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A feasibility study on maintenance of docetaxel after paclitaxel-carboplatin chemotherapy in patients with advanced ovarian cancer

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Objective: To test the concept of taxane sequencing, this feasibility trial evaluated maintenance of docetaxel after paclitaxel and carboplatin combination chemotherapy in patients with stage IC–IV ovarian cancer.

Methods: All patients received debulking surgery followed by paclitaxel and carboplatin chemotherapy. Attainment of clinically defined complete or partial response was confirmed by image scanning. Maintenance of docetaxel started at an initial dose of 70 mg/m^2 every 4 weeks for 6 cycles and was extended to 10 cycles unless disease progression and/or recurrence during the protocol therapy or unacceptable toxicities were seen.

Results: Stage subsets in 20 eligible patients were as follows: IIIB, 2 patients (10%); IIIC, 13 patients (65%); IV, 5 patients (25%). Neutropenia was common (40% with grade 3 or 4) and was most frequent during first or second cycle although the disabling peripheral neuropathy was not observed. Twelve patients completed protocol therapy (6≤cycles), while 8 patients failed to complete 6-cycle chemotherapy, because of progressive disease (5 patients) or grade 4 toxicities (3 patients). Median PFS was 20 months and 3-year PFS rate was 12%. Median overall survival was 39 months and 3-year OS rate was 69%.

Conclusion: Six cycles of single-agent docetaxel maintenance chemotherapy is feasible and generally tolerable to women with advanced ovarian cancer who attained a clinically defined response to initial paclitaxel and carboplatin based chemotherapy.

Keywords: Chemotherapy, Docetaxel, Maintenance, Ovarian cancer

INTRODUCTION

Surgery and systemic chemotherapy are the current standard treatment modality for epithelial ovarian cancer and this combination induces complete and partial response in up to 80% of patients [1,2]. Unfortunately, recurrences occur in the majority of patients, and barely 30% of patients with distant metastases survive after a 5-year follow-up period [3]. The role of sequential maintenance chemotherapy in patients responding to first-line chemotherapy, however, has not been clearly defined in ovarian cancer, although some attempts have been made with several approaches such as topotecan, paclitaxel and bevacizumab [4-7].

Except for bevacizumab, a number of justifications can be provided to support the concept that paclitaxel would be a most promising cytotoxic drug to treat ovarian cancer as a maintenance strategy. Southwest Oncology Group (SWOG) and Gynecologic Oncology Group (GOG) have conducted a

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phase 3 trial exploring the concept of paclitaxel maintenance in ovarian cancer [6]. In this trial, patients were randomized to receive either 3 or 12 additional cycles of single-agent paclitaxel on every 28-day (monthly) schedule. This study has confirmed the 7-months improvement in median progression-free survival (PFS) associated with the extended paclitaxel treatment regimen.

On the other hand, a particular issue with any maintenance chemotherapy strategy in the management of malignant disease is the documented potential for the development of cumulative toxic effects that would not be observed during the initial treatment cycles. Examples include the occurrence of secondary malignancies, congestive heart failure and chronic renal insufficiency. In the above study with single-agent paclitaxel, while alopecia will continue as long as the drug is delivered, a level of bone marrow suppression will be observed, and neuropathy may develop or worsen, extended use of paclitaxel does not appear to result in such serious effects as chronic heart, kidney, liver dysfunction, or the development of secondary malignancies. However, the important point is that paclitaxel-induced greater peripheral neuropathy provokes severe deterioration in quality of life, although there is no adverse fatal effect. Considering these distinguished efficacy and safety, taxane sequencing in ovarian cancer is highly evaluable when neuropathy could be minimized.

The efficacy of docetaxel in ovarian cancer and its adverse effect spectrum have been reported and generally accepted worldwide [8]. Compared with paclitaxel, docetaxel produced significantly less frequency of neuropathy while the efficacy stayed in the same level [8]. Taken together, testing the concept of taxane sequencing with maintenance of docetaxel is a potential therapeutic strategy in advanced ovarian cancer because of the potential curability of this patient subset and the high level of activity of docetaxel in the primary treatment [8].

