nocarcinoma, two poorly differentiated adenocarcinoma, and remaining cases included clear cell carcinoma and carcinosarcoma. Metastatic lesions varied; eight cases had lung metastasis and four cases had brain metastasis. Histology of metastatic lesions was recorded in 11 cases and five of them were pure choriocarcinoma.

The management of choriocarcinoma is well established by the FIGO 2000 staging and risk factor scoring system, however, that of the rare uterine endometrial carcinoma with trophoblastic differentiation has not been well developed. The present authors' review of the previously reported cases show that most patients received surgery followed by multiagent chemotherapy such as MEA, EMACO (etoposide, methotrexate, and actinomycin D, followed by cyclophosphamide and vincristine), or BEP (bleomycin, etoposide, cisplatin) regimens. Yamada *et al.* in 2009 reported that recurrent vaginal tumor was completely diminished by administration of EMACO [15]. In the present case, tri-weekly AP was ineffective for lung metastasis and subsequent MEA could only temporarily reduce lung tumor volume. The fact that metastatic brain tumor showed pathologically pure choriocarcinoma supported the idea that metastatic lung tumors are also composed of choriocarcinomatous component.

Conclusion

The present review of the field has shown that there are few case reports of uterine choriocarcinoma in postmenopausal women. Furthermore, uterine endometrial carcinoma with trophoblastic differentiation is an extremely rare form of nongestational choriocarcinoma. Since prognosis of the rare tumor is thought to be worse than that of pure gestational choriocarcinoma, the early accurate diagnosis is clinically important.

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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

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

A single-institution study of gemcitabine plus docetaxel yielded high objective response rates among patients with advanced LMS in both the second-line [31] and first-line settings [32]. Recently, gemcitabine plus docetaxel has been shown to yield higher response rates, and longer progression-free and overall survivals than single-agent gemcitabine in a randomized trial for patients with soft tissue sarcoma who had received up to three prior regimens [30]. In a Gynecologic Oncology Group (GOG) phase II trial for women with advanced leiomyosarcoma who had received one prior cytotoxic regimen, gemcitabine plus docetaxel achieved objective responses in 28 % of patients, with an additional 50 % having stable disease (SD). The high dose of docetaxel (100 mg/m$^{2)}$ in this study, however, produced profound myelosuppression necessitating the use of growth factor support [33].

A prospective study of gemcitabine plus docetaxel has been eagerly anticipated in Japan. However, such studies have not been conducted because the GOG regimen, as either prophylactic G-CSF at a dose of 150 μg/m^2 or docetaxel at a dose of 100 mg/m^2, is not approved in Japan. The maximum approved dose of docetaxel in Japan is 70 mg/m^2.

Therefore, the aim of this single-institution study was to evaluate the efficacy and toxicity of a regimen of gemcitabine 900 mg/m^2 plus dose-reduced docetaxel 70 mg/m^2 without prophylactic G-CSF support in Japanese patients with advanced or recurrent LMS and UES.

Patients and methods

Patients

Women with measurable advanced or recurrent LMS and UES with non-resectable disease were eligible. All tumors were histologically confirmed. Patients were permitted to have had prior chemotherapy and pelvic radiotherapy; however, patients previously treated with either docetaxel or gemcitabine were excluded. Patients were required to have an ECOG performance status of 0–2, and adequate bone marrow function [absolute neutrophil count (ANC) greater than or equal to 1500/μl, and platelets greater than or equal to 100,000/μl]; renal function (creatinine less than or equal to 1.5 × the institutional upper limit of normal); hepatic function (bilirubin less than or equal to 1.5 × the institutional upper limit of normal, and serum glutamic oxaloacetic transaminase [sGOT] and alkaline phosphatase less than or equal to 2.5 × the institutional upper limit of normal); and neurological function [baseline neuropathy, sensory and motor, less than or equal to National Cancer Institution Common Toxicity Criteria version 3.0 (CTC 3.0) grade 1]. Patients with a history of another invasive malignancy within the past 5 years were not eligible. All patients provided written, informed consent. The protocol and consent were reviewed and approved annually by Institutional Review Boards of Tohoku University Hospital.

Treatment

All participants had baseline imaging with a computed tomography (CT) scan of the chest, abdomen, and pelvis, within 4 weeks of starting therapy. CT imaging was repeated following every other cycle of treatment to assess response. A history was taken, and a physical examination and assessment of toxicities were performed at each cycle. Complete blood counts and comprehensive metabolic panels were monitored weekly. Participants received gemcitabine 900 mg/m^2 on days 1 and 8 intravenously infused over 90 min, followed by docetaxel 70 mg/m^2 on day 8 intravenously infused over 60 min. Treatment cycles were repeated approximately every 3 weeks, and patients continued on the study treatment until disease progression, achievement of discontinuation criteria as defined in the study protocol, or at the discretion of the investigator. Recommended pre-medication for the docetaxel was dexamethasone 8 mg orally twice a day starting the day prior to docetaxel. Early intervention with diuretics was encouraged for signs of docetaxel-related fluid retention. Patients received the day 1 treatment of each cycle provided the ANC was greater than or equal to 1500/μl and the platelet count was greater than or equal to 100,000/μl. Patients received full-dose day 8 treatment provided the ANC was greater than or equal to 1000/μl and platelet count greater than or equal to 100,000/μl. Seventy-five percent of the planned day-eight dose was given if the ANC was between 500 and 1000/μl or the platelet count was between 50,000 and 100,000/μl, and provided bilirubin levels from day 1 or after were within institutional normal limits. Day-8 treatment with docetaxel was omitted if the bilirubin remained above normal on day 8. Day-8 gemcitabine and docetaxel were both omitted if the day-8 ANC was under 500/μl or the platelet count was less than 50,000/μl. Patients were given therapeutic and second-line prophylactic G-CSF if they had grade 4 neutropenia. Doses of both docetaxel and gemcitabine were reduced by 25 % in subsequent cycles if a patient experienced grade 3 elevations in sGOT, serum glutamic pyruvic transaminase (sGPT), or alkaline phosphatase, and treatment was not resumed until such grade 3 elevations had resolved to grade 1 or less. Patients who experienced grade 2 or worse neurotoxicity had treatment held for a maximum of 2 weeks and could resume treatment at 75 % of the prior docetaxel dose if the neuropathy had improved. Other non-hematological toxicities with an impact on organ function of grade 2 (or greater) required 25 % dose reduction and delay in subsequent therapy for a maximum of 2 weeks until it recovered to no worse than grade 1.

Assessment of response and toxicity

All patients who received at least 1 cycle of study treatment were considered assessable for response. Response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST). Responses according to these criteria are defined as follows: Complete response (CR) is the disappearance of all target and non-target lesions and no evidence of new lesions documented by 2 disease assessments at least 4 weeks apart. Partial response (PR) is at least a 30 % decrease in the sum of the longest dimensions (LD) of all target measurable lesions taking as the reference the baseline sum of LD. There could be no unequivocal progression of non-target lesions and no new lesions. Documentation by 2 disease assessments at least 4 weeks apart is required. In the case where the only target lesion is a solitary pelvic mass measured by physical examination, and which is not radiographically measurable, a 50 % decrease in the LD is required. Progression of disease (PD) requires at least a 20 % increase in the sum of LD of target lesions taking as references the smallest sum of LD, the appearance of new lesions, death due to disease or global deterioration due to disease. SD is any condition not meeting the above criteria. All 11 patients enrolled in the study were included in the assessment of response, apart from 1 patient who was not treated because of ileus. The primary endpoint was the overall response rate (RR: CR + PR), and secondary endpoints were progression-free survival (PFS), overall survival (OS), and adverse events. Time to treatment failure (TTF) was defined as the time from enrollment to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death. Adding to PFS, TTF is generally not accepted as a valid endpoint, but was also included as an endpoint in this study because 3 SD patients electively opted to change chemotherapy. Toxicities were graded according to CTC 3.0.

