum and/or taxane (refractory disease); (3) age >20 and <75 years; (4) an Eastern Cooperative Oncology Group (ECOG) performance status of <2; (5) >3 months life expectancy; (6) presence of a measurable target lesion; (7) adequate bone marrow, liver and kidney function, white blood cell (WBC) count $\geq$3000 ($\geq$4000*)/mm^3, neutrophil count $\geq$1500 ($\geq$2000*)/mm^3, platelet count $\geq$100 000, hemoglobin $\geq$9.5 g/dl/mm^3, serum creatinine level of $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ($\geq$60*) ml/min, serum bilirubin $\leq$1.5 mg/dl, alanine aminotranferease/aspartate aminotransferase ratio $\leq$2 ($\leq$1.5*) times the upper limit of normal; (8) signed informed consent.

Patients were excluded from the study if any of the following applied: (1) active or uncontrolled infection; (2) other active malignancy; (3) life expectancy of $\leq$3 months; (4) clinically significant morbidity, such as history of myocardial infarction, congestive heart failure; (5) poor oral intake due to intestinal obstruction; (6) large amount of pleural effusion, pericardial fluid, or ascites requiring repeated drainage; (7) previous abdominal radiation therapy; (8) apparent pulmonary fibrosis or interstitial pneumonia; (9) interval of $\leq$3 weeks (JGOG) or 4 weeks (WJGOG) since any previous chemotherapy.

Treatment schedule

Irinotecan 60 mg/m^2 was administrated as a 90-min intravenous infusion on days 1 and 8, and docetaxel 60 mg/m^2 was administered as a 60-min intravenous infusion on day 1. The treatment cycles were repeated at 21-day (JGOG) or 28-day (WJGOG) intervals until there was evidence of disease progression or unacceptable toxicity. A 5HT3-antagonist was given before the administration of the anticancer agents. Granulocyte colony-stimulating factor (G-CSF) could be administered according to Japanese health insurance guidelines [neutrophil count $\leq$1000/mm^3 with fever ($\geq$38°C) or neutrophil count $\leq$500/mm^3 or neutrophil count $\leq$1000/mm^3 in patients with grade 4 neutropenia in the previous cycle]. Subsequent treatment was not started until patients had a neutrophil count of $\geq$1500/mm^3, platelet count $\geq$100 000, grade 0 diarrhea, and grade 1 neurotoxicity. The dose of irinotecan was reduced to 50 mg/m^2 and that of docetaxel reduced to 55 mg/m^2 (50 mg/m^2*) if grade 4 neutropenia persisted more than 5 days (3 days*) or grade 4 platelet count (level 1). If the patients had grade $\geq$2 diarrhea, only the dose of irinotecan was reduced, while if patients had grade $\geq$2 neurotoxicity, only the dose of docetaxel was reduced. If patients showed toxicity under level 1 dose reduction, further dose reduction was offered to the patients following the same protocol. The minimum dose of irinotecan an docetaxel was 40 and

50 mg/m^2, respectively. Patients were able to withdraw from the study at any time.

Study evaluation and endpoints

Antitumor effects were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. The CA-125 level was determined at the end of every treatment cycle and evaluated by Rustin's criteria [11]. Adverse effects were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC) version 2 (National Cancer Institute, National Institutes of Health, Bethesda, MD). Survival was calculated from the date of study treatment to the date of death, or time of last contact. Subsequent treatment after recurrence was not regulated.

The primary endpoint was the clinical response rate. The secondary endpoints were adverse effects, CA125 response, progression-free survival (PFS), and overall survival (OS). The protocol was reviewed and approved by the institutional review board of each participating institute.

Statistical method

According to Simon's minimax design, the expected response rate was 15% (JGOG), 20% (WJGOG), $\alpha = 0.05$, and $\beta = 0.20$. The estimated number of patients was 55 (JGOG) and 40 (WJGOG). Interim analysis was scheduled when more than half of the patients were evaluable. If the response rate was below the threshold (10%), the trial would be stopped. The Kaplan–Meier method was used in the analysis of the PFS and OS.

Results

Patients' characteristics and treatment summary

Between December 2001 and November 2003 (JGOG3015) and between December 2001 March 2005 (WJGOG002), 45 patients were registered for this study from 27 Japanese institutions. Among these patients, the background characteristics of 41 patients who were eligible for enrollment are shown in Table 1. The median age was 53.6 years (range 23–72). There were 33 patients with FIGO stage III and IV disease, two patients with mucinous histology, and five with clear cell histology. All patients had received paclitaxel and/or platinum treatment as a front-line chemotherapy, and responses had been assessed as refractory in 14 patients (34.1%) and resistant in 27 (65.9%). Sixteen patients had received more than two chemotherapy regimens. Toxicity evaluation was possible in all patients, and clinical response was evaluable in 32 patients. Overall, 159 courses of treatment were delivered to 41 patients, with 21 patients (51.2%) receiving more than four treatment cycles. Two patients stopped treatment after only one cycle because of disease progression. No patients discontinued the treatment because of toxicity.

