A pilot study of weekly docetaxel therapy for recurrent ovarian cancer, tubal cancer, and primary peritoneal cancer

S. Komiyama, *M.D.*; **H. Tsuji,** *M.D.*; **S. Asai,** *M.D.*; **J. Dokoh,** *M.D.*; **M. Ishikawa,** *M.D.*; **M. Mikami,** *M.D.*

Department of Obstetrics and Gynecology, National Saitama Hospital, Wako-shi, Saitama (Japan)

Summary

We investigated the efficacy and toxicity of salvage chemotherapy with weekly docetaxel for recurrent ovarian cancer, tubal cancer, and primary peritoneal cancer after treatment with regimens containing platinum or paclitaxel. The 15 subjects were managed as outpatients and received at least two courses of docetaxel therapy (35 mg/m^2 on days 1, 8 and 15). Antitumour activity was assessed radiologically and from the CA-125 level. Among five patients with measurable lesions, one showed partial remission and three showed stable disease. Based on CA-125 levels, there were three partial remissions and five patients with stable disease (progression-free survival was 7.5 months and 7.6 months, respectively). During 61 courses, the severe toxicities were grade 3 leukopaenia/neutropaenia (6.7%) or grade 2 oedema and pleural effusion (13.3%). Weekly docetaxel may be useful salvage chemotherapy for recurrent ovarian cancer, tubal cancer, and peritoneal cancer, especially as tumour dormancy therapy.

Key words: Ovarian cancer; Tubal cancer; Primary peritoneal cancer; Salvage chemotherapy; Weekly docetaxel therapy.

Introduction

In general, the treatment of advanced epithelial ovarian cancer, tubal cancer, and primary peritoneal cancer involves either radical surgery or a multidisciplinary approach (tumour debulking combined with chemotherapy). First-line chemotherapy regimens often comprise a taxane such as paclitaxel and a platinum compound such as carboplatin. Even if remission is achieved after adequate tumour debulking and chemotherapy, approximately 70% of patients suffer from recurrence within two years [1]. Treatment options for recurrent tumours include further debulking surgery or chemotherapy, with the latter being chosen more often. However, there is no gold standard for salvage chemotherapy, and the choice of regimen is made more difficult by problems such as cumulative toxicities and the development of drug resistance.

In recent years, the efficacy of weekly administration of taxanes for various recurrent solid tumours has been reported [2-9]. We previously reported a patient with advanced ovarian cancer (Stage IIIc serous adenocarcinoma), in whom remission was initially achieved with paclitaxel plus carboplatin and recurrence was treated with irinotecan, again achieving remission. However, further recurrence occurred, so paclitaxel and carboplatin were administered, but without success. Salvage chemotherapy with weekly docetaxel was then performed and progression-free survival was obtained for seven months [10]. Because toxicity was extremely mild, treatment could be administered on an outpatient basis and the patient was able to maintain a good quality of life. As far as we know, this was the first report to indicate the efficacy of weekly docetaxel for the treatment of ovarian cancer.

Based on this experience, we conducted an exploratory study of the efficacy of weekly docetaxel salvage chemotherapy for recurrent ovarian cancer, tubal cancer, and primary peritoneal cancer in patients who had been previously treated with platinum or paclitaxel.

Materials and Methods

The subjects were patients with recurrent epithelial ovarian cancer, recurrent tubal cancer, and recurrent primary peritoneal cancer who had finished prior therapy at least four weeks earlier and who gave informed consent. Recurrence was defined as either the detection or progression of radiographically measurable lesions, the development or exacerbation of carcinomatous peritonitis, or a serum CA-125 level greater than twice the baseline level for at least four weeks. The enrollment criteria for this study were as follows: a definitive tissue diagnosis, age between 20 and 75 years, performance status of 0-2 (according to Eastern Cooperative Oncology Group (ECOG) criteria [11]); neutrophil count > 2,000/mm^3, haemoglobin > 9.5 g/dl, platelet count > 100,000/mm^3, serum bilirubin < 1.5 mg/dl, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than 1.5 times the institutional reference values, serum creatinine < 1.5 mg/dl; and predicted survival of at least three months. The exclusion criteria were as follows: borderline malignancy, active infection, psychiatric disorders, poorly controlled hypertension or diabetes, a history of drug hypersensitivity, and a history of interstitial pneumonia.