Results

Patient characteristics

Between February 2009 and June 2011, 11 women were enrolled in this phase II study. One patient (No. 8) underwent and was diagnosed by intrauterine cytology and curettage. One patient (No. 11) developed a prolonged postoperative ileus shortly after enrollment and was not included in the analysis. The remaining cases were included in the calculation of the objective response rate (Table 2). The median age of the cohort was 60.1 years (range 50–74 years). Nine patients had an ECOG performance status of 0 or 1, one had a performance status of 2. Eight of 10 patients had confirmed LMS, and 2 had UES. Nine of 10 patients had undergone a total abdominal hysterectomy plus bilateral salpingo-oophorectomy. Five of 6 recurrent patients had received 1 or more prior cytotoxic regimens, and in the majority, the prior therapy had been doxorubicin and ifosfamide-based. Three IVB stage patients were enrolled for first-line treatment. The main target regions were lung (40 %), pelvis (40 %), liver (10 %), and omentum (10 %). After 3 cycles, 3 SD patients (Nos. 4, 6, and 7) requested to be switched to other chemotherapies, and 1 patient (No. 5) refused further treatment. One patient (No. 3) desired surgical resection of the downsized pelvic tumor. Nine of 10 (90 %) received three or more cycles of study treatment. The median number of cycles of study treatment delivered per patient was five (range 2–18 cycles).

Response and survival

The RECIST-measured objective RR was observed in 3 of the 10 patients enrolled (30 %). One patient had CR (10 %), 2 had confirmed PR (20 %), and 4 (40 %) had SD (Table 2). The disease control rate (DCR; CR + PR + SD) was 70 %. Three of 10 (30 %) had PD. Mean PFS was 5.4 months (range 1.3–24.8 months), and mean TTF was 3.1 months (range 2.4–15.4 months). Mean OS was 14 months (range 5.3–38.4 months). Among 3 objective responses, the median response duration was 19.7 months (range 5.9–28.3 months).

Adverse events

Among the total of 50 cycles, the median number of cycles per patient was 5 (range 2–18 cycles); 22 cycles (44 %, median 5 times/cycle: range 3–7 times) were for 4 patients who required G-CSF at a dose of 75 $\mu g/m^2$ (half the dose used in the GOG trials). Myelosuppression was the major toxicity: neutropenia grade 3 in 20 %, grade 4 in 50 %; anemia grade 3 in 10 %, grade 4 in 10 %; thrombocytopenia grade 3 in 10 %, grade 4 in 20 %. There were no cases of grade 4 febrile neutropenia. One patient had grade 3 liver toxicity (Table 3). No grade 3/4 pulmonary toxicity was observed.

Discussion

Efficacy

In Japan, prophylactic G-CSF at a dose of 150 $\mu g/m^2$ and docetaxel at a dose of 100 mg/m^2 are not approved for use. For this reason, we performed the current feasibility study of gemcitabine 900 mg/m^2 plus dose-reduced docetaxel

Table 2 Patient characteristics and results

No.	Age (years)	PS	Stage	Hist.	Preprotocol treatments	Target lesion	Cycles	BR	Reason for discontinuation	Post treatments		Status
										Surgery	Chemo./ irradiation	
1	51	0	IVB	LMS	TAH + BSO	Omentum	6	CR	NA	None	None	NED
2	66	0	Rec.	LMS	TAH + BSO IAP × 3, TC × 3	Lung	18	PR	PD	None	Irradiation	DOD
3	53	0	Rec.	LMS	TAH + BSO IAP × 6	Pelvis	6	PR	Change strategy	Lt. pelvic tumor resection	GD × 2	DOD
4	59	0	IVB	UES	TAH + BSO	Lung	3	SD	Patient preference	None	IP × 3	DOD
5	74	0	Rec.	LMS	TAH + BSO IAP × 3	Liver	3	SD	Patient's reason	None	None	DOD
6	51	0	Rec.	UES	TAH + BSO IAP × 3	Pelvis	3	SD	Patient preference	None	TC × 2	DOD
7	50	0	Rec.	LMS	TAH + BSO	Lung	3	SD	Patient preference	None	IA × 3	DOD
8	55	1	IVB	LMS	None	Uterus Pelvic LN	2	PD	PD	None	Irradiation	DOD
9	40	1	Rec.	LMS	TAH + BSO	Lung	3	PD	PD	Lt. lower lobectomy	None	DOD
10	74	1	Rec.	LMS	TAH + BSO, CPT11 × 8, AP × 3	Pelvic LN	3	PD	PD	None	None	DOD
11[a]	60	2	Rec.	LMS	TAH + BSO	Lung	0	NA	NA	None	None	DOD

PS Performance status, *Rec.* recurrence, Hist., histology, *LMS* leiomyosarcoma, *UES* undifferentiated endometrial sarcoma, *TAH* total abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *IAP* ifosfamide + doxorubicin + cisplatin, *TC* paclitaxel + carboplatin, *CPT-11* irinotecan, *AP* doxorubicin + cisplatin, *IP* ifosfamide + cisplatin, *IA* ifosfamide + doxorubicin, *GD* gemcitabine + docetaxel, *BR* best response, *NA* not applicable, *NED* no evidence of disease, *DOD* dead of disease, *CR* complete response, *SD* stable disease, *Lt.* left, *PD* progression of disease, *LN* lymph node

[a] Patient No. 11 developed a prolonged postoperative ileus shortly after enrollment and was not treated with gemcitabine and docetaxel

70 mg/m^2 without prophylactic G-CSF support in Japanese patients with advanced or recurrent LMS and UES.

The GOG conducted a phase II trial for women with advanced, unresectable LMS whose disease had progressed after one previous cytotoxic regimen (gemcitabine–docetaxel as second-line therapy) [33]. This study enrolled 51 patients, of whom 48 were evaluable for response. Ninety percent of the patients had received previous doxorubicin-based therapy. Patients were treated with gemcitabine 900 mg/m^2 on days 1 and 8 over 90 min, and docetaxel 100 mg/m^2 on day 8 of a 21-day cycle with G-CSF support. Patients who had received previous pelvic radiation were given 25 % lower doses. Three of 48 patients (6.3 %) achieved CR, and 10 (20.8 %) achieved PR for an overall objective RR of 27 %. An additional 50 % of women had SD lasting a median duration of 5.4 months. The median number of cycles per patient was 5.5 (range 1–22 cycles). The PFS rate at 12 weeks was 73 %, and at 24 weeks was 52 %. Median PFS was 5.6+ months (range 0.7–27+ months). The median duration of objective response exceeded 9 months (range 3.9–24.5+ months). The GOG has conducted a prospective phase II trial to assess the efficacy of first-line, fixed-dose-rate gemcitabine plus docetaxel in women with advanced LMS [34]. The doses and schedule are the same as in their previously reported second-line treatment study. Objective responses were observed in 35.8 % of patients, CR in 4.8 % and PR in 31 %. An additional 26.2 % had SD. Half of the patients received 6 or more cycles of study treatment. The median PFS was 4.4 months (range 0.4–37.2+ months). Among the patients with an objective response, the median response duration was 6 months (range 2.1–33.4+ months). Median OS exceeded 16 months (range 0.4–41.3 months). The RR (30 %, 27.1 % [33], 35.8 % [34]), PFS (5.4 months), DCR (70 %), OS (14 months), and duration of objective response (19.7 months) in our study nearly equaled those of the 2 prior GOG trials (RR: 27.1 % [33], 35.8 % [34]; PFS: 5.6+ [33], 4.4 months