Table 1 Patients' characteristics

Characteristics	WJGOG002	JGOG3015	Total
Mean age, years (range)	53 (23–72)	54.5 (36–72)	53.6 (23–72)
Number of patients (*n*)			
Eligible (toxicity)	22	19	41
Eligible (response)	17	16	33
FIGO stage (*n*)			
IA	2		2
IC	1	3	4
IIA	1		1
IIC	1		1
IIIA		1	1
IIIB	3	2	5
IIIC	8	11	19
IV	6	2	8
Histological type (*n*)			
Serous	16	12	28
Mucinous	0	2	2
Clear cell	2	3	5
Endometrioid	3	2	5
Undifferentiated	1		1
Eastern Cooperative Oncology Group (ECOG) performance status (*n*)			
0	12	13	25
1	7	6	13
2	3	0	3
Prior treatment (*n*)			
One regimen	15	16	31
Two regimens	7	3	10
Refractory or resistant (*n*)			
Refractory	11	5	16
Resistant	11	14	25
Number of cycles			
Mean	4.1	3.6	3.9
Four cycles completion rate (%)	9/22 (40.9)	12/19 (63.1)	21/41 (51.2)

JGOG Japan Gynecologic Oncology Group, *WJGOG* West Japan Gynecologic Oncology Group

Toxicity profiles

Toxicity data were available for all patients. The number and type of hematologic toxicity events are shown in

Table 2 Incidence of different grades of hematologic/non-hematologic toxicity events associated with the treatment

Hematologic/non-hematologic toxicity events	Toxicity profile			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic toxicity				
Leukopenia	3 (7.3)	6 (14.6)	20 (48.8)	9 (22.0)
Neutropenia	1 (2.4)	1 (2.4)	12 (29.3)	23 (56.1)
Thrombocytopenia	4 (9.8)	0	1 (2.4)	0
Anemia	5 (12.2)	19 (46.3)	11 (26.8)	2 (4.9)
Liver dysfunction	6 (14.6)	4 (9.8)	0	0
Non-hematologic toxicity				
Nausea	20 (48.8)	11 (26.8)	1 (2.4)	0
Vomiting	10 (24.3)	5 (12.2)	3 (7.3)	0
Diarrhea	5 (12.2)	11 (26.8)	8 (19.5)	2 (4.9)
Constipation	6 (14.6)	1 (2.4)	1 (2.4)	0
Alopecia	14 (34.1)	11 (26.8)	N/A	N/A
Neutropenic fever	N/A	N/A	2 (4.9)	0
Edema	5 (12.2)	4.9	0	0
Neurotoxicity (sensory)	11 (26.8)	0	0	0

Data are presented as the number of patients, with the percentage of total study cohort ($n = 41$ patients) given in parenthesis

Table 2. The incidence of grade 4 leukopenia and neutropenia was 22.0 and 56.1%, respectively, among the patients. Grade 3 anemia was observed in 26.8% of patients, but grade 4 anemia was found in only 4.9% of the patients. Thrombocytopenia was rarely seen, and only one patient had grade 3 toxicity. Many patients required G-CSF support during the course of treatment and two patients developed neutropenic fever.

Table 2 also shows the incidence of non-hematologic toxicity events. The most frequent subjective adverse event was diarrhea, with 19.5 and 4.9% of patients experiencing grade 3 and grade 4 diarrhea, respectively. Nausea and vomiting were generally mild but did not occur in patients at grade 3 or 4 toxicity. Neurotoxicity was also mild. Only grade 1 sensory neuropathy was observed (11 patients; 26.8%). Grade 2 alopecia was seen in 11 patients (26.8%). Other non-hematologic toxicities, such as skin or mucosal toxicity, were not observed, with the exception of one grade 2 stomatitis. Dose reduction occurred in 46.3% (19/41) of patients, including 14 patients who required reduction of the docetaxel dose due to grade 4 neutropenia and 16 patients who required reduction of the irinotecan dose reduction due to grade 2 or 3 diarrhea. The dose intensity of docetaxel was 19.6 ± 3.6 mg/m^2/week in the JGOG patient group and 19.8 ± 3.5 mg/m^2/week in the WJGOG group, while that of irinotecan was 35.9 ± 5.5 mg/m^2/week (JGOG) and 39.0 ± 7.95 mg/m^2/week (WJGOG).

Response and survival

Among 41 patients, eight patients were not evaluable for response because they failed to complete more than two cycles of treatment or had no radiologically measurable lesions. Thus, 33 patients were assessed for clinical response (23 resistant, 10 refractory) (Table 3). Two patients showed a clinical response [1 complete response/remission (CR) and 1 partial response/remission (PR)], and another ten patients had stable disease (SD). The remaining patients showed progressive disease (PD). The overall objective response rate (CR + PR) was 6.1%, and the disease control rate [complete response/remission (CR) + PR + SD] was 36.4%. According to the stopping rule, this study was forced to discontinue at this stage.

Table 3 Tumor response and CA-125 response rate to treatment

	Number of patients assessed ($n = 33$)	Refractory ($n = 10$)	Resistant ($n = 23$)
Clinical response			
CR	1	0	1
PR	1	0	1
SD	10	1	9
PD	21	9	12
Response rate (%)	2/33 (6.1)	0/10 (0)	2/23 (8.7)
Disease CTL rate (%)	12/33 (36.4)	1/10 (10)	11/23 (47.8)
CA-125 response			
75% response	3	0	3
50% response	3	0	3

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CTL* control

Data are presented as the number of patients, with the percentage of each group given in parenthesis

The median PFS was 12.1 weeks (range 19–720 days) and the median OS was 45.3 weeks (range 90–1032 days)