To improve the quality of life, all patients were given chemotherapy on an outpatient basis. Dexamethasone was administered as premedication to prevent hypersensitivity reactions and fluid retention. A dose of 8 mg was dissolved in 100 ml of physiological saline and was infused intravenously over 30 minutes. Then docetaxel (35 mg/m^2) was dissolved in 200 ml of physiological saline and infused intravenously over one hour. In each course, these drugs were administered on days 1, 8, and

Revised manuscript accepted for publication December, 2004

15, followed by one week-off therapy. Each subject received at least two courses. Antinausea agents (such as serotonin receptor antagonists) or granulocyte-colony stimulating factor (G-CSF) were not administered prophylactically. If patients did not meet the haematological criteria (neutrophil count > 2,000/mm^3 and platelet count > 100,000/mm^3) before a scheduled dose or if a non-haematological adverse event of grade 2 or higher occurred, that dose was skipped. If there was no recovery after two doses had been skipped, treatment was cancelled. Treatment was also cancelled if there was obvious disease progression or if the patient requested it.

Antitumour activity was assessed by measuring the serum CA-125 level and by performing computed tomography (CT) or magnetic resonance imaging (MRI) after each course. Serum CA-125 levels were used to evaluate tumour response based on the criteria of Rustin *et al.* [12] and Goff *et al.* [13]. Complete response (CR) was defined as normalisation of a previously elevated CA-125 level for four weeks, while partial response (PR) meant a 50% or greater reduction of CA-125 from baseline for at least four weeks. Progressive disease (PD) was defined as a 50% or greater increase of CA-125 from baseline, while stable disease (SD) was any outcome that did not fit into the above categories. Evaluation of radiological findings was based on the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines [14]. Toxicity was evaluated after each course using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [15].

Results

The clinical characteristics of the 15 enrolled patients are displayed in Table 1. Each patient had received cytoreductive surgery and various prior chemotherapy regimens, including paclitaxel/carboplatin, paclitaxel/cisplatin, irinotecan/cisplatin, cyclophosphamide/doxorubicin/cisplatin, irinotecan (single agent), and oral etoposide (single agent).

Table 1. — *Clinical characteristics of the patients.*

No. of patients	15
Mean age (range)	59.3 (42-69)
Mean follow-up in months (range)	14.1 (3-26)
ECOG performance status	
0	7
1	6
2	2
Diagnosis	
epithelial ovarian cancer	11
tubal cancer	2
primary peritoneal cancer	2
FIGO stage	
IIIc	12
IV	3
Histology	
serous	15
Site of recurrence	
pelvis	1
abdomen	3
lung	1
unclear	10
Prior chemotherapy (No. of regimens)	
1	4
2	5
≥ 3	6
Prior chemotherapy with platinum/paclitaxel	
< 6 months	6
≥ 6 months	9
Pretreatment serum CA-125 (IU/ml)	215 ± 365.7

When the five patients with radiographically measurable disease were evaluated by RECIST guidelines, one showed PR, three showed SD, and one showed PD. The progression-free survival time was seven months in the patient with PR. This patient had a tumour that was resistant to platinum and paclixatel (defined as recurrence within six months of prior therapy or relapse during treatment with platinum or paclixatel). Among the three patients with SD, one had a tumour that was resistant to platinum or paclixatel.

Evaluation using CA-125 showed three patients with PR, five with SD, and seven with PD. Two of the patients with PR and three with SD had tumours that were sensitive to platinum or paclixatel. Both patients with PR and three of those with SD were heavily treated (≥ 2 prior regimens). The progression-free survival time of the PR and SD patients was 7.5 months (range: 7-8 months) and 7.6 months (range: 3-16 months), respectively, whereas the overall survival time was 13.5 months (range: 8-19 months) and 14.3 months (range: 11-20 months).

During a total of 61 courses, the only haematological toxicities of grade 3 or higher were one case each (6.7%) of leukopaenia and neutropaenia (both grade 3 and in the same subject). There were no cases of grade 3 or 4 anaemia or thrombocytopaenia. The non-haematological toxicities of grade 2 or higher were 2 cases (13.3%) each of pleural effusion and oedema (both grade 2). When pleural effusion occurred, treatment was ceased and further investigations were performed. The onset of pleural effusion was noted when the cumulative dose of docetaxel had reached 600 mg in one patient and 840 mg in the other. In both patients, no accumulation of fluid or oedema was seen elsewhere, but investigations confirmed that the pleural effusion was a transudate rather than a malignant exudative effusion. After drainage and two months of furosemide therapy (40 mg/day), the pleural effusion resolved completely in one patient. In the other patient, it resolved after simple observation for three months. Other non-haematological toxicities were all grade 1, being nail changes in four patients (26.7%) and salivary gland changes in three patients (20.0%) (Table 2).

The outcome of weekly docetaxel therapy was death from progressive cancer in nine patients, while six patients remained alive with disease. Among the survivors, treatment was ceased for reasons other than adverse drug reactions, except in the two patients with pleural effusions. In four patients, weekly docetaxel therapy was ceased in order to recommence paclitaxel and carboplatin chemotherapy with the aim of inducing remission, and one patient went off docetaxel to allow further tumour debulking surgery. Of the two patients who developed pleural effusions, one remains alive without further treatment, whereas the other showed tumour progression two months after the cessation of treatment and then died.