Table 3 Adverse events compared with GOG first-line [32] and second-line [33] studies, all grades, by number of patients experiencing the event

Adverse event	Grade by National Cancer Institution Common Toxicity Criteria version 3.0					
	0	1	2	3	4	3/4 (%)
Neutropenia						
This study	0	0	3	2	5	70.0
GOG first-line	27	2	6	2	5	16.7
GOG second-line	19	9	10	6	4	20.8
Anemia						
This study	5	1	2	1	1	20.0
GOG first-line	0	7	25	10	0	23.8
GOG second-line	4	6	26	10	2	25.0
Thrombocytopenia						
This study	5	1	1	1	2	30.0
GOG first-line	9	22	5	4	2	14.3
GOG second-line	8	11	10	14	5	39.6
RBC transfusion						
This study	10	0	0	0	0	0.0
GOG second-line	24	0	0	24	0	50.0
Platelet transfusion						
This study	10	0	0	0	0	0.0
GOG second-line	42	0	0	6	0	12.5
Nausea/vomiting						
This study	3	7	0	0	0	0.0
GOG second-line	29	12	6	0	1	2.1
Anorexia						
This study	3	7	0	0	0	0.0
GOG first-line	12	12	12	5	1	14.3
GOG second-line	18	15	12	2	1	6.3
Liver dysfunction						
This study	5	3	1	1	0	10.0
GOG first-line	35	7	0	0	0	0.0
GOG second-line	38	6	3	1	0	2.1
Pulmonary						
This study	10	0	0	0	0	0.0
GOG first-line	32	6	3	0	1	2.4
GOG second-line	36	4	4	3	1	8.3
Fatigue						
This study	3	3	4	0	0	0.0
GOG first-line	11	15	9	7	0	16.7
GOG second-line	40	2	5	1	0	2.1
Alopecia						
This study	6	4	0	0	0	0.0
GOG second-line	21	1	26	0	0	0.0
Infection						
This study	9	0	0	1	0	10.0
GOG first-line	30	3	8	1	0	2.4
GOG second-line	43	2	1	2	0	4.2
Genitourinary						
This study	9	0	0	1	0	10.0
GOG first-line	36	3	3	0	0	0.0
GOG second-line	45	2	1	0	0	0.0

Table 3 continued

Adverse event	Grade by National Cancer Institution Common Toxicity Criteria version 3.0					
	0	1	2	3	4	3/4 (%)
Neurotoxicity						
This study	10	0	0	0	0	0.0
GOG first-line	32	7	2	1	0	2.4
GOG second-line	26	15	7	0	0	0.0
Allergic reaction						
This study	10	0	0	0	0	0.0
GOG first-line	33	5	3	1	0	2.4
GOG second-line	46	0	2	0	0	0.0

RBC red blood cell, *GOG* Gyencologic Oncology Group

[34]; DCR: 77 % [33], 62 % [34]; OS: 14.7 [33], 16.1 months [34]; and durations of objective response: 9+ [33], 6 months [34]). Thus, we conclude that 900 mg/m^2 gemcitabine plus dose-reduced docetaxel (70 mg/m^2)was highly efficacious in treated and untreated Japanese patients with advanced or recurrent LMS and UES (Table 1).

Toxicity

The toxicities associated with treatment were mainly bone marrow suppression: neutropenia grade 3 in 20 %, grade 4 in 50 %; anemia grade 3 in 10 %, grade 4 in 10 %; thrombocytopenia grade 3 in 10 %, grade 4 in 20 %. In the GOG second-line study, which employed G-CSF for 7 days, the toxicities associated with treatment were mainly uncomplicated myelosuppression: thrombocytopenia grade 3 (29 %), grade 4 (10.4 %); neutropenia grade 3 (12.5 %), grade 4 (8.3 %); and anemia grade 3 (20.8 %), grade 4 (4.2 %) [33]. Although neutropenia (grade 3 in 12.5 %, grade 4 in 8.3 %) was less frequent than that in this study (grade 3 in 20 %, grade 4 in 50 %), we had no episodes of life-threatening neutropenia. In the GOG first-line study, grade 3/4 myelosuppression was less frequent than that in the second-line study, with neutropenia grade 3 in 5 %, grade 4 in 12 %; anemia grade 3 in 24 %; and thrombocytopenia grade 3 in 9.5 %, grade 4 in 5 % [34]. In the GOG second-line study, the median number of cycles was 5.5, with a range extending up to 22 cycles [33] and in the first-line study, half of patients received more than 6 cycles of therapy [34]. In our study, among the total 50 cycles, 22 cycles (44 %) were for 4 patients who required the use of G-CSF (half the dose of and shorter term than the GOG trials). No grade 4 febrile neutropenia was observed. The median number of treatment cycles per patient was 5 (range 2–18 cycles), fewer than in the GOG second-line (5.5) [33] and first-line (6+) [34] studies. This was expected because 3 SD patients in the present study elected to change the chemotherapeutic regimen after the third cycle. These data support the suggestion that gemcitabine plus docetaxel without prophylactic G-CSF support is a tolerable regimen, and should be considered as a treatment option for advanced or recurrent LMS and UES in Japanese patients.

Active study

Further research is required to assess whether molecularly targeted therapies are effective in LMS and UES. In a phase I study in which gemcitabine, docetaxel, and bevacizumab (5 mg/kg) were all given concurrently every 2 weeks to patients with previously untreated soft tissue sarcoma (LMS, 5 patients; angiosarcoma, 3 patients; other histologies, 19 patients), 11 of 25 assessable patients had objective responses, including three with a complete remission [35]. The results of a randomized phase III trial of docetaxel and gemcitabine plus G-CSF with bevacizumab versus docetaxel and gemcitabine plus G-CSF with placebo in the treatment of advanced LMS (GOG0250) are awaited.

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

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ORIGINAL ARTICLE

Clinical outcome of pelvic exenteration in patients with advanced or recurrent uterine cervical cancer

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Abstract
Background Pelvic exenteration has attained an important role in the treatment of advanced or recurrent cervical cancer for obtaining a complete cure or longer disease-free survival. The purpose of this study was to evaluate patients undergoing pelvic exenteration and to determine the clinical features associated with outcome and survival.
Methods We retrospectively analyzed the records of 12 patients who underwent pelvic exenteration for uterine cervical cancer between July 2002 and August 2011.
Results Two patients had primary stage IVA cervical adenocarcinoma and 10 patients had recurrent cervical cancer. Eight patients underwent anterior pelvic exenteration, 3 patients underwent total pelvic exenteration, and 1 patient underwent posterior pelvic exenteration. With a median duration of follow-up of 22 months (range 3–116 months), 5 patients were alive without recurrence. Of 5 patients with no evidence of disease, 4 were recurrent or residual tumor, all of whom had common factors, such as a tumor size $\leq$30 mm, negative surgical margins, complete resection, and no lymph node involvement. The 5-year overall survival rate for 12 patients was 42.2 %. Ileus was the most common complication (42 %) and post-operative intestinal anastomosis leaks developed in 3 patients, but no ureteral anastomosis leaks occurred.
Conclusions Pelvic exenteration is a feasible surgical procedure in advanced and/or recurrent cervical cancer patients with no associated post-operative mortality, and the only therapeutic option for complete cure or long-term survival; however, post-operative complications frequently occur.