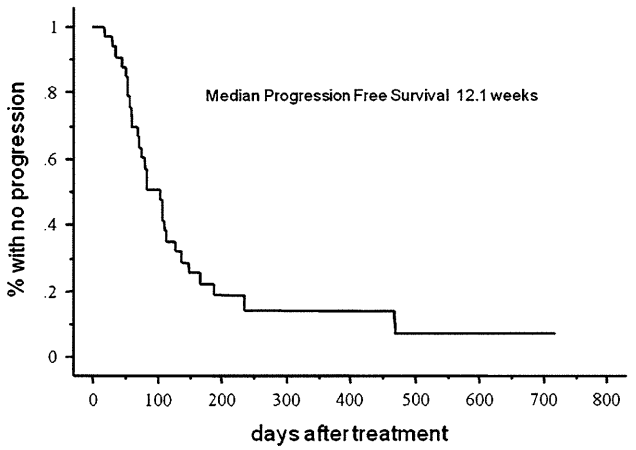

Fig. 1 Progression-free survival with docetaxel/irinotecan treatment

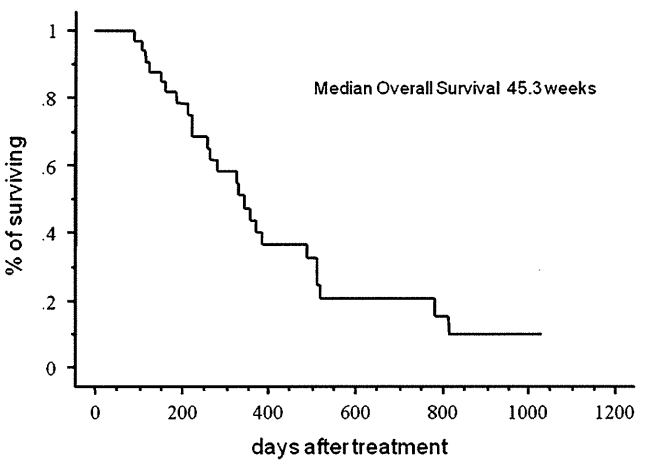

Fig. 2 Overall survival with docetaxel/irinotecan treatment

(Figs. 1, 2). CA-125 response data were available for 28 patients, of whom six were responders (21.4%), including three patients with a 75% decrease in CA-125 level and three patients with a 50% decrease. Among the 23 patients with platinum/paclitaxel-resistant tumor, the disease control rate was 47.8% (CR, PR, SD: 1, 1 and 9 patients, respectively). On the other hand, among the ten patients with platinum/paclitaxel-refractory tumor, the disease control rate was 10 % (SD, 1 patient). All CA-125 responders were patients with platinum/paclitaxel-resistant tumor (6/22). There was a significant difference in the disease control rate between resistant and refractory cases ($P < 0.05$).

Discussion

Recurrence is a leading cause of death in patients with ovarian cancer, with those patients with platinum-resistant or -refractory disease having less chance to obtain remission of disease. Therefore, the primary aim of any treatment for these patients is to control the disease with minimal toxicity. Previous studies have reported that the administration of docetaxel alone for platinum-refractory ovarian cancer achieved approximately a 35% response rate and 10 months of OS [8, 9]. However, the 100 mg/m^2 dose of docetaxel used in these studies gave rise to significant bone marrow toxicity, with grade 4 neutropenia occurring in up to 83–87% of patients and neutropenic fever occurring in 44%. In addition, 69% of the patients developed fluid retention, of whom 67% required diuretics and/or corticosteroids. The combination of a smaller dose of docetaxel (60 mg/m^2) in combination with irinotecan used in this study appeared to reduce the toxicity of docetaxel. In another study, weekly paclitaxel was expected to have anti-angiogenetic activity on platinum/taxane refractory ovarian cancer at the expense of severe neurotoxocity [12]. However, docetaxel did not show significant neurotoxicity in that study.

In our study, patients with platinum/paclitaxel-refractory or -resistant disease responded differently. Vershragen et al. [13] reported that docetaxel achieved only a 11% response rate in patients with absolute paclitaxel-refractory tumor, while a 45% response rate was observed among those with paclitaxel-resistant tumors. Therefore, in terms of treatment response, these patients should be analyzed separately. In our study, we found only a 10% disease control rate and no CA-125 responders among patients with platinum/paclitaxel-refractory tumor, as was expected. On the other hand, patients with platinum/paclitaxel-resistant tumor showed a 47.8% disease control rate and 27.3% CA-125 response.

In terms of the doectaxel/irinotecan combination therapy for platinum-resistant ovarian cancer, Polyzos et al. [14] reported that a combination with docetaxel 60 mg/m^2 and a single dose of irinotecan 200 mg/m^2 achieved a 20% response rate and 27% SD, a median PFS of 5 months, and 11 months of OS. Despite the prophylactic administration of G-CSF from days 2 to 6, 16% of patients on their regimen showed febrile neutropenia and one patient died of sepsis. The incidence of diarrhea was relatively low (13%), but two patients had grade 3 or 4 diarrhea. In comparison, in our study protocol, irinotecan 60 mg/m^2 was given on day 1 and day 8. Among our patients, 56% showed grade 4 neutropenia and 4.9% developed grade 4 diarrhea. The dose reduction of irinotecan was caused by bone marrow toxicity (neutropenia) rather than by gastrointestinal toxicity (diarrhea). Weekly administration of both drugs was studied by an Austrian study group, but the patients failed to show a good response or reduced toxicity [15].

Long-term disease control with less toxicity would be the most important aim when treating patients with platinum/taxane-resistant or -refractory EOC because the

disease at this stage is not curable. When this trial was planned, a number of new agents, such as topotecan, pegylated liposomal doxorubicin (PLD), and gemcitabine were not available for treating ovarian cancer in Japan. Since 2000, a number of phase II or phase III studies for platinum-resistant EOC using these agents have been published [4, 6, 16, 17], and Japanese health insurance currently covers the cost of these agents for recurrent EOC. Topotecan, PLD, and gemcitabine achieved a 44–66% disease control rate but a relatively short PFS (9–14 weeks). The PFS and disease control rates in these phase 2 studies of new agents were similar to those observed in our study for the patients with the platinum/paclitaxel-resistant disease, but they were significantly better than the response obtained in patients with platinum/paclitaxel-refractory disease. An agent which has different toxicity profiles from those used in first-line chemotherapy, such as PLD, might be a good candidate for second-line chemotherapy for platinum/paclitaxel-resistant tumors.

