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Weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer: a preliminary study

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Abstract
Background. The aim of this study was to evaluate the toxicity and efficacy of weekly paclitaxel in patients with recurrent endometrial cancer.
Methods. Nine patients with recurrent endometrial cancer who had previously received chemotherapy or radiotherapy participated in the study, between May 1999 and August 2001. Paclitaxel was given at a dose of 70 mg/m^2 as a 1-h infusion every week for at least 20 consecutive weeks unless lesions became progressive. Intravenous dexamethasone and cimetidine and oral diphenhydramine were administered 30 min before paclitaxel infusion.
Results. The nine patients received a total of 149 cycles of therapy. No hypersensitivity reactions were elicited. Grade 3 leukopenia, neutropenia, and anemia occurred in 22%, 33%, and 33% of the patients, respectively. Granulocyte colony-stimulating factor was required for two patients and no patients experienced febrile neutropenia. Neurotoxicity was commonly observed. Grade 1 peripheral neuropathy and myalgias were observed in 78% and 11% of the patients, respectively. No grade 3 or higher nonhematological toxicities were observed. Partial responses were seen in six of the nine patients (67%). The median progression-free interval was 8 months (range, 0–12 months) and the median overall survival was 10 months (range, 4–24 months).
Conclusion. Weekly 1-h paclitaxel administration is considered safe and effective as a salvage therapy for recurrent endometrial cancer, with this schedule and delivery making its use more convenient and easier in the outpatient setting. The current results support further evaluation.

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Introduction

Endometrial cancer is one of the common gynecologic malignancies. Nearly 80% of the patients have disease confined to the uterus at diagnosis and have a good prognosis.[1] For patients with risk factors for recurrence, postoperative radiotherapy and/or chemotherapy is generally given. Patients with recurrent or advanced disease, however, will rarely be cured with second-line treatment. Cisplatin and doxorubicin have been effective for advanced and recurrent endometrial cancer, respectively, and the combination of cisplatin and doxorubicin with or without cyclophosphamide (AP or CAP) has been considered to be an adjuvant or salvage regimen.[2–5] One possible way to decrease the toxicity of treatment without compromising efficacy is to give lower doses more frequently.

Recently, paclitaxel (Taxol; Bristol Myers Squibb, Princeton, NJ, USA) has also been used as an active agent against endometrial cancer.[6–8] Clinical trials of the drug have been performed with different administration schedules of 1 to 3-h and 24-h infusions, with doses ranging from 135 to 250 mg/m^2, every 3 weeks.[9–13] These trials suggested that the observed toxicity profile seemed to depend on dose and schedule. Therefore, the efficacy of shorter infusion schedules of paclitaxel (TXL) has been investigated, and some phase I/II studies have reported that 1-h infusion of TXL at doses of 60 to 90 mg/m^2 weekly yielded low toxicity profiles.[14–19] The decreased leukocyte toxicity associated with short infusion times allows for reduced intertreatment periods, from the standard 3-week to a 1-week interval. Moreover, the response rate with weekly TXL administration appears to be comparable to that of the 3-week schedule.[14–19]

This short-infusion time weekly strategy supports more frequent and prolonged formation of stable cellular microtubules with subsequent mitotic arrest, which forms the pharmacological basis for TXL's antitumor activity.

This preliminary study was carried out to evaluate the safety and efficacy of weekly TXL administration by 1-h infusion for recurrent endometrial cancer, in the outpatient setting.

Patients and methods

Patients with recurrent endometrial cancer that developed after chemotherapy and/or radiotherapy were eligible for the preliminary study. All patients had at least one measurable lesion which had been documented radiographically. The eligibility criteria were as follows: performance status (PS; World Health Organization; WHO), less than 2, good general health with no history of cardiac disorder or congestive heart failure, and an expected survival of least 3 months. Before patients received treatment, laboratory tests showed that all patients conformed to the following criteria: white blood cell count, 4000–12 000/μl; platelet count, more than 100 000/μl; hemoglobin, more than 9.5 g/dl; aspartate amino-transferase (AST) and alanine amino transferase (ALT), less than twice the normal upper limit; total serum bilirubin, less than 1.5 mg/dl; serum creatinine, less than 1.5 mg/dl; creatinine clearance, more than 60 mg/min; and blood urea nitrogen (BUN), less than 25 mg/dl.

This study was approved by the Ethics Committee of Kurume University School of Medicine, and all patients signed an informed consent document that described the investigational nature of the proposed treatment.