Keywords Pelvic exenteration · Uterine cervical cancer · Positron emission tomography/computed tomography · Urinary diversion · Complications

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Introduction

Cervical cancer is the fifth most common cancer among women in Japan; the mortality from cervical cancer in 2010 was 4.1 per 100,000 of the female population [1]. Radiotherapy and surgery are the cornerstones of management for patients with cervical cancer. Indeed, radiotherapy or concurrent chemoradiotherapy (CCRT) is recommended for patients who are at high risk for recurrence following radical hysterectomy or for patients with advanced stage disease [2]. Despite the clinical advantage of CCRT for cervical cancer, recurrence rates are 50–70 % for patients with locally advanced disease (The International Federation of Gynecology and Obstetrics (FIGO) IIB, III, and IVA stage) [3]. Treatment options in patients with locally recurrent cervical cancer are limited. In fact, approximately 25 % of patients with recurrences outside the irradiated field respond to chemotherapy while only 5 % of patients respond to chemotherapy if the tumor recurs within the irradiated field [4].

Pelvic exenteration (PE) was initially introduced as a palliative procedure in the treatment of advanced pelvic cancer [5]. Of note, the operative mortality rate was as high as 23 % [5]. Due to improvements in reconstructive procedures, surgical techniques, patient selection, and

peri- and post-operative care, the operative mortality rate has decreased dramatically [6, 7]. Currently, PE has attained an important role in the treatment of advanced or recurrent cervical cancer for obtaining a complete cure or longer disease-free survival.

We performed PEs on 16 patients with uterine cervical cancer, uterine sarcoma, or vulvar cancer between July 2002 and August 2011. In the current study, 12 patients with cervical cancer who underwent PE at a single institution in Japan were reviewed. The purpose of this study was to describe the incidence and severity of complications associated with PE, and to define which patients were more likely to benefit from PE.

Materials and methods

We retrospectively studied the medical records of 12 patients who underwent PE for uterine cervical cancer between July 2002 and August 2011 at the Tohoku University Hospital. The medical records were reviewed and information was gathered with respect to age at the time of surgery, the histologic features of the primary cancer, prior treatment(s), FIGO stage, extent of disease, method of urinary and stool diversion, operative time, blood loss, tumor size, tumor residual, tumor margin status, lymph node metastasis, complications, and present disease status. The survival times of patients alive or lost to follow-up were censored in June 2012.

The selection criteria for PE were central recurrence; age (<70 years); no gross pelvic side-wall involvement; no para-aortic lymph node enlargement; no distant metastases; and good performance status. An informed consent, including the rationale for the procedure and a statement that the procedure could be terminated intra-operatively without completing the resection, was obtained in every case. The diagnosis of recurrent tumor was confirmed by pathologic examinations of a biopsy specimen from each patient, but we did not perform surgical explorations, such as open or laparoscopic biopsies.

All surgical procedure was performed by gynecologic oncologists in collaboration with urologists and general surgeons. Total pelvic exenteration (TPE) involves removal of the reproductive tract, bladder, portions of the ureters, and rectosigmoid colon. Anterior pelvic exenteration (APE) is removal of the reproductive tract, bladder, and portions of the ureters, while posterior pelvic exenteration (PPE) is removal of the reproductive tract and rectosigmoid colon. Pelvic lymphadenectomy is performed for primary stage IVA patient who undergo PE. The recurrent patients after CCRT receive selective biopsy for lymph nodes with suspected metastasis. Intra-operative radiation therapy was not administered to any patient.

All statistical analyses were performed with StatFlex 6.0 (Artec, Inc., Osaka, Japan). Survival probabilities were estimated using the Kaplan–Meier method, and statistical significance was determined by the log-rank test.

Results

Patient characteristics and surgical data of the 12 patients are presented in Table 1. The median age at the time of surgery was 46 years (range 34–63 years). Of the 12 patients, 2 had primary cervical adenocarcinoma (stage IVA) and 10 had recurrent cervical cancer (squamous cell carcinoma, $n = 6$; and adenocarcinoma, $n = 4$). All 10 patients with recurrences had received radiotherapy, 6 of whom underwent hysterectomies before PE.

The median tumor size at the time of PE was 32.5 mm (range 15–82 mm). The operative procedures were APE ($n = 8$), TPE ($n = 3$), and PPE ($n = 1$). The median operative time was 491.5 min (range 266–683 min) and the estimated blood loss was 2537.5 g (range 1565–5572 g). Eight of 12 patients had no macroscopic residual tumor after PE, and as a result the surgical margins had no malignant cells microscopically in 8 cases. The resected specimens from nine patients contained lymph nodes. Of the nine patients, three had positive lymph node metastases and the histopathologic diagnoses were adenocarcinomas. The median hospital stay post-PE was 65.5 days (range 16–103 days).

The surgical outcomes and complications are summarized in Table 2. Ileus was the most common complication, occurring in 5 patients (42 %). Post-operative leaks of intestinal anastomoses developed in 3 patients (25 %). Two patients (17 %) required re-laparotomies because of ileus, a wound infection, or peritonitis. In contrast, no post-operative leaks of ureteral anastomoses were documented. There were no peri-operative deaths and no cardiovascular or thromboembolic events. Two patients (17 %) had no major post-operative complications.

The types of urinary reconstructive procedures and leakages are summarized in Table 3. Before performing PE, 10 patients received pelvic radiation therapy. Only one patient (no. 88) did not require urinary diversion because a PPE was performed. The methods of urinary diversion were ileal conduits ($n = 4$); ureterocutaneostomy ($n = 3$); transverse colon conduits ($n = 3$); and sigmoid colon conduit ($n = 1$). Three patients with ureterocutaneostomies did not require intestinal anastomoses. No patients had ureteral anastomosis leakages. Two patients had ileoileal anastomosis leaks in the ileal conduit using the ileum within the radiation field.

With a median duration of follow-up of 22 months (range 3–116 months), 5 patients were alive without

Table 1 Backgrounds and characteristics

Case	Age	Stage	Histology	Status	Prior treatment	Site of recurrence	PET/CT	Tumor size (mm)	Exent type	Operation hours (min)	Blood loss (g)	Tumor residuals	Margin status	Positive lymph nodes	Length of hospital stay after PE (days)	Survival Period after PE (months)	Progression free period after PE (months)	Disease status
1	63	IB2	SCC	Relapse	Surgery, CCRT	Vaginal stump	(−)	50	TPE	677	3205	None	(−)	(−)	90	3	2	DOD
2	41	IIB	SCC	Relapse	CCRT, Chemotherapy	Uterus	(−)	28	APE	395	2650	None	(−)	(−)	84	116	116	NED
3	45	IB2	AC	Relapse	Surgery	Vaginal stump	(−)	35	APE	490	2600	None	(−)	(+)	100	54	44	DOD
4	41	IVA	AC	Primary	None		(−)	82	APE	502	5572	None	(−)	(+)	103	106	106	NED
5	49	IIIA	SCC	Relapse	CCRT	Uterus	(+)	15	APE	425	1910	None	(−)	(−)	47	99	99	NED
6	34	IIB	SCC	Relapse	CCRT, chemotherapy	Uterus,pelvic lymph nodes	(+)	39	APE	266	1565	None	(−)	Not removed	23	7	2	DOD
7	60	IIB	AC	Relapse	Surgery, CCRT	Vaginal stump	(+)	38	APE	470	1700	<1 cm	(+)	(+)	88	21	10	DOD
8	56	IIIB	SCC	Relapse	CCRT, chemotherapy	Uterus	(+)	25	PPE	342	1780	<1 cm	(+)	Not removed	100	18	5	DOD
9	42	IIB	SCC	Relapse	NAC, surgery, RT, chemotherapy	Vaginal stump	(−)	50	TPE	591	2755	>2 cm	(+)	(−)	32	24	24	AWD
10	47	IVA	AC	Primary	Residual tumor after CCRT		(+)	20	APE	493	1330	None	(−)	(−)	16	23	23	NED
11	36	IB2	AC	Relapse	Surgery, RT, chemotherapy	Vaginal stump, bladder	(+)	25	TPE	683	2475	<1 cm	(+)	Not removed	43	12	4	DOD
12	52	IB2	AC	Relapse	Surgery, CCRT, chemotherapy	Vaginal stump	(+)	30	APE	662	4517	None	(−)	(−)	20	14	14	NED