Table 2. — *Haematological and non-haematological toxicities (no. of patients).*

Toxicity	Grade			
	1	2	3	4
Leukopaenia	2	2	1	0
Neutropaenia	2	2	1	0
Febrile neutropaenia	0	0	0	0
Anaemia	3	1	0	0
Thrombocytopaenia	0	0	0	0
Nausea and vomiting	1	0	0	0
Alopecia	1	0	0	0
Nail changes	4	0	0	0
Sensory neuropathy	1	0	0	0
Salivary gland changes	3	0	0	0
Fatigue	2	0	0	0
Oedema	1	2	0	0
Pleural effusion	0	2	0	0

Discussion

Epithelial ovarian cancer, tubal cancer, and primary peritoneal cancer are often detected at an advanced stage, so even if remission is achieved by debulking surgery and chemotherapy with a taxane plus platinum regimen, effective salvage chemotherapy is still required to improve the long-term prognosis after recurrence. A variety of agents, methods of administration, and regimens have been tried so far, but progression-free survival generally remains at only six to eight months. Because of severe side-effects and difficulty in compliance, some of the reported regimens are very burdensome for patients. If the cancer is thought to be incurable, we are obliged to not only consider the potential success rate of a new regimen, but also how tolerable it will be, how long it can be continued, and how long a relatively normal lifestyle can be maintained. In recent years, chemotherapy regimens that aim at achieving tumour stabilisation (dormancy) have attracted attention, and the demand has also increased for treatments that can handle recurrence and relapse of solid cancer or advanced cancer when curative surgery is impossible. Such regimens attempt to maintain stable disease for a prolonged period so that further attempts to induce remission can be tried or so that long-term survival can be obtained despite persistence of the cancer [7-9]. This type of therapy is also needed for recurrent ovarian cancer, tubal cancer, and primary peritoneal cancer because cure is often impossible [12].

Similar to paclitaxel, docetaxel is a taxane antineoplastic agent that promotes the assembly of tubulin into stable microtubules during cell division and inhibits disassembly, arresting the cell cycle in the G2/M phase secondary to a marked decrease of free tubulin. Docetaxel has been reported to be active against 23% of paclitaxel-resistant mullerian carcinomas (a combined term for ovarian cancer, tubal cancer, and primary peritoneal cancer), suggesting that it may be useful as second-line chemotherapy in patients who have received treatment with paclitaxel, and also that cross-resistance between these two agents may only be partial [16]. In recent years, weekly taxane therapy has been used to improve the ease of administration, increase the dose intensity, and reduce adverse reactions, and it has been reported to be effective by a number of authors, combining a good quality of life with some toxicity [2-9].

We were unable to find any reports on weekly docetaxel therapy for ovarian cancer, tubal cancer, and primary peritoneal cancer apart from our own case report. Normally, a phase I study should be conducted to determine the optimum dosage, but the recommended weekly dosage of docetaxel for breast, lung, and stomach cancer is 35-40 mg/m^2 [4, 6, 22], so we used the lower end of this range for our study. Despite a high percentage (60.0%) of platinum or paclitaxel-sensitive tumours in the present patients, progression-free survival was 7.5 months when PR was achieved, and 7.6 months in those with SD. These results suggest that weekly docetaxel is a useful regimen for stabilising cancer. Among the six patients who had tumours resistant to platinum or paclitaxel, PR was achieved in one and SD in two. Also, among the 11 heavily treated patients ($\geq$ 2 prior regimens), PR was achieved in two and SD in two. These PR and SD patients subsequently underwent further chemotherapy with paclitaxel and carboplatin to induce remission or had further debulking surgery, which considerably prolonged their survival (overall survival was 13.5 months for the PR patients and 14.3 months for the SD patients). Such results indicate that weekly docetaxel may be useful for maintaining tumour stability, allowing less mentally and physically taxing treatment during long-term therapy, and also allowing a platinum-free interval. The toxicities of this regimen were generally acceptable, and there were no problems with neutropenia, which is the most important dose-limiting toxicity of docetaxel. Treatment was administered on an outpatient basis to all patients, allowing them to continue work and normal social activities, thus maintaining a high quality of life.

Because this was a small study, further investigation of the regimen in a larger number of subjects is needed. We have not established whether conventional therapy (triweekly administration) or weekly administration is more appropriate, and our evaluation of efficacy, quality of life, and toxicity was not rigorous. Comparative trials will need to be conducted to clarify these points.