In conclusion, docetaxel and irinotecan combination chemotherapy was well tolerated but failed to show the expected tumor response in patients with platinum/patclitaxel- refractory and -resistant EOC. Therefore, we conclude that it was not the suitable treatment choice for the chosen population and that further study, including phase III trials, is not warranted.

Conflict of interest K. Tamura received honoraria from Kyowa Hakko Kirin, Astellas Pharma, Yakult Honsya, Ono Pharmaceutical, Takeda Pharmaceutical, Asahi Kasei Pharma, as well as research funding from Shionogi, Taisho Toyama Pharmaceutical, Kyowa Hakko Kirin, and Astellas Pharma. The other authors declare that they have no conflict of interest.

Appendix

The following institutions participated in this study:

JGOG3015: Gifu Prefectural Tajimi Hospital, Mie Prefectural General Medical Center, West Shizuoka Hamamatsu Medical Center, Niigata Prefectural Saiseikai Sanjyo Hospital, Kawasaki Municipal Kawasaki Hospital, Nagasaki Municipal Hospital, Jichi Medical University Omiya Medical Center, Keio University Hospital, Tottori University Hospital, Osaka Medical University Hospital, Jikei University Third hospital, Dokkyo Medical University Hospital, Niigata Prefectural Cancer Center Hospital, Yamada Red-Cross Hospital, Nantan General Hospital.

WJGOG002: Kagoshima University Hospital, Kyushu University Hospital, Kyushu University Beppu Medical Center, Kurume University Hospital, Miyazaki Prefectural Hospital, Saga Medical University Hospital, Nagasaki University Hospital, Fukuoka University Hospital, Beppu Medical Center, Kyusyu Medical Center, Kitakyushu Municipal Medical Center, Aso Iizuka Hospital, Ryukyu University Hospital.

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ORIGINAL ARTICLE

Paclitaxel–carboplatin for advanced or recurrent carcinosarcoma of the uterus: the Japan Uterine Sarcoma Group and Tohoku Gynecologic Cancer Unit Study

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Abstract
Background Paclitaxel and carboplatin (PC) have shown antitumor activity in carcinosarcoma of the uterus (CS). The purpose of this prospective multi-institutional study was to determine the response rate (RR), progression-free survival (PFS) and overall survival (OS) and to assess the toxicity of paclitaxel and carboplatin in patients with CS.
Methods We conducted a phase II study in which patients were administered paclitaxel 175 mg/m^2 over a 3-h period followed by carboplatin (area under the serum concentration–time curve = 6) intravenously over a 30-min period on day 1 of each treatment cycle (3 weeks) until disease progression or adverse effects prohibited further therapy. Eligible patients had histologically confirmed, advanced stage (III or IV), persistent or recurrent measurable disease, and no prior chemotherapy.
Results Six patients were enrolled between February 2006 and April 2009. The median age of the patients was 61 (range 48–77) years; one patient was stage IIIC (17 %) and five were stage IVB (83 %). Three patients (50 %) (1 at stage IIIC and 2 at stage IVB) received total abdominal hysterectomy plus bilateral salpingo-oophorectomy as part of the initial treatment; five (83 %) had homologous tumors and one (17 %) had a heterologous tumor. The median cycle number administered was 4.8 (range 2–7). The RR was 66.7 % (complete response, 2; partial response, 2); the PFS was 9.1 months and OS was not reached. The frequently observed Grade 4 toxicities were

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neutropenia (3 patients, 50 %). Manageable neutropenic sepsis developed in one patient.
Conclusion This is the first prospective multi-institutional study in Asia showing that PC may be effective and tolerable for the treatment of advanced or recurrent CS.

Keywords Carcinosarcoma of the uterus · Paclitaxel + carboplatin · Prospective multi-institutional study

Introduction

Carcinosarcoma of the uterus (CS), also known as malignant mixed Mullerian tumor, is a rare and aggressive neoplasm that contains both carcinomatous and sarcomatous histologic elements. Overall, the survival of women of Caucasian ethnic groups is significantly better than that of African–American women according to the surveillance, epidemiology, and end results (SEER) data [1]. CSs are monoclonal in original rather than true collision tumors [2, 3], suggesting that CS may be metaplastic, with the implication that the sarcomatous elements of CS are derivatives of the carcinomatous elements [4]. Even with surgery and adjuvant radiotherapy, the overall prognosis of CS is extremely poor due to its tendency to metastasize and its high local and distant relapse rate [5]. While initially grouped with sarcomas in early clinical trials, the clinical behavior of carcinosarcomas has subsequently been shown to be a reflection of the carcinomatous element. In light of this, carcinosarcomas have now been classified for staging purposes with carcinomas of the endometrium. Consequently, chemotherapeutic regimens for aggressive high-grade endometrial carcinoma, including the combination paclitaxel–carboplatin (PC), may also be effective in CS [6–8]. The Gynecologic Oncology Group (GOG) has reported a series of phase II trials to identify potentially active cytotoxic agents for the treatment of advanced or recurrent CS: ifosfamide [response rate (RR) 32 %] [9–12]; doxorubicin, 19 % [13, 14]; cisplatin, 8 % [15, 16], paclitaxel, 18 %] [17]. In addition, the GOG reported two large phase III trials. In these trials, the cisplatin–ifosfamide combination demonstrated significant improvements in RR (54 vs. 36 %) and progression-free survival (PSF) over cisplatin alone, but no statistical difference was seen in overall survival (OS) [18]. The combination of Ifosfamide–paclitaxel–filgrastim also demonstrated significant improvements in RR (45 vs. 29 %), PFS (6 vs. 4 months), and OS (14 vs. 8 months) over ifosfamide alone [19]. The toxicity, multiday schedule, and limited activity of these regimens, however, support further investigation of new treatments. A recent GOG study by Powell et al. [20] and our retrospective pilot study suggest that PC has activity in CS patients (RR 80 %; four of five evaluable patients) with minimal toxicity [21]. We therefore designed the present prospective multi-institutional study for CS to determine the RR, PFS and OS in CS treated with PC and to assess the toxicity of this treatment.