SCC squamous cell carcinoma, *AC* adenocarcinoma, *CCRT* concurrent chemo-radiation therapy, *NAC* neoadjuvant chemotherapy, *RT* radiation therapy, *PET/CT* positron emission tomography/computed tomography, *PE* pelvic exenteration, *TPE* total pelvic exenteration, *APE* anterior pelvic exenteration, *PPE* posterior pelvic exenteration, *DOD* dead of disease, *AWD* alive with disease, *NED* no evidence of disease

recurrences, 1 was alive with disease, and 6 died of disease at the time the study was concluded. We calculated the predictable overall survival (OS) and progression-free survival (PFS) after undergoing PE for the 12 patients. As shown in Fig. 1, the 5-year OS rate for all patients was 42.2 %. We performed univariate analysis on the previously-described patient prognostic factors; however, none of the factors were statistically significant.

Discussion

Pelvic exenteration was initially introduced in 1948 as a palliative procedure for patients with advanced pelvic cancer [5]. With the advent of surgical diversion techniques, advances in post-operative management, thromboprophylaxis, and the use of prophylactic antibiotics, the associated operative mortality has improved. In the most recently published studies, the operative mortality rate has been reduced to 0–2 % [8–10]. Therefore, the exact surgical indications for PE have gradually changed over time, and PE is currently considered a safe and feasible procedure for select patients.

To select the appropriate candidates for PE, pre-operative imaging is the most important diagnostic tool for assessment. Computed tomography (CT) scans and/or magnetic resonance imaging system (MRIs) have not been reported in sufficient numbers as imaging methods before performing PEs to assess efficacy as therapeutic modalities and in the pre-operative evaluation of lesions [11]. In fact, most of the patients in our series had previously undergone pelvic surgery and/or radiation therapy, thus it was difficult to distinguish between post-radiation pelvic fibrosis and recurrent lower genital tract cancers using CT scans and/or MRIs as imaging modalities. We performed positron emission tomography/CT (PET/CT) scans to identify the recurrent tumors in six patients who had surgery after 2004. All of the patients with central disease detected by PET/CT had histopathologic confirmation of the surgical specimens. These six patients underwent CT and/or MRI prior to PET/CT; uterine relapse was not detected in two patients by CT scan and 3 patients by MRI. These results, as well as the results in previous reports [11, 12] indicate that PET/CT is the most useful modality with which to determine eligibility for PE.

Factors such as positive node status, tumor size, side wall fixation, histologic type, and margin status, have been shown to be associated with prognosis in patients with advanced cervical cancer [7, 8, 13–19]. In our series, 5

Table 2 Surgical outcome and complications ($n = 12$)

	Patients
Early and late operative complications	
Ileus	5 (42 %)
Insufficiency of the intestinal anastomosis	3 (25 %)
Re-laparotomy	2 (17 %)
Wound infection	2 (17 %)
No complication	2 (17 %)
Pelvic abscess	1 (8 %)
Infectious lymphocele	1 (8 %)
Infection of urinary tract	1 (8 %)
Severe appetite loss	1 (8 %)
Cardiovascular and/or thromboembolic events	0 (0 %)
Insufficiency of the ureteral anastomosis	0 (0 %)
Secondary bleeding	0 (0 %)
Operative mortality	0 (0 %)

Table 3 Types of urinary reconstructive procedures and leak

Case	Exent type	Method of urinary diversion	RT before PE	Leak of intestinal anastomosis	Leak of ureteral anastomosis
1	TPE	Sigmoid colon conduit	+	–	–
2	APE	Ileal conduit	+	+	–
3	APE	Ileal conduit	–	–	–
4	APE	Ileal conduit	–	–	–
5	APE	Ureterocutaneostomy	+	–[a]	–[b]
6	APE	Ureterocutaneostomy	+	–[a]	–[b]
7	APE	Ileal conduit	+	+	–
8	PPE	No urinary diversion	+	–[a]	–[b]
9	TPE	Ureterocutaneostomy	+	–[a]	–[b]
10	APE	Transverse colon conduit	+	–	–
11	TPE	Transverse colon conduit	+	–	–
12	APE	Transverse colon conduit	+	–	–

RT radiation therapy, *PE* pelvic exenteration, *TPE* total pelvic exenteration, *APE* anterior pelvic exenteration, *PPE* posterior pelvic exenteration

[a] No intestinal anastomosis

[b] No ureteral anastomosis

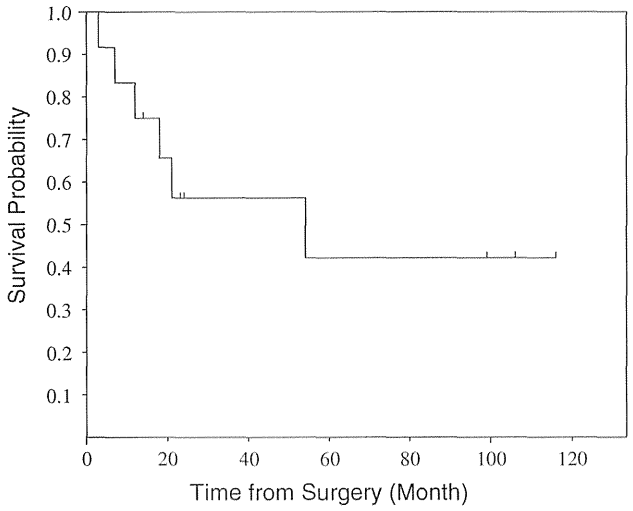

Fig. 1 Overall survival for the entire patients

patients (41.7 %) had no evidence of disease after PE (nos. 2, 4, 5, 10, and 12). Moreover, 2 patients (nos. 2 and 5) had long-term survival >8 years in spite of recurrence. Of the 5 patients with no evidence of disease, 4 (nos. 2, 5, 10, and 12) were treated for recurrences or residual tumor. All 4 patients had common factorstumor size ≤30 mm, negative surgical margins, complete resection, and no lymph node involvement. Although the number of patients was too small to demonstrate a statistical difference, these factors are thought to be important in selecting candidates for PE. In contrast, patient no. 4 had long-term survival, despite a bulky tumor (>80 mm), positive lymph nodes, and cervical adenocarcinoma. Patient no. 4 was diagnosed with FIGO stage IVA cervical adenocarcinoma and underwent PE primarily. The therapeutic strategy for stage IVA cervical cancer remains controversial. Surgical resection for patients with stage IVA cervical cancer is not recommended in the United States and Japan [2, 20]. In contrast, half of the patients with stage IVA undergo PE primarily in Germany [17]. Marnitz et al. [17] reported that the overall cumulative survival after PE was 52.5 % in the primary treatment group and tumor-free resection margin was significantly correlated with a good prognosis. Our cases also achieved tumor-free surgical margins; therefore, PE may be an alternative to primary chemoradiation if the tumor is considered to be completely resectable.

PE, in some situations, is associated with severe complications. Intestinal anastomosis leaks cause peritonitis and inevitably lead to re-laparotomies, resulting in lengthy hospital stays. In our series, insufficiency of the intestinal anastomosis occurred in 3 of 8 cases (37.5 %), which is higher than previous reports (19.1–29.8 %) [21, 22]. All three patients with intestinal leakages had irradiated small intestines with normal appearances. On the basis of these results, we used a transverse colonic conduit for urinary diversion in the current three patients, and had no post-operative intestinal leakages at the time the study was concluded. We deem transverse colonic conduits to be suitable in patients with previous radiation therapy.