Toxicities of docetaxel such as oedema and nail changes are known to occur in proportion to the cumulative total dosage [5, 8]. Oedema showed a low incidence in this study. When pleural effusion is detected in a patient with recurrent cancer, it is important to determine whether it is caused by tumour progression with intrathoracic metastasis. Cytology of fluid obtained at thoracentesis or histological examination of pleural biopsy specimens and biochemical testing of the drain fluid should be performed to exclude malignant pleural effusion and confirm that it is a transudate. In our experience, the pleural effusion resolved after several months of observation in one patient, but furosemide (40 mg daily) was needed in the other. Both effusions occurred despite adequate pretreatment with dexamethasone, so if weekly

docetaxel therapy is continued for a long period, patients must be observed carefully to avoid the development of irreversible toxicity and modifications to the prophylactic dexamethasone regimen may also be necessary.

At present, chemotherapy regimens containing paclitaxel and carboplatin are firmly established as first-line therapy for ovarian cancer, tubal cancer, and primary peritoneal cancer, but the best salvage chemotherapy for recurrent disease is far from clear. Our findings suggest that weekly docetaxel can be considered as salvage therapy, and this regimen merits further studies to confirm its usefulness.

References

[1] Ozols R.F., Bundy B.N., Greer B.E. *et al.*: "Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study". *J. Clin. Oncol.,* 2003, *21*, 3194.

[2] Hainsworth J.D., Burris H.A. 3rd, Erland J.B. *et al.*: "Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer". *J. Clin. Oncol.,* 1998, *16,* 2164.

[3] Loffer T.M., Freund W., Droge C. *et al.*: "Activity of weekly Taxotere in patients with metastatic breast cancer" (abstract). *Proc. Am. Soc. Clin. Oncol.*, 1998, *17,* 113a .

[4] Akerley W., Glantz M., Choy H. *et al.*: "Phase I trial of weekly paclitaxel in advanced lung cancer". *J. Clin. Oncol.,* 1998, *16,* 153.

[5] Briasoulis E., Karavasilis V., Anastasopoulos D. *et al.*: "Weekly docetaxel in minimally pretreated cancer patients: A dose escalation study focused on feasibility and cumulative toxicity of long term administration". *Ann. Oncol.,* 1999, *10,* 701.

[6] Kouroussis C., Agelaki D., Mavroudis D. *et al.*: "A dose escalation study of weekly docetaxel in patients with advanced solid tumors". *Cancer Chemother. Pharmacol.,* 2000, *46,* 488.

[7] Hainsworth J.D., Burris H.A. 3rd, Litchy S. *et al.*: "Weekly docetaxel in the treatment of elderly patients with advanced non-small cell lung carcinoma: A Minnie Pearl Cancer Research Network phase II trial". *Cancer,* 2000, *89*, 328.

[8] Burstein H.J., Manola J., Younger J. *et al.*: "Docetaxel administered on a weekly basis for metastatic breast cancer". *J. Clin. Oncol.,* 2000, *18,* 1212.

[9] Hainsworth J.D., Burris H.A. 3rd, Yardley D.A. *et al.*: "Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: A Minnie Pearl Cancer Research Network phase II trial". *J. Clin. Oncol.,* 2001, *19,* 3500.

[10] Komiyama S., Mizusawa Y., Onouchi M., Takehara K., Suzuki A., Mikami M.: "Effective weekly docetaxel for recurrent ovarian cancer: A case report". *Int. J. Gynecol. Cancer,* 2003, *13,* 683.

[11] Oken M.M., Creech R.H., Tormey D.C. *et al.*: "Toxicity and response criteria of the Eastern Cooperative Oncology Group". *Am. J. Clin. Oncol.,* 1982, *5*, 49.

[12] Rustin G.J., Nelstrop A.E., Crawford M. *et al.*: "Phase II trial of oral altretamine for relapsed ovarian carcinoma: evaluation of defining response by serum CA125". *J. Clin. Oncol.*, 1997, *5,* 172.

[13] Goff B.A., Thompson T., Greer B.E. *et al.*: "Treatment of recurrent platinum resistant ovarian or peritoneal cancer with gemcitabine and doxorubicin: A phase I/II trial of the Puget Sound Oncology Consortium (PSOC 1602)". *Am. J. Obstet. Gynecol.,* 2003, *188,* 1556.

[14] Therasse P., Arbuck S.G., Eisenhauer E.A. *et al.*: "New guideline to evaluate the response to treatment in solid tumors". *J. Natl. Cancer Inst.*, 2000, *92,* 205.

[15] National Cancer Institute common toxicity criteria, Version 2.0 Revised March 23, 1998, http://ctep.info.nih.gov/CTC3/default.htm.

[16] Verschraegen C.F., Sittisomwong T., Kudelka A.P. *et al.*: "Docetaxel for patients with paclitaxel-resistant Mullerian carcinoma". *J. Clin. Oncol.,* 2000, *14,* 2733.

Address reprint requests to:
S. KOMIYAMA, M.D.
Department of Obstetrics and Gynecology
National Saitama Hospital
2-1 Suwa, Wako-shi,
Saitama
351-0102 (Japan)