Patients and methods

Eligibility

Eligible patients had histologically confirmed, advanced stage III, IV, or recurrent CS with a measurable target lesion of $\geq$20 mm when measured by computed tomography (CT) and magnetic resonance imaging or of $\geq$10 mm when measured by spiral CT. Patients had to have at least one target lesion to assess response on this protocol, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [22]. Two gynecologic pathologists performed a pathologic slide review of the primary malignancy for all patients. Patients who had received prior cytotoxic chemotherapy were ineligible for entry into the study, and patients with a history of another invasive malignancy within the previous 5 years other than a non-melanoma skin cancer were also excluded. Patients of childbearing potential had to undergo a negative serum pregnancy test before entry onto the study and had to be practicing some effective form of contraception. A minimum Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, granulocytes of $\geq$1,500/μL, platelets of $\geq$100,000/μL, serum creatinine of $\leq$1.5× institutional upper limit of normal (ULN), and adequate liver function [bilirubin of $\leq$1.5× institutional ULN and aspartate aminotransferase and alkaline phosphatase of $\leq$2.5× the institutional ULN] were also required. Patients were to have recovered from previous treatments and have no evidence of infection. Patients with neuropathy (sensory or motor) Grade $\geq$1, according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 were excluded. All patients who entered the study provided written informed consent consistent with institutional review board regulations before study entry.

Therapy

One treatment cycle consisted of 3 weeks. Paclitaxel 175 mg/m^2 was delivered over a 3-h period followed by carboplatin dosed to an area under the serum concentration–time curve (AUC) = 6 intravenously over a 30-min interval on day 1 of each treatment cycle until disease progression or adverse effects prohibited further therapy. The dosing of carboplatin was calculated according to the Calvert formula to reach a target AUC of concentration multiplied by time using an estimated glomerular filtration rate (Cockgroft–Gault equation); a minimum creatinine value of 0.6 was stipulated. The maximum body surface

area used for paclitaxel dose calculations was set at 2.0 m^2. The number of cycles given beyond a clinical complete response (CR) was at the discretion of the principal physician. Patients with a partial response (PR) or stable disease were encouraged to continue unless adverse effects prohibited further therapy.

Dose modification and evaluation

Subsequent doses were modified for prolonged (>7 days) Grade 4 granulocytopenia, Grade 4 thrombocytopenia, or select non-hematologic toxicity. Grade ≥2 peripheral neuropathy required the reduction of one dose level of both paclitaxel and carboplatin and a delay in subsequent therapy for a maximum of 2 weeks until recovery to Grade 1. Dosing modifications for patients with renal, hepatic, and hypersensitivity reaction were mandated. Granulocyte-colony stimulating factor (G-CSF) was permitted in the setting of febrile neutropenia and/or recurrent documented Grade 4 neutropenia persisting for ≥7 days (after initial dose reduction). A history and physical exam and a laboratory evaluation were performed before each cycle of chemotherapy. CT or magnetic resonance imaging was performed every other cycle. Hematologic parameters were checked weekly. Response was determined according to RECIST criteria. CR and PR were classified as responses. Adverse effects were categorized and graded according to CTCAE v3.0.

Histopathology

Disease stage was determined using the clinical staging system of the International Federation of Gynecology and Obstetrics (FIGO) [23]. All slides in this study were examined by two pathologists (K.I. and H.N.) to review the histologic types of carcinomatous and sarcomatous components. Carcinomatous components were classified histologically as endometrioid adenocarcinoma and clear cell adenocarcinoma, respectively. All endometrioid adenocarcinomas were graded based on the proportion of nonsquamous solid growth pattern (Grade 1, ≤5 %; Grade 2, 6–50 %; Grade 3, >50 %) according to the World Health Organization classification [24]. Clear cell adenocarcinomas were classified as Grade 3 because the prognosis in these histologic types is reported to be poor [25]. Sarcomatous components were classified into homologous and heterologous types, respectively.

Statistical design

The primary endpoint was defined as RR, including CR and PR for patients with measurable disease. Toxicity and PFS were secondary endpoints. According to the historical GOG RR, the expected efficacy rate was set at 50 % and the threshold efficacy rate at 30 % for the study treatment under the conditions of $\alpha = 0.05$ and $\beta = 0.20$; the required number of subjects was 34. We targeted an enrollment of 35 subjects, anticipating one case of dropout.

Results

The study was closed in April 2009 due to slow accrual. Simultaneously, the GOG began a multicenter phase II trial studying this same combination of drugs for CS in 2005 that completed accrual in 2008 [20]. We also conducted a feasibility study with PC for CS patients who underwent an optimal surgery around the same time as this study. Fifty-one patients were enrolled from 30 institutions, of whom 22 and five were stage III and IV patients, respectively; all patients underwent optimal surgery (unpublished data). Our surgeons are particularly skilled and achieved high rates of optimal surgery; therefore, very few patients had residual tumors.