In conclusion, PE is a feasible surgical procedure, especially in select patients with recurrent tumors ≤30 mm in size, negative surgical margins, and no lymph node involvement, and is a valuable option for cure or long-term survival, although post-operative complications remain high. Intra-operative procedures, such as urinary diversion, affect complications during the early post-operative period and will continue to be revised to further reduce the complication rate. Cooperation with general surgeons and/or urologists, intensive post-operative management, and patient selection are the cornerstones to improve survival and quality of life in patients with advanced and/or recurrent cervical cancer.

Conflict of interest The authors have no conflicts of interest to declare.

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Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian cancer (JCOG0503) ☆

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HIGHLIGHTS

- A phase 2 study with oral etopocide and IV irinotecan for 60 pts (14 elderly) with platinum-resistant ovarian cancer
- The response rate, PFS, and OS was 21.7% (less than boundary), 4.1 and 11.9 months, respectively.
- Febrile neutropenia and possible TRDs occurred in 11 (4 elderly) and 3 (2 elderly) pts, respectively.

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ABSTRACT

Objective. To assess the safety and efficacy of the combination of oral etoposide and intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian cancer.

Methods. Eligible patients (age, 20–75 years; platinum-free interval, ≤28 weeks) with an adequate organ function received oral etoposide (50 mg/m^2 once a day) from day 1 to day 21 and intravenous irinotecan (70 mg/m^2) on days 1 and 15. The regimen was repeated every 28 days up to 6 cycles. The primary endpoint was the response rate (RR) with a threshold of 20%. The response was evaluated according to RECIST 1.0 and Gynecologic Cancer Intergroup CA-125 Response Definition, and toxicities were evaluated according to CTCAE version 3.0. This trial was registered at UMIN-CTR as UMIN000001837.

Results. Between April 1, 2009 and January 20, 2012, 61 patients were enrolled. Sixty patients were eligible. 1 CR and 12 PRs were confirmed; RR was 21.7% ($p = 0.42$, the exact binomial test). PFS and OS were 4.1 and 11.9 months, respectively. Major toxicities of ≥grade 3 were neutropenia (60%), anemia (36.7%), thrombocytopenia (11.7%), febrile neutropenia (18.3%), fatigue (13.3%), anorexia (11.7%), and nausea (11.7%). Three patients died from treatment related death (interstitial pneumonia, a pulmonary embolism, and DIC due to infection). Two of these patients were aged ≥65 years.

Conclusions. Oral etoposide and intravenous irinotecan had a moderate RR but did not meet the primary endpoint. Because of toxicity, we do not recommend this regimen outside of clinical trials. In particular, when considering this regimen for elderly patients, extreme caution is advised.

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Introduction

Ovarian cancer is the most lethal gynecological cancers in Japan. The standard first-line chemotherapy regimen is carboplatin plus paclitaxel [1,2]. Although the first-line chemotherapy is effective, more than 60% of the patients with advanced-stage cancer die of recurrent disease. After relapse, the choice of second-line chemotherapy depends on the platinum-free interval (PFI), which is a predictive factor of the effect of repeating platinum agents. The cutoff point of PFI is generally 6 months. Patients who experience recurrence within 6 months after previous chemotherapy are regarded as platinum resistant and receive subsequent line chemotherapy with a single agent, such as pegylated liposomal doxorubicin [3], topotecan [3], or gemcitabine [4]. When administered as monotherapy, many cytotoxic agents have shown activity against recurrent ovarian cancer; however, response rates (RRs) are generally low, such as 6–12% [3,4], and the responses last for a short duration because of resistance to monotherapy. Combination chemotherapy may circumvent this resistance and halt disease progression because a lower dose of two drugs with different mechanisms may reduce toxicity and enhance efficacy [5].

Irinotecan, a semisynthetic derivative of camptothecin, is a prodrug with little inherent inhibitory activity against topoisomerase I and is converted by carboxylesterases to its more active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin). In vitro, SN-38 is 250–1000 times more potent than irinotecan as a topoisomerase inhibitor. For platinum-resistant patients, irinotecan shows modest activity [6–8] as monotherapy when administered once a week, once every 2 weeks, and once every 3 weeks.

Etoposide is a semisynthetic glucosidic derivative of podophyllotoxin [9]. Intravenous etoposide has been tested in two phase II trials and has shown a relatively low RR (0% and 8.3%) [10,11] in patients with recurrent ovarian cancer. In contrast, oral etoposide has shown better efficacy, with RR of 26.8% in patients with a platinum-resistant relapse of ovarian cancer [12].

Topoisomerase I inhibitor treatment induces an increase in the S-phase cell population with an increase in topoisomerase II mRNA expression. Thus, topoisomerase I inhibitor can modulate topoisomerase II levels to enhance the effect of topoisomerase II inhibitors [13,14].

Eder et al. reported the results of an in vivo study. They showed that a combination of irinotecan and etoposide has a synergistic effect according to both a tumor excision assay and a tumor growth delay assay [15]. A phase I trial of topotecan and oral etoposide revealed severe myelosuppression but promising efficacy against platinum- and taxane-pretreated ovarian cancer [16].

The dose limiting toxicity of irinotecan is diarrhea, different from that of topotecan (myelosuppression). Accordingly, combining etoposide with irinotecan may improve the risk–benefit balance of dual inhibition of topoisomerase. The results of a phase I trial of this combination in patients with platinum-treated advanced epithelial ovarian cancer were reported at ASCO 2002 [17]. The recommended dose for a further study was as follows: oral etoposide 50 mg/m^2/day on days 1–21 and intravenous irinotecan 70 mg/m^2 on days 1 and 15. The regimen was repeated every 4 weeks.

In this phase I trial, four objective responses [2 complete responses (CRs) and 2 partial responses (PR)] were achieved among 24 patients, including 1 PR in clear cell carcinoma. Nishio et al. reported the results of a feasibility study in patients with platinum- and taxane-resistant ovarian cancer; the study was conducted by selected hospitals in Tohoku and Kyushu districts in Japan [18]. RR, time to progression, and overall survival (OS) were 44%, 9 months, and 17 months, respectively. This promising result led us to undertake a nationwide phase II trial.

Methods

Patients

Eligible patients (age, 20–75 years) had progressive or recurrent epithelial ovarian cancer, tubal cancer, or peritoneal cancer, with PFI (measured from the most recent platinum-containing regimen) of ≤28 weeks and a history of taxane treatment. The eligibility criteria included a measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) or a non-measurable disease meeting the GCIG CA-125 response definition [19]. Measurable lesion was defined as maximum tumor diameter of 20 mm or larger in CT with a slice of 6–10 mm or that of 10 mm or larger in CT with a slice ≤5 mm. Patients must be able to eat and drink without requiring parenteral nutrition. Other criteria included ECOG performance status, 0–2; absolute neutrophil count, ≥2000/μL; platelet count, ≥100,000/μL; serum creatinine, ≤1.5 mg/dL, total bilirubin, ≤1.5 mg/mL; and aspartate aminotransferase (AST), ≤100 IU/L. The patients were excluded if they had prior irinotecan, topotecan, or etoposide treatment; prior radiation; uncontrolled hypertension; a history of myocardial infarction or heart failure within 6 months; current unstable angina; mental illness or mental symptoms that would affect the participant's decision to participate; pregnancy or lactation; bowel obstruction; chemotherapy or a surgical procedure within 28 days; continuous systemic steroid; an active bacterial or fungal infection with a fever of ≥38.5 °C; hormonal or biological therapy within 14 days; malignancy within 5 years (except carcinoma in situ or intramucosal cancer); drainage of effusion, or ascites within 28 days; effusion or ascites to be drained at registration; pulmonary embolism or a history of pulmonary embolism with deep vein thrombosis requiring treatment.