The treatment schedule was designed on the basis of previous reports describing weekly administrations of TXL.[14–19] Chemotherapy consisted of TXL (70 mg/m^2) in 250 ml of 5% glucose, given in 1-h infusions. Infusions were repeated each week with no planned pause during the treatment period of at least 20 weeks, unless progressive disease was detected or intolerable nonhematological toxicity was observed. All patients were premedicated with dexamethasone (10 mg) i.v., cimetidine (50 mg) i.v., and diphenhydramine (50 mg) orally, 30 min prior to each weekly administration.[20]

All patients were treated on an outpatient basis unless they had been hospitalized for other reasons before TXL therapy was initiated. A physician was present during the first 15 min of therapy. Blood pressure was monitored after the first 15 min of infusion.

Total blood cell counts were examined at least twice weekly and serum chemistry and liver function tests were monitored weekly. Before the next cycle was initiated, leukocyte counts were confirmed to be more than 2000/μl and platelets more than 100 000/μl, with liver and renal functions within the eligibility criteria. No premedication was given for neutropenia. Patients were evaluated for response to treatment. Patients who progressed were considered treatment failures and the therapy was stopped. Those with stable disease or objective tumor responses continued the therapy.

Toxicity evaluations were based on WHO criteria. Although the determination of antitumor activity was not the primary objective of this study, all patients were assessed for responses by computed tomography and/or ultrasonography at least every four to six cycles.

The criteria for tumor responses were as follows: complete response (CR) was defined as the complete disappearance of all known disease for a minimum of 4 weeks; partial response (PR) was defined as a more than 50% reduction in the sum of the length-width products of measurable lesions for a minimum of 4 weeks; progressive disease (PD) was defined as a more than 25% increase in the sum of products of all indicator lesions, reappearance of any lesion that had disappeared, or appearance of any new lesion; and stable disease (SD) was defined as any situation that did not qualify as a response or progression. The time to response was recorded from the beginning of treatment until the first objective response was detected. The progression-free interval was determined from the first cycle of treatment until PD was elicited.

Results

The patients' characteristics are listed in Table 1. Between May 1999 and August 2001, nine patients entered the study. The median age was 68 years (range, 40–79 years) and the median performance status was 1 (range, 0–2). Seven of the

Table 1. Patients' characteristics (n = 9)

No. of patients	Primary stage (FIGO)	Histology	PS (WHO)	Measurable lesions	Postoperative treatment	Treatment-free interval (months)
1	Ic	Endometrioid (G1)	0	Lung	Radiotherapy	12
2	Ic	Endometrioid (G2)	0	Lung	CAP	63
3	Ic	Endometrioid (G3)	0	Lung	CAP	11
4	IIb	Endometrioid (G3)	0	Lung, pelvic cavity	CAP, 5-FU	21
5	IIIa	Endometrioid (G1)	1	Lung	Radiotherapy	160
6	IIIa	Endometrioid (G3)	1	Lung, pelvic cavity	AP, CDDP	4
7	IIIa	Endometrioid (G3)	0	Pelvic cavity	AP, CDDP	7
8	IIIc	Endometrioid (G2)	2	Lung, pelvic cavity	CAP	38
9	IIIc	Endometrioid (G2)	2	Pelvic cavity	AP, CBDCA	35

PS, Performance status; FIGO, International Federation of Gynecology and Obstertrics; WHO, World Health Organization; CAP, cyclophosphamide, doxorubicin, cisplatin; AP, doxorubicin, cisplatin; CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil

nine patients had previously received heavy treatment with one or more platinum-based chemotherapies, and two of the patients had undergone radiotherapy. The nine patients received a total of 149 cycles of therapy, with an average of 16.6 cycles (range, 4–30 cycles) per patient. All patients received 70 mg/m^2 per week. One of the nine patients had a treatment delay. The median duration of the treatment-free interval was 21 months (range, 14–160 months). All patients were evaluated for toxicity and response.

Toxicity

No treatment–related deaths occurred in this study. Table 2 lists the nonhematological toxicities encountered during treatment. No hypersensitivity reactions to TXL were exhibited. Neurotoxicity was commonly observed. Grade 1 peripheral neuropathy and myalgias were observed in 78% and 11% of the patients, respectively. Nausea/emesis, diarrhea, and mucositis were uncommon, and none of the patients needed antiemetic support. Alopecia was of moderate intensity. Although significant nail discoloration and onychorrexis were noted in one patient after the tenth cycle of TXL, the nails grew back completely after completion of the treatment.