Six patients were enrolled in the study between February 2006 and April 2009. Table 1 summarizes the patient characteristics for the eligible patients. The median age of the patients was 61 (range 48–77) years. Of these six patients, five (83.3 %) had newly diagnosed disease (stage IVB), and one patient (16.7 %) had recurrent disease (stage IIIC) after post-surgical pelvic radiation therapy. Three patients (50 %; 1 at stage IIIC; 2 at stage IVB) underwent a total abdominal hysterectomy plus bilateral salpingo-oophorectomy as part of the initial treatment. The remaining three IVB patients could not undergo surgery because of the wide dissemination of their tumors (2 had lung metastases and 1 had peritonitis carcinomatosa). Even though surgical intervention after PC was not permitted in the protocol, we performed surgical intervention in two PR patients (no. 2 and 5) and in one patient with stable disease (SD; no. 6) because of their anxiety concerning surgical resection. We estimated the best response at the time of surgical intervention. Considering that both patients with optimal surgery (no. 5 and 6) had no evidence of disease after surgery, the RR of this study may have been higher.

The carcinomatous component was endometrioid adenocarcinoma in five patients (83.3 %), and one patient (16.7 %) had endometrioid plus clear cell adenocarcinoma. All endometrioid adenocarcinomas were Grade 1 adenocarcinoma. The sarcomatous component was undifferentiated homologous sarcoma in five tumors and contained rhabdomyosarcoma in one tumor. Unfortunately, we could not find any histopathologic characteristic relationships in this study. Table 2 summarizes the number of chemotherapy cycles each patient received and the best responses. The median number of cycles was 4.8 (range 2–7).

Table 1 Characteristics of the six patients enrolled in the study

Patient no.	Age (years)	Performance status	Stage	Carcinomatous component/ grade	Sarcomatous component	Pre-protocol treatments	Target lesion	Non-target lesion
1	68	0	IIIC	Endo./1	Homozygous	TAH + BSO + PLA, WP40 Gy	PAN	
2	54	0	IVB	Endo./1	Homozygous	None	Uterus, Rt. Ischial and Sacral bone	Lung
3	60	0	IVB	Endo. + Clear/ 3	Homozygous	TAH + BSO	Uterus, PLN-Subclavicular LN	
4	60	0	IVB	Endo./1	Heterozygous	TAH + BSO + OMT	Pelvis	
5	77	1	IVB	Endo./1	Homozygous	None	Uterus, Pelvis	Peritonitis carcinomatosa
6	48	0	IVB	Endo./1	Homozygous	None	Uterus, Lt. PLN, PAN	Lung
	61.2 (average)							

Endo. Endometrioid adenocarcinoma, *Clear* clear cell adenocarcinoma, *TAH* total abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *PLA* pelvic lymphadenectomy, *OMT* omentectomy, *LN* lymph node, *PLN* pelvic lymph node, *PAN* para-aortic lymph node

Table 2 Clinical treatments and results for all six patients

Patient no.	Cycles of PC (*n*)	Best response	Reason for discontinuation	Post-treatment		Status	Progression-free survival	Overall survival
				Surgery	Chemotherapy			
1	2	PD	Progressive disease	None	None	DOD		
2	7	PR	Patient's reason	TAH + BSO	Weekly PC	DOD		
3	6	CR	Complete remission	None	None	NED		
4	4	CR	Bone marrow suppression	None	PC × 2	AWD		
5	4	PR	Change of therapeutic strategy	TAH + BSO + PLA	PC × 5	NED		
6	6	SD	Change of therapeutic strategy	SemiRH + BSO	None	NED		
	4.8 (average)						9.1 months (50 % of patients)	Not reached (67 %)

CR Complete response, *PR* partial response, *SD* Stable disease, *PD* progressive disease, *AWD* alive with disease, *NED* no evidence of disease, *DOD* dead of disease, *PC* Paclitaxel-carboplatin

Treatment was discontinued for the following reasons: disease progression (1 patient, 16.7 %), change of therapeutic strategy to surgery (2 patients, 33.3 %), person reason (1 patient, 16.7 %), and toxicity (1 patient, 16.7 %). The RR was 66.7 % (CR, 2; PR, 2), and one patient (16.7 %) achieved SD. One patient (16.7 %) had progression of disease (PD). Four patients were alive (3 without and 1 with PD), and two had died due to complications from their cancer at the time of this analysis. The median PFS was 9.1 months, and the median OS was not reached. All reported adverse events are summarized in Table 3. The frequently observed Grade 3 and 4 toxicities were neutropenia (5 patients, 83.3 %), anemia (1 patient, 33.3 %), thrombocytopenia (1 patient, 33.3 %), and motor neuropathy (1 patient, 33.3 %). There was no Grade 4 motor and sensory neuropathy. One patient developed neutropenic sepsis (Grade 3) that responded to treatment.

Discussion

Carcinosarcoma of the uterus is aggressive and frequently diagnosed at an advanced stage. The 5-year disease-free survival of CS by stage is poor (stage I, 56 %; stage II,

Table 3 Adverse events

Adverse events	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Leukocytes (total white blood cells)	0	0	2	4	0	67
Neutrophils/granulocytes	0	0	1	2	3	83
Hemoglobin	0	1	3	2	0	33
Platelets	3	0	1	1	1	33
Anorexia	3	1	2	0	0	0
Nausea/vomiting	3	1	2	0	0	0
Constipation	3	3	0	0	0	0
Diarrhea	5	1	0	0	0	0
Fatigue	3	2	1	0	0	0
Hair loss/alopecia	1	2	3	0	0	0
Mucositis/stomatitis	6	0	0	0	0	0
Febrile neutropenia	6	–	–	1	0	17
Neuropathy–motor	5	0	0	1	0	17
Neuropathy–sensory	3	3	0	0	0	0
Allergic reaction/hypersensitivity	4	2	0	0	0	0