Treatment

The patients received oral etoposide at 50 mg/m^2 (for patients with body surface area <1.0, 1.0–<1.5, 1.5–<2.0, or ≥2.0 m^2: 25, 50, 75, or 100 mg/day, respectively) once a day from day 1 to day 21, and received intravenous irinotecan (70 mg/m^2 over 90 min) on days 1 and 15. The regimen was repeated every 28 days up to 6 cycles until disease progression, unacceptable toxicity, or patient refusal occurred.

To begin the subsequent cycle, the pretreatment absolute neutrophil cell and platelet counts, AST, total bilirubin, and serum creatinine were ≥1000/μL, 10×10^4/μL, ≤100 IU/L, ≤1.5 mg/dL, and ≤1.5 mg/dL, respectively. Other criteria to begin the subsequent cycle included non-hematological toxicities (nausea, vomiting, anorexia, diarrhea, fatigue, fever, febrile neutropenia, and infection) ≤grade 1, constipation ≤grade 2, and no G-CSF within the last 2 days. Treatment modification criteria are listed in Appendix A1–2.

Endpoints

The primary endpoint was RR in all eligible patients. In patients with a measurable lesion, the response was evaluated according to RECIST 1.0 [20] and reviewed by independent radiology review. In patients with a non-measurable lesion, the response was assessed according to Gynecologic Cancer Intergroup CA-125 Response Definition [19]. To calculate RR, the sum of the number of responders was divided by the number of all eligible patients. The secondary endpoints were progression-free survival (PFS), OS, and adverse events. OS is defined as days from registration to death from any cause. OS was censored on the last day of follow-up when a patient was alive. PFS is defined as days from registration to disease progression (radiological, CA-125, or symptomatic) or death from any cause. PFS was censored on the latest day when the patient was alive without any evidence of progression.

Study design and statistical analysis

This study was a phase II trial with a two-stage design according to the Southwest Oncology Group (SWOG) [21]; we intended to evaluate this regimen as a test arm for a subsequent phase III trial. We assumed that the expected value of the primary endpoint was 35% and the threshold value was 20%. In this situation, the sample size ensuring at least 80% power with a one-sided alpha of 0.05 was 55 participants.

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Considering the likelihood of some ineligible patients among those enrolled, the total number of patients was set to 60.

Primary endpoint, RR, was tested by the exact binomial test and confidence interval of proportion was calculated by the exact method. According to the SWOG's two-stage design, preplanned interim analysis for futility was done after 30 patients enrolled, setting the threshold of the number of minimum responders as four. Then final analysis was conducted with one-sided alphas of 0.02 and 0.055, respectively. OS and PFS curves, median PFS and OS were estimated by Kaplan–Meier method, and confidence intervals for proportion were calculated with Greenwood's formula and median OS and PFS with Brookmeyer and Crowley's method. Exploratory analyses for RR were carried out by Fisher's exact test. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Interim monitoring

In-house monitoring was to be performed every 6 months by the Japan Clinical Oncology Group (JCOG) Data Center to evaluate the study progress and to improve study quality.

Ethical considerations

The Protocol Review Committee of JCOG approved the study protocol in January 2009, and the study was initiated in April 2009. The protocol was reviewed and approved at all the participating hospitals. Every patient signed a written informed consent form. This trial was registered at UMIN-CTR as UMIN000001837 (http://www.umin.ac.jp/ctr/).

Results

Patient characteristics

From April 1, 2009 to July 5, 2010, 30 patients were enrolled and patient accrual was suspended for interim analysis. After the planned interim analysis, the study was resumed on November 22, 2010, and a total of 61 patients were enrolled until January 20, 2012. One patient was ineligible and excluded from this analysis because the days from surgery to registration were shorter than the eligibility criteria. Patient characteristics are summarized in Table 1. There were 14/60 (23.3%) elderly patients, defined as ≥65 years. Eleven of 60 (18.3%) patients had clear cell carcinoma, who were mostly (10 of 11) enrolled in the study after the interim analysis. Among 39 patients with serous carcinoma, two of them (5%) were diagnosed as low grade serous carcinoma. Nine of 60 patients (15%) received ≥3 prior chemotherapy regimens. Twenty-seven of 60 patients (45%) had platinum-refractory disease that progressed during or within 3 months after previous chemotherapy with a platinum-based drug.

Treatment administration

The median number of delivered treatment cycles was 4 (range, 1–6). Twenty-one patients completed 6 cycles of treatment. Thirty-nine patients did not complete treatment because of the following reasons: disease progression ($n = 29$), patient refusal ($n = 5$), adverse event ($n = 3$), intercurrent death ($n = 1$), and earthquake ($n = 1$).

Three treatment-related deaths (TRDs) were reported: interstitial lung disease (judged as a *probable* TRD by the Data and Safety Monitoring Committee), DIC due to infection (judged as a possible TRD), and a recurrent pulmonary embolism (judged as a possible TRD). The first 2 patients listed above were aged ≥65 years.

For etoposide, a median total dose, median dose intensity, and median relative dose intensity were 2852.3 mg/m^2, 179.3 mg/m^2/week, and 88.9%, respectively. For irinotecan, the median total dose, median dose intensity, and median relative dose intensity were 452.8 mg/m^2, 30.7 mg/m^2/week, and 88.0%, respectively.

Table 1
Patient characteristics.

Characteristics		Number of patients (%)	Median	Range
Age, years			58	31–75
	<65	46 (77)		
	≥65	14 (23)		
PS	0	51 (85)		
	1	8 (13)		
	2	1 (2)		
Histology	Serous	39 (65)		
	(LGS)	2 (5)		
	Clear cell	11 (18)		
	Endometrioid	5 (8)		
	Other	5 (8)		
Lesion	Measurable	52 (87)		
	Non-measurable	8 (13)		
Prior chemo regimens	1	34 (57)		
	2	17 (28)		
	≥3	9 (15)		
PFI	<3 months	27 (45)		
	≥3 months	33 (55)		

Abbreviations. PS: performance status, PFI: platinum-free interval, chemo: chemotherapy, LGS: low grade serous.

Toxicity

Toxicities are summarized in Table 2. Only treatment-related adverse events (definite, probable, or possible) were counted as toxicities. Grades 3–4 hematological toxicities were: neutropenia (60%), anemia (36.7%), and thrombocytopenia (11.7%). Grades 3–4 non-hematological toxicities were: febrile neutropenia (FN; 18.3%), fatigue (11.7%), anorexia (11.7%), and nausea (11.7%). FN was more frequent in patients aged ≥65 years (28.6%) or those with ≥3 prior chemotherapy regimens (44.4%) compared with patients aged <65 years (15.2%) or those with 1 or 2 prior chemotherapy regimens (13.7%). One patient was diagnosed with acute myeloid leukemia 234 days after completing 6 cycles of the present regimen. She received carboplatin plus paclitaxel for 6 cycles and PLD for 6 cycles before the study entry, and gemcitabine for 3 cycles after this regimen.

Efficacy

One patient achieved CR and 12 patients achieved PR (Table 3); accordingly, RR was 21.7% (13/60) [design-based 89% confidence interval (CI) 13.5–31.9%; 95% CI 12.1–34.2%]. This RR did not exceed the preplanned threshold (one-sided $p = 0.42$ by the exact binomial test for the null hypothesis that RR ≤20%). RR was 30.3% (10/33) in patients with PFI of ≥3 months, while it was 11.1% (3/27) in patients

Table 2
Grade 3/4 toxicities affecting >5% of the patients.