MATERIALS AND METHODS

1. Selection of patients

Eligible patients were registered after six cycles of chemotherapy with paclitaxel and carboplatin. At registration, patients with cytologic or histologic diagnosis of epithelial ovarian carcinoma and an Eastern Cooperative Oncology Group performance status ≤2 were eligible after written informed consent was obtained to receive maintenance chemotherapy with docetaxel. Eligibility criteria were as follows: complete response or partial response to paclitaxel and carboplatin chemotherapy, including patients without evidence of cancer after primary surgery or interval debulking surgery; normal bone marrow function (neutrophils≥2,000/μL, platelets≥100,000/μL and hemoglobin≥9 g/dL); normal renal function (creatinine≥1.5 mg/dL); and normal liver function (AST or ALT≤3 times the upper level of institutional norm, except if caused by cancer metastasis). Exclusion criteria were prior or concurrent malignant cancer, brain metastases, inadequate bone marrow function and abnormal renal or liver function.

2. Study design

The study was a multi-institutional feasibility study involving 4 Japanese centers. Registration and data-management procedures were performed at Jikei Daisan Hospital. The protocol was approved by the independent ethical committee of each participating center.

3. Treatment plan

All registered patients received docetaxel maintenance within 4 weeks after the end of first-line chemotherapy. Patients received docetaxel 70 mg/m^2/day every 28 days. Treatments were repeated every 4 weeks for six cycles. Patients received four additional cycles of chemotherapy unless disease progression and/or recurrence during the protocol therapy or unacceptable toxicities were seen. Antiemetic premedication was given according to each center's standard practice. Minimum requirements for continuing docetaxel were no evidence of tumor progression and the following criteria: neutrophils≥2,000/μL, platelets≥100,000/μL, and no non-hematologic toxicities of grade≥1 recorded in the previous cycle (excluding alopecia). Treatment modification schedule is summarized in Table 1. Treatment was delayed for a maximum of 14 days if bone marrow toxicity was present on the day scheduled for chemotherapy. When the recovery was achieved between 6 and 7 weeks, the docetaxel dosage was reduced to 60 mg/m^2. If hematologic recovery was inadequate by 7 weeks, the patient was removed from the study. Treatment dose was reduced to 60 mg/m^2 when grade 4 neutropenia or leukopenia was observed continuously for ≥5 days at previous cycle. In patients experiencing any other National Cancer Institute (NCI) common toxicity criteria (CTC) grade 3 or greater toxicity, with the exception of nausea and vomiting, dosage adjustment or treatment discontinuation was done at the discretion of the investigator. Granulocyte colony-stimulating factors were permitted in patients with grade 4 neutropenia or leukopenia (with or without fever).

4. Clinical, laboratory, and radiologic assessments

Before entering the study, clinical, laboratory, and radiologic

Table 1. Treatment modification for docetaxel maintenance

Treatment delay	1. Hematologic criteria for starting successive cycles neutrophils ≥2,000/mm^3, platelets ≥100,000/mm^3
	2. In patients experiencing any other National Cancer Institute (NCI) common toxicity criteria (CTC) grade 3 or greater toxicity, with the exception of nausea and vomiting, treatment delay was at the discretion of the investigator.
	3. Hematologic recovery should be achieved between 4 and 6 weeks after previous maintenance cycle. When the recovery was achieved between 6 and 7 weeks, the docetaxel dosage was reduced to 60 mg/m^2.
Dose reduction criteria	Treatment dose was reduced to 60 mg/m^2 when:
	1. Grade 4 neutropenia or leukopenia was observed continuously for ≥5 days at previous cycle
	2. Febrile neutropenia (>38 degrees in centigrade, neutrophils <500/mm^3) was observed continuously for ≥3 days at previous cycle.
	3. Hematologic recovery was achieved between 6 and 7 weeks.
Criteria for discontinuing protocol-directed therapy	1. Adverse events such as:
	1) Treatment delay more than 3 weeks
	2) Grade 4 non-hematologic toxicities (except alopecia, fatigue, nausea, or constipations)
	3) Patients requiring more than one dose reduction.
	2. Patient's request to discontinue the study therapy
	3. Patient's death during protocol therapy
	4. Disease progression or recurrence during the protocol therapy
	5. When the investigator judges that the protocol therapy is no longer appropriate for the patient