Table 4 Responses of chemotherapeutic trials in uterine carcinosarcoma

Drug/drug combination	First and/or second-line therapy	Response rate	Progression-free survival (months)	Overall survival (months)
Doxorubicin (GOG0087A) [6]	First	5/26 (19 %)	5	NR
Ifosfamide (GOG0087B) [3]	First	9/28 (32 %)	NR	NR
Cisplatin (GOG0026C) [9]	First	5/63 (8 %)	NR	NR
Paclitaxel (GOG0130B) [10]	First/second	8/44 (18 %)	4.2	NR
Ifosfamide/cisplatin (GOG0180) [11]	First	50/92 (54 %)	6	9.4
Ifosphamide/paclitaxel (GOG0261) [12]	First	40/88 (45 %)	5.8	13.5
Carboplatin/paclitaxel (Tohoku University) [19]	Retrospective	4/5 (80 %)	18	25
Carboplatin/paclitaxel (GOG0232B) [21]	First	25/46 (54 %)	17 %, 7.6	35 %, 14.7
Carboplatin/paclitaxel [24]	Retrospective	8/13 (62 %)	7.9	15
Carboplatin/paclitaxel (this study)	First	4/6 (67 %)	50 %, 9.1	67 %, not reached

31 %; stage III, 13 %; stage IV, 0 %) [26, 27], and most patients present with extrauterine disease. The GOG reported that the combination of cisplatin, ifosfamide, and paclitaxel has significant activity, and these agents were evaluated in subsequent phase III trials (Table 4) [10, 13, 16–21, 28]. Sutton et al. reported on the cisplatin–ifosfamide combination, which resulted in a significant increase in PFS (6 vs. 4 months), but no difference was seen in OS (RR 0.80; 95 % upper confidence limit 1.03; $p = 0.07$). Based on these results, ifosfamide–paclitaxel–filgrastim demonstrated statistically significant improvements in all three parameters (RR, PFS, and OS) over ifosfamide alone, establishing this regimen as the standard comparator regimen for further GOG trials.

In our retrospective study published in 2004, PC showed the potential for significant activity in the treatment of CS (RR 80 %, four of five evaluable patients) [21]. The study we report here is the first prospective study in Asia for advanced or recurrent CS. Taking into account data from the SEER publication, we suggest that Japanese patients may have survival rates that are comparable to or higher than those of Caucasian women [1] (Table 4). Our results suggest that PC for advanced or recurrent CS is feasible. PC is highly tolerable and may be administered on an outpatient basis. In addition, paclitaxel-induced neuropathy is generally mild.

Powell et al. [20] recently reported that the RR of CS to PC (AUC = 6) in patients with prior radiation therapy was 25 of 46 (54 %; CR, 6; PR,19) and that the PFS was 7.6 months. Lacour et al. [29] also reported on the RR of PC (AUC = 5) in patients with prior radiation therapy; in this study the RR of PC was 8 of 13 (62 %; CR 3; PR, 5) and the time to tumor progression was 7.9 months. Our results in terms of RR (66.7 %) and PFS (9.1 months) are comparable; however, the strength of our conclusions is limited by our small sample

size. While these results are promising, there is clearly still room for improvement that will likely be achieved through the incorporation of targeted therapeutics.

Although data in the literature are conflicting, recent studies have found that the behavior and overall prognosis of uterine carcinosarcoma is much more dependent on the characteristics of the epithelial elements than on those of the stromal elements [30]. In neoplasms where the epithelial element is Grade 3 endometrioid, serous, or clear cell in type, there is a higher frequency of metastasis and deep myometrial and cervical involvement. The results of older studies suggested that the presence of heterologous elements was associated with more aggressive behavior [31, 32], but more recent studies have found that the histologic features of the stromal component have no relationship to the likelihood of metastasis or overall prognosis [2, 4, 33]. Thus, it is still controversial whether the characteristics of the epithelial and stromal components impact survival; we could not find any histopathologic characteristic relationships in this study.

Novel molecular-targeted agents, including imatinib mesylate, sorafenib, VEGF-Trap, AZD0530, sunitinib, temozolomide, liposomal doxorubicin (+ carboplatin), lapatinib + ixabepilone, and bortezomib + gemcitabine are now also under investigation in trials of CS (clinicaltrials.gov). PC is one of the most common regimens in gynecologic malignancies, since severe adverse events are well characterized, predictable, and manageable. The results of our study indicate that PC is an effective and well-tolerated regimen for the treatment of advanced and recurrent CS and is therefore a likely candidate for use in conjunction with novel targeted agents. A randomized phase III trial of paclitaxel + carboplatin versus ifosfamide + paclitaxel in chemotherapy-naïve patients with newly diagnosed stage I–IV, persistent or recurrent carcinosarcoma of the uterus or ovary (GOG0261) is ongoing. We anticipate opening additional trials in Asia with targeted therapeutics in the near future.

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Feasibility study of gemcitabine plus docetaxel in advanced or recurrent uterine leiomyosarcoma and undifferentiated endometrial sarcoma in Japan