Table 3 shows the hematological toxicities manifested in the patients. Myelosuppression was commonly observed, but was mild to moderate in most patients. Grade 3 leukopenia and neutropenia occurred in two (22%) and three (33%) of the patients, respectively, and there were no episodes of febrile neutropenia. Granulocyte colony-stimulating factor (G-CSF) was required for two patients. Thrombocytopenia was not observed. Grade 3 anemia was noted in three patients (33%), but they did not require red blood cell transfusion. There was no evidence or cumulative hematological toxicity.

Response

Table 4 lists the response to weekly TXL in the patients. The clinical response rate was 67%, with six partial responses (67%). Stable disease was seen in one patient (11%) and the remaining two (22%) manifested PD. The median progression-free interval was 8 months (range, 0–12 months) and the median overall survival was 10 months (range, 4–24 months).

Table 2. Nonhematologic toxicity (per patient; $n = 9$)

Toxicities	Grade (WHO)				
	0	1	2	3	4
Peripheral neuropathy	0	9	0	0	0
Myalgias	8	1	0	0	0
Fatigue/weakness	7	2	0	0	0
Alopecia	0	6	3	–	–
Nausea/emesis	9	0	0	0	–
Diarrhea	9	0	0	0	0

Discussion

Single-agent (such as cisplatin or doxorubicin) and combination chemotherapy regimens (AP or CAP) are associated with substantial response rates in patients with metastatic or recurrent endometrial cancer, but the responses have not been durable and appear to have little impact on survival.[2–5] Because treatment for patients with recurrent

Table 3. Hematologic toxicity (per patient; $n = 9$)

Toxicities	Grade					≥Grade 3	
	0	1	2	3	4	No. of patients	Percentage
Leukopenia	3	1	3	2	0	2	22
Neutropenia	3	2	1	3	0	3	33
Thrombocytopenia	9	0	0	0	0	0	0
Anemia	1	4	1	3	0	3	33

Table 4. Response to weekly paclitaxel

No. of patients	No. of cycles	Response	Progression-free interval (months)
1	20	PR	5+
2	12	PR	4
3	20	PR	9+
4	30	SD	12
5	20	PR	8
6	14	PR	9
7	24	PR	8+
8	5	PD	0
9	4	PD	0

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease

gynecological tumors is mostly palliative, it is very important to maintain good quality of life (QOL) during the treatment period. Three phase II studies of TXL in advanced or recurrent endometrial cancer have shown overall response rates of up to 30%.[6–8] Lissoni et al.[8] reported that TXL was active in patients with endometrial cancer pretreated with CAP. Woo et al.[7] reported that TXL had activity for platinum-resistant endometrial cancer.

The choice of a second-line drug in this situation is dependent on toxicity and QOL considerations, in addition to efficacy. Weekly administration of TXL by 1-h infusion has been reported to have less toxicity than other schedules and a promising effect in patients with pretreated gynecological cancers.[14–18] Greco and Hainsworth[12] demonstrated that the 1-h infusion schedule was feasible. Actually, the 1-h weekly infusion of TXL seems to have promising activity in a variety of pretreated solid tumors, including those of recurrent ovarian cancer.[11,14] Using this 1-h infusion, we can anticipate the advantage of the limited hematologic toxicity associated with the shorter TXL infusion schedule, and the use of a weekly schedule will increase the intensity of TXL exposure. Previous reports have demonstrated that weekly i.v. TXL administration in a 1-h infusion at doses of 60–90 mg/m^2 is an acceptable salvage regimen.[14–18] In the present study, we administered 70 mg/m^2 of TXL without dose escalation in order to maintain dose density and to avoid adverse effects. All patients underwent this therapy. One patient suffered treatment delays due to neutropenia. Grade 3 or higher neutropenia was observed in 33% of patients, and two patients with grade 3 neutropenia required G-CSF support for long-term neutropenia (2 weeks).

Hematologic toxicity was uncommon and mild with the weekly administration of TXL 70 mg/m^2, despite the fact that the overall dose intensity was increased compared with standard TXL treatment at 175 mg/m^2 every 3 weeks. The intravenous premedication given immediately before TXL administration was effective in preventing hypersensitivity reactions.

In conclusion, weekly 1-h TXL administration is considered safe and effective as a salvage therapy for endometrial cancer. This low toxicity profile and the short duration of therapy is advantageous for outpatient treatment and is favorable for maintaining or improving the patient's quality of life during treatment.

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