assessments were carried out. Clinical assessment included complete medical history, physical examination, weight, height, performance status, and electrocardiogram. Laboratory measurements included complete blood cell count, creatinine clearance, serum bilirubin level, transaminase levels, alkaline phosphatase levels, electrolytes and CA-125 levels. Radiologic assessment included chest X-ray and abdominal-pelvic scan (CT, magnetic resonance imaging or ultrasound). Complete blood count was done at least weekly thereafter and clinical and other laboratory assessments, including CA-125 levels, were repeated before each treatment. Chest X-ray and abdominal-pelvic scan were repeated at least every three cycles.

5. Study evaluation

Toxicities were graded according to the NCI CTC ver. 3.0. The highest grade of toxicity encountered during treatment was recorded before each cycle and during follow-up. Follow-up visits were basically planned every 2 months for 2 years, then every 3 months for 5 years or until death. All patients receiving at least one cycle of treatment were assessable for toxicity.

Response assessments were made, but response was not required for completion of the protocol because the primary end point was the evaluation of toxicities and compliance to treatment. However the progressive disease (PD) should be diagnosed by physical examination or radiologic assessment mentioned above every 2 months. For this purpose, CT scan was taken to confirm whether patient has measurable disease right before maintenance chemotherapy and the images were used as baseline scan. Patients were followed from the start of docetaxel maintenance until her death of disease, and the time with site(s) of first relapse was ascertained. Follow-up studies included a post-treatment CT scan at 4 to 8 weeks from completion of all chemotherapy. Subsequently, follow-up was every 2 months for 1 year, every 3 months for 3 years, then every 6 months. Patients were removed from the protocol for disease progression, unacceptable toxicity as assessed by the investigator, development of intercurrent, non-cancer-related illnesses precluding continued treatment, or on patient request. Progression free and overall survivals were determined on the basis of Kaplan and Meier method [9].

RESULTS

Between September 2006 and December 2009, 22 patients were participated in the trial; 20 patients were eligible for maintenance of docetaxel after 6 cycles of carboplatin plus paclitaxel. Main characteristics of the 20 patients are listed in Table 2. Median age of the patients was 66 years old. The majority of patients were in advanced stage at diagnosis (75% of patients had stage III; 25% of patients had stage IV). More

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than half of the patients were optimally debulked (<1 cm, 55%).

Toxicity data were available for all 20 patients who received docetaxel and are listed in Table 3. Neutropenia was fairly common during maintenance of docetaxel, where 6 patients (30%) receiving maintenance developed grade 4 neutropenia. However, febrile neutropenia was not observed in this study population. Pneumonitis (grade 4) possibly or probably related to treatment was reported in one patient (5%). Grade 3 anemia occurred in two (10%) patients. At least one treatment cycle was delayed in 6 patients (33%) and the dose of the study drugs was reduced in 6 patients (33%). There were no episodes of docetaxel-associated fluid accumulation such as asymptomatic weight gain or peripheral edema. Grade 2 or 3 neuropathy was observed in three (15%) patients, however, it is hard to determine if this was the continuation of adverse effect of previous paclitaxel treatment. No toxic death occurred during treatment, and no relevant long-term toxicity was recorded during follow-up of patients.