	G1	G2	G3	G4	% G3–4
Leukopenia	7	17	26	10	60
Anemia	7	29	12	10	36.7
Thrombocytopenia	4	2	5	2	11.7
Neutropenia	7	17	15	21	60
Hypoalbuminemia	30	11	5	–	8.3
Hyponatremia	13	–	4	0	6.7
Hypokalemia	18	–	1	3	6.7
Febrile neutropenia	–	–	11	0	18.3
Fatigue	23	9	7	0	11.7
Anorexia	23	13	7	0	11.7
Nausea	20	15	7	0	11.7
Vomiting	13	8	4	0	6.7
Diarrhea	14	4	3	0	5

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with PFI of <3 months (Fisher's exact test, p = 0.12). RR was 26.5% (13/49) in patients with a non-clear cell histology, while it was 0% (0/11) in patients with a clear cell histology (p = 0.10). Age and the number of prior chemotherapy regimens did not seem to affect RR (21.7 (10/46), 21.4 (3/14), 23.5 (12/51), and 11.1 (1/9) % in young patients, elderly patients (p = 1.00), patients received <3 prior regimen, and patients received ≥3 prior chemotherapy regimens (p = 0.67), respectively).

Median PFS was 4.1 months (95% CI 3.5–4.9 months), and 33.3% of patients (95% CI 21.8–45.2%) survived without progression at 6 months (Fig. 1A). Median PFS was 5.6 months in patients with PFI of ≥3 months, while it was 3.6 months in patients with PFI of <3 months (Fig. 1B). Median PFS was 4.3 months in patients with a non-clear cell histology, while it was 3.6 months in patients with a clear cell histology.

One patient was progression-free at last follow-up (PFS, >1221 days). She was diagnosed with stage 3c ovarian serous adenocarcinoma and was treated with carboplatin plus paclitaxel for 5 cycles. After 16.6 months, she had a recurrent tumor and received carboplatin plus docetaxel for 5 cycles. After 1 month, she experienced platinum-resistant recurrence and was treated with the present regimen; she showed CR.

Median OS was 11.9 months (95% CI 9.4–14.6 m) (Fig. 2A). Median OS was 16.9 months in patients with PFI of ≥3 months, while it was 8.1 months in patients with PFI of <3 months (Fig. 2B). Median OS was 12.4 months in patients with a non-clear cell histology, while it was 10.4 months in patients with a clear cell histology.

Discussion

This is the first phase II trial evaluating this combination regimen in patients with platinum-resistant ovarian cancer. This study demonstrates that the combination of oral etoposide and intravenous irinotecan has moderate efficacy in patients with platinum-resistant ovarian cancer. The overall RR was 21.7%. Disappointingly, this result does not meet the preplanned criteria for proceeding to a further phase III trial.

Preceding randomized controlled trials of combination chemotherapy against platinum-resistant ovarian cancer are summarized in Table 4. As for efficacy, our study shows a better RR, including CR lasting more than 3 years, compared with OVATURE [22], OVA301 [23] and ASSIST-5 studies [24], although PFS is in the same range. The CARTAXHY trial [25] shows a better RR and PFS compared with other studies, even in a paclitaxel single-agent arm. Nonetheless, this efficacy may not be reproduced in Japan, because weekly paclitaxel has already been adopted as a component of first-line treatment according to the results of JGOG3016 [2]. In addition, an Italian collaborative phase 3 study comparing epidoxorubicine plus paclitaxel with paclitaxel alone for patients with PFI ≤12 months, did not prove the efficacy of cytotoxic doublets in terms of neither PFS nor OS [26]. All these preceding studies concluded that combination chemotherapy utilizing two cytotoxic agents is not effective strategy. Combination chemotherapy utilizing one cytotoxic agent with one biologic agent is a promising strategy. AURELIA [27] has proved the efficacy of bevacizumab for patients with platinum resistant ovarian cancer, showing almost doubled RR and PFS, comparing with monotherapy such as weekly paclitaxel, PLD, or topotecan. Another study, TRINOVA-1 [28], also proved the efficacy of trebananib for patients with PFI ≤12 months.

Table 3
Overall response.

	RECIST (%)	CA-125 (%)	Total (%)
CR	1 (2)	–	1 (2)
PR	10 (19)	2 (25)	12 (20)
SD	21 (40)	2 (25)	23 (38)
PD	16 (31)	4 (50)	20 (33)
NE	4 (8)	0 (0)	4 (7)
Total	52	8	60

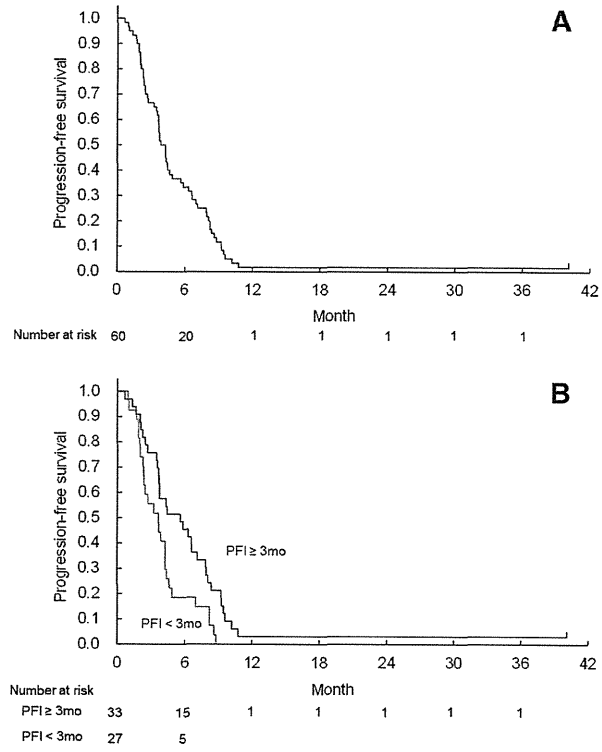

Fig. 1. A depicts PFS of all the patients. B depicts PFS by PFI <3 m (pink curve) or ≥3 m (blue curve). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

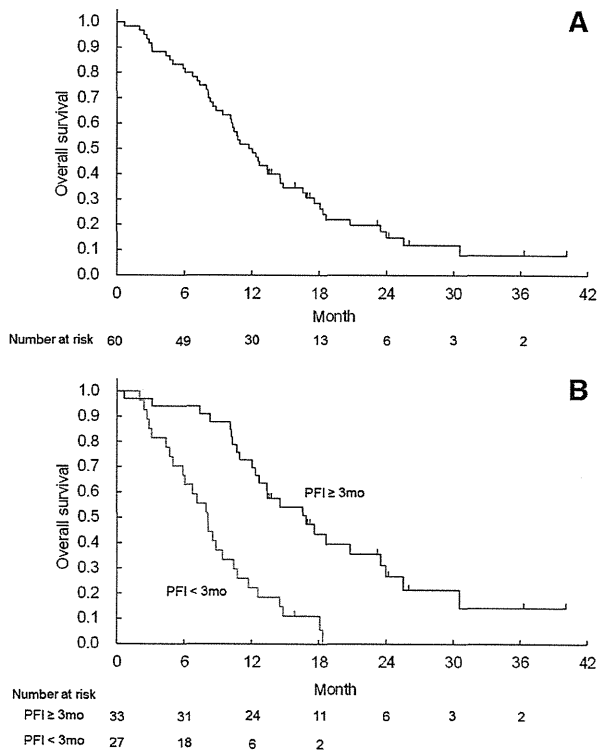

Fig. 2. A depicts OS of the patients. B depicts OS by PFI <3 m (pink curve) or ≥3 m (blue curve). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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