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Abstract
Background Uterine leiomyosarcoma (LMS) and undifferentiated endometrial sarcoma (UES) are rare, aggressive malignancies. Both are treated similarly; however, few chemotherapy agents are effective. Recently, the combination of gemcitabine (900 mg/m^2, days 1 and 8) plus docetaxel (100 mg/m^2, day 8) with granulocyte colony-stimulating factor (G-CSF, 150 μg/m^2, days 9–15) has been shown to have activity in LMS. In Japan, neither prophylactic G-CSF at a dose of 150 μg/m^2 nor docetaxel at a dose of 100 mg/m^2 are approved for use. For this reason, we evaluated the combination of 900 mg/m^2 gemcitabine plus 70 mg/m^2 docetaxel regimen without prophylactic G-CSF support in advanced or recurrent LMS and UES in Japanese patients.
Methods Eligible women with advanced or recurrent LMS and UES were treated with 900 mg/m^2 gemcitabine on days 1 and 8, plus 70 mg/m^2 docetaxel on day 8, every 3 weeks. The primary endpoint was overall response rate, defined as a complete or partial response.
Results Of the eleven women enrolled, 10 were evaluated for a response. One complete response and 2 partial responses were observed (30 %) with an additional 4 (40 %) having stable disease. Mean progression-free survival was 5.4 months (range 1.3–24.8 months), and overall survival was 14 months (range 5.3–38.4 months). Grade 4 neutropenia was the major toxicity (50 %). The median number of cycles was 5 (range 2–18). Twenty-two cycles (44 %) employed G-CSF.
Conclusion The gemcitabine plus docetaxel regimen without prophylactic G-CSF support was tolerable and highly efficacious in Japanese patients with advanced or recurrent LMS and UES.

Keywords Chemotherapy · Uterine leiomyosarcoma · Gemcitabine · Docetaxel · G-CSF · Japanese patients

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Introduction

Uterine leiomyosarcoma (LMS) and undifferentiated endometrial sarcoma (UES) together account for approximately 1 % of all uterine malignancies [1–3] and thus are diagnosed in only a few hundred women each year in Japan [4]. Systemic therapy for LMS and UES is similar [5]. Women who present with advanced disease and those with recurrence have a poor prognosis [6]. Median

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survival among women with advanced disease is less than 1 year.

Single-agent doxorubicin remains the standard first-line therapy in many treatment settings, with first-line response rates of approximately 25 %. The combination of doxorubicin plus ifosfamide (response rate 28–30 %) has not been shown to improve outcomes among patients with soft tissue sarcoma compared with doxorubicin alone [7, 8] (Table 1). Other single agents with moderate activity in leiomyosarcoma include ifosfamide (response rate 17.2 %) [9], gemcitabine (bolus infusion achieved a 20 % response rate) [10], trabectedin (response rate of 8 % among patients without prior treatment, and 45 % second-line treatment) [11, 12] and temozolomide (15.5 % objective response with daily oral treatment) [13]. Multiple chemotherapy agents, including cisplatin [14–16], liposomal doxorubicin [17], intravenous etoposide [18], oral etoposide [19], paclitaxel [20, 21], topotecan [22], trimetrexate [23], sunitinib malate [24], and thalidomide [25] have been tested in the first- and second-line settings with negligible activity demonstrated.

Docetaxel disrupts mitosis by the promotion of abnormal microtubular assembly and suppression of the depolymerization of microtubular bundles to free tubulin [26]. Gemcitabine is an S-phase-specific, fluorine-substituted pyrimidine analog, which is phosphorylated by deoxytidine kinase to the active diphosphate and triphosphate metabolites. This metabolite inhibits ribonucleotide reductase and DNA synthesis [27]. The clinical development of the gemcitabine–docetaxel regimen is outlined, and data demonstrating the efficacy of this regimen in soft tissue sarcoma are reviewed [28–30].

Table 1 Responses of chemotherapeutic trials in LMS

Drugs	Treatment lines	Response rate	Progression-free survival (months)
Doxorubicin [7]	First/second	7/28 (25 %)	3.5
Doxorubicin [36]	First	5/26 (19 %)	5
Cisplatin [16]	First	1/33 (3 %)	Not reported
Ifosfamide [9]	First	6/35 (17 %)	Not reported
Liposomal doxorubicin [17]	First	5/32 (16 %)	4.1
Etoposide IV [18]	First	0/28 (0 %)	2.1
Etoposide PO [19]	First/second	2/29 (7 %)	2.1
Paclitaxel [20]	First/second	3/33 (9 %)	Not reported
Topotecan [22]	First	4/36 (11 %)	Not reported
Trimetrexate [23]	Second	1/24 (4.3 %)	2.2
Paclitaxel [21]	First	4/48 (8 %)	1.5
Gemcitabine (bolus infusion) [10]	First/second	9/42 (20 %)	Not reported
Gemcitabine (fixed-dose rate, 10 mg/m^2/min) [37]	Second	4/21 (19 %)	5.5
Sunitinib malate [24]	Second	2/23 (8.7 %)	1.5
Temozolomide [13]	Second	1/13 (8 %)	Not reported
Thalidomide [25]	Second	0/29 (0 %)	1.7
Trabectedin [11]	Second	6/35 (17.1 %)	Not reported
Trabectedin [12]	Second	5/11 (45 %)	Not reported
Vincristine/dactinomycin/cyclophosphamide [38]	First	29 %	Not reported
Doxorubicin/dacarbazine [7]	First/second	24 %	Not reported
Doxorubicin/cyclophosphamide [36]	First	5/26 (19 %)	Not reported
Doxorubicin/ifosfamide [8]	First	10/33 (30 %)	4
Mitomycin/doxorubicin/cisplatin [39]	First	8/35 (22.8 %)	Not reported
DMAP, sargramostim (GM-CSF) [40]	First	5/18 (28 %)	5.9
Doxorubicin/ifosfamide [41]	First	12/25 (48 %)	Not reported
Gemcitabine + docetaxel [31]	First	18/34 (53 %)	5.6
Gemcitabine + docetaxel [33]	Second	13/48 (26 %)	5.6+
Gemcitabine + docetaxel [34]	First	15/42 (36 %)	4.4
Gemcitabine + docetaxel [37]	Second	5/21 (24 %)	4.7
Gemcitabine + docetaxel (this study)	Second/third	3/10 (30 %)	5.4

LMS Leiomyosarcoma, *DMAP* dacarbazine, mitomycin, doxorubicin, and cisplatin, *GM-CSF* granulocyte–macrophage colony-stimulating factor