Table 2. Characteristics of patient enrolled in this study

Characteristic	No. (%)
Patients	20
Age* (yr)	66 (36–75)
Stage	
IIIB	2 (10)
IIIC	13 (65)
IV	5 (25)
Histologic type	
Serous	15 (75)
Clear cell	1 (5)
Mucinous	1 (5)
Endometrioid	0 (0)
Others or not specified	3 (15)
Residual lesion size (cm)	
≤1	11 (55)
>1	9 (45)

*Median (range).

Treatment was discontinued before the 6 cycles in 8 patients because of toxicity (2 patients) or progression (6 patients) (Table 4). Eight patients completed 6-cycle maintenance chemotherapy and 4 patients received extended maintenance. One patient received 8 cycles but discontinued maintenance before 10 cycles because of disease progression. One patient receiving 9 cycles maintenance discontinued treatment because of grade 4 hematologic toxicity. Two patients completed 10 cycles without any severe toxicities and survived without disease progression for 11 and 29 months each.

Fig. 1 showed the survival curves from the start of docetaxel maintenance in 20 cases. Median PFS was 20 months with median follow up period of 24 months and 3-year PFS rate was 12% (95% CI, 1 to 39) (Fig. 1A). Median overall survival was 39 months with median follow up period of 40 months and 3-year survival rate was 69% (95% CI, 41 to 86) (Fig. 1B).

Among 13 reported sites of first failure, 5 (38%) were retroperitoneal lymph node, 3 (23%) were local-regional intrapelvic, and 2 (15%) were peritoneal dissemination (Table 4). Isolated brain metastasis as a site of first failure was reported in one patient, being 8% of the total failures.

DISCUSSION

Several types of maintenance treatments have been tested in women with ovarian cancer, however most of them reported significant improvement in PFS without any overall survival benefit. Markman et al. [6] showed that 12 cycles of single-agent paclitaxel, compared with 3 cycles of the same

Table 4. Patterns of failure during docetaxel maintenance therapy

Site of failure	No. of patients
Retroperitoneal lymph node	5
Intrapelvic tumor	3
Peritoneal dissemination	2
Liver parenchyma	2
Brain	1

Table 3. Frequent adverse effect during docetaxel maintenance therapy

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	4 (20)	5 (25)	3 (15)	2 (10)	6 (30)
Anemia	9 (45)	6 (30)	3 (15)	2 (10)	0 (0)
Thrombocytopenia	15 (75)	5 (25)	0 (0)	0 (0)	0 (0)
Neuropathy-sensory	7 (35)	10 (50)	2 (10)	1 (5)	0 (0)

Values are presented as number (%).

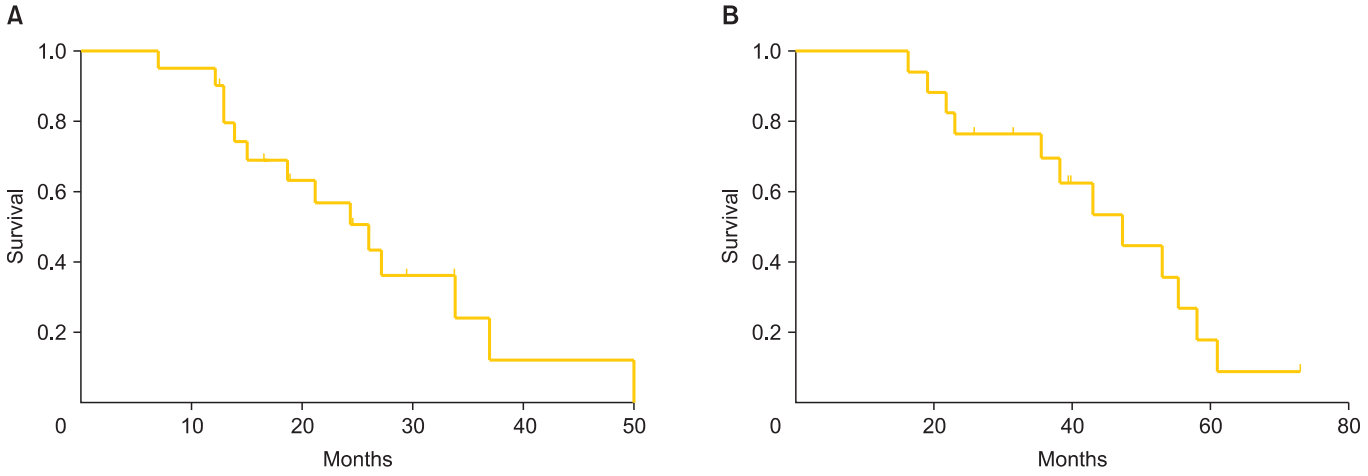

Fig. 1. Progression-free survival (PFS) (A) and overall survival (OS) (B) of 20 patients treated with single-agent docetaxel as maintenance therapy. Median PFS was 20 months and 3-year PFS rate was 12%. Median OS was 39 months and 3-year OS was 69%.

drug, significantly prolonged PFS in patients with clinical complete response to first-line paclitaxel and carboplatin. Another trial with the use of bevacizumab during and after paclitaxel and carboplatin chemotherapy prolongs the median PFS by about 4 months [7]. Furthermore, Perren et al. [10] demonstrated for the first time that the maintenance use of bevacizumab produced survival benefit in patients with advanced epithelial ovarian cancer. However, the utility of any additional treatment beyond standard therapy, particularly a treatment with the potential to occupy another months of the patient's life, should be carefully evaluated before it is recommended. This study is an attempt to determine the feasibility of maintenance chemotherapy following paclitaxel and carboplatin chemotherapy using the drug of the same cytotoxic mechanism and different spectrum of adverse effects in patients who have achieved a major response and have tolerated the treatment regimen. Two major issues should be discussed in this study.

First, since this study did not include a formal quality-of-life assessment, it would be hard to argue this extended docetaxel program is associated with an unacceptable adverse effect profile. The incidence of grade 4 neutropenia observed (30%) was comparable to that noted in topotecan consolidation treatment (29%) [5] and was a bit more frequent compared with the recently reported study in continuation of bevacizumab (17%) [10]. However, this degree of neutropenia is generally believed to be acceptable in routine clinical practice.

Second question to be asked is whether the dose level of docetaxel 70 mg/m^2/day every 4 weeks was optimal as maintenance setting. Previous studies have indicated that a dose level of 75 mg/m^2 is equally effective and less toxic compared to our dosing schedule. Vasey et al. [8] reported that docetaxel 75 mg/m^2 combined with cisplatin 75 mg/m^2 demonstrated grade 3 or 4 neutropenia in 75% of patients, a rate similar to that observed for docetaxel 75 mg/m^2 as a single agent. Although we hypothesize that systemically effective dose levels of docetaxel are required during maintenance to adequately address the issue of loco-regional and distant metastases, this single trial could not confirm whether the docetaxel 70 mg/m^2 used in maintenance therapy would achieve equivalent results. As shown in Table 3, 5 patients (25%) revealed the retroperitoneal lymph-node relapse, which is suggestive of the lack of docetaxel dosing to control the lymph-node micrometastases. Further, Table 4 shows that 80% of patients discontinued treatment because of disease progression during the maintenance rather than severe toxicity. While a mechanism for the persistent taxane sensitivity of tumor cells or the incidence of the taxane resistant clones in clinical settings have yet to be elucidated [11], those data are implying that a bit higher dose level of docetaxel would be recommended in future study. On the other hand, raising the dose of docetaxel in any future study should make the issue of neutropenia more of a concern, and so the schedule of docetaxel dosing level and interval should be carefully reconsidered. Unfortunately, it should be noted that our study provides no data on either the efficacy or toxicity associated with initiating maintenance of docetaxel at a higher dose level.

Finally, although this trial could not establish a new standard of care in the management of advanced ovarian cancer, the data demonstrated the potential use of a docetaxel maintenance strategy in the subset of patients who achieved a response to paclitaxel and carboplatin.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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