Weekly paclitaxel/5-fluorouracil followed by platinum retreatment for patients with recurrent ovarian cancer: a single institution experience

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Summary

Purpose: Since the prognosis of recurrent ovarian cancer patients is still poor, we need to establish a useful treatment strategy to achieve their long-term survival. We treated recurrent ovarian cancer patients with weekly paclitaxel (PTX)/5-fluorouracil (5-FU) followed by platinum retreatment to investigate its clinical efficacy in a preliminary manner. *Methods:* Sixteen patients with recurrent ovarian cancer, pretreated with taxane and platinum, were treated with weekly paclitaxel (PTX)/5-fluorouracil (FU). PTX (80 mg/m^2) on day 1, 8, and 15 was combined with a bolus injection of 5-FU (500 mg/m^2) on day 2, 9, and 16. Chemotherapy was given every four weeks. Patients with stable disease or progressive disease were subsequently retreated with a platinum-containing regimen. Response was evaluated by RECIST criteria or CA125 criteria. Toxicities were evaluated according to the National Cancer Institute-common toxicity criteria (NCI-CTC) version 3. *Results:* Among five patients with sensitive disease, one of four patients with measurable tumor and one without measurable tumor responded to weekly PTX/5-FU. Among 11 patients with resistant disease, none of five patients with measurable tumor and three of six patients without measurable tumor responded to weekly PTX/5-FU. Overall objective response rate by weekly PTX/5-FU was 31.3% (5/16). Among 16 patients, 13 patients who showed no response or progressive disease (three with sensitive disease, ten with resistant disease) received platinum retreatment after weekly PTX/5FU. All three patients with sensitive disease and three of ten patients with resistant disease revealed response to platinum retreatment. Overall objective response rate by platinum retreatment after weekly PTX/5-FU was 46.2% (6/13). *Conclusions:* Weekly PTX/5FU followed by platinum retreatment could be a useful treatment strategy for recurrent ovarian cancer patients. We need to establish the standard treatment strategy for recurrent ovarian cancer patients with a poor prognosis.

Key words: Paclitaxel; 5-fluorouracil; Recurrent disease; Platinum-free interval; Ovarian cancer.

Introduction

With advances in treatment, the median 5-year survival rate among ovarian cancer patients has improved to approximately 50% in women diagnosed in the mid-1990s, compared with approximately 40% in those diagnosed a decade earlier [1, 2]. In the setting of long-term management for advanced-stage disease, patients may experience a number of relapses, each of which represents a particular challenge. With the availability of newer agents, combinations, and alternative dosing schedules, it has become increasingly apparent that the choice of sequential treatments may have an important impact on future treatment options based on tolerability, cumulative toxicity, and patterns of drug resistance.

Although only a minority of patients with advanced-stage disease can be "cured", extended survival (often measured in years) is observed in a substantial percentage of women with recurrence. Unfortunately, there are currently very few phase III trials with long-term outcomes to help clinicians select an optimal regimen, or sequence of regimens, for management of persistent or recurrent disease. Furthermore, for a patient whose cancer has stabilized or responded, the optimal duration of therapy is unknown. In this setting, the concern is for the potential toxicity and impact on quality of life associated with prolonged therapy versus the theoretical benefits of sustained suppression of tumor growth, including delayed onset of symptoms and enhanced opportunity for extended survival.

As paclitaxel (PTX) is known to be a cell-cycle-specific agent, a number of alternative schedules have been explored to enhance efficacy and minimize toxicity. In particular, Markman *et al.* [3] and the Gynecologic Oncology Group [4] reported that weekly PTX (80 mg/m^2) is generally well tolerated with activity against measurable platinum-resistant ovarian cancer, including patients with early relapse after front-line platinum/PTX delivered on a conventional 3-week schedule. Since platinum sensitivity is related to the time between completion of platinum-based therapy and relapse, it has been hypothesized that prolongation of the platinum-free interval with the use of other drugs might improve responses to subsequent platinum therapy [5-7]. Weekly PTX could be utilized as a component of sequential chemotherapy to extend the platinum-free interval. The optimal use of sequential or combined therapy in the management of platinum-resistant recurrence has not been defined. However, two randomized trials have suggested that multiagent therapy might be superior in the setting of platinum-sensitive recurrence [8, 9].

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Murad *et al.* reported that a combination of PTX and 5-fluorouracil (5-FU) was effective for advanced gastric cancer with a response rate of 65.5% in a phase II trial [10]. Loesch *et al.* also reported that weekly PTX/5-FU with leucovorin was active as first-line therapy for metastatic breast cancer with a response rate of 48% in a phase II study [11]. As far as we know, no report on weekly PTX/5-FU for ovarian cancer has been published in the literature yet. We, therefore, explored the toxicity and efficacy of weekly PTX/5-FU for patients with recurrent ovarian cancer pretreated with PTX or docetaxel (DTX)/carboplatin (CBDCA). Patients showing stable disease or progressive disease after treatment by weekly PTX/5-FU were subsequently retreated with platinum-containing regimen such as irinotecan (CPT-11)/cisplatin (CDDP), which has been reported to be an active regimen for refractory or recurrent ovarian cancer [12]. We, then, evaluated the clinical efficacy of our treatment strategy, consisting of weekly PTX/5FU followed by platinum retreatment, for recurrent ovarian cancer.

Patients and Methods

Patients (Table 1)

All patients were treated with surgery including extended total hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, omentectomy, and appendectomy except two cases, and systemic chemotherapy (PTX: 175 mg/m^2 or DTX: 70 mg/m^2 + CBDCA: AUC 5) on an every-3-week schedule at Hokkaido University Hospital and had clinical diagnoses of relapsed ovarian cancer. All patients had pathological diagnosis of serous papillary adenocarcinoma. Fourteen patients had Stage IIIc, one Stage IIc and one Stage IIIb disease. A median of nine cycles of initial platinum treatment was given. All patients provided their informed consent to participate in the study.

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), neutrophil count > 1500/mm^3, hemoglobin > 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.

Treatment regimen weekly PTX/5FU

PTX (80 mg/m^2) was administered intravenously on day 1, 8, 15. After 24 hours of starting time of PTX administration, 5-FU (500 mg/m^2) was administered by bolus injection on day 2, 9, 16.

CPT-11/CDDP

CPT-11 (60 mg/m^2) and CDDP (60 mg/m^2) were administered intravenously on day 1 and CPT-11 (60 mg/m^2) alone was administered on day 8, 15.

DTX/CBDCA (CDDP)

DTX (70 mg/m^2) and CBDCA (AUC 5) was administered intravenously on day 1 and repeated with 3-week intervals. DTX (30 mg/body) and CDDP (30 mg/body) was administered intravenously on day 1, 8, 15. This regimen was employed when CPT-11/CDDP was not used after weekly PTX/5FU.

For all above-mentioned treatment regimens, an anti-emetic agent (5-HT antagonist) was administered prophylactically from day 1 to 2, from day 8 to 9, and day 15 to 16 to reduce the gastrointestinal toxicity. Granulocyte colony stimulating factor (G-CSF) was administered subcutaneously when the WBC count was < 2000.

Definition of toxicity

Toxicities were evaluated according to the National Cancer Institute-common toxicity criteria (NCI-CTC) version 3.

Criteria for response

For the cases with measurable tumors, evaluation of radiographic findings was based on the response evaluation criteria in solid tumors (RECIST) guidelines [13]. For the cases without measurable tumors, 50% response definition was employed to evaluate the response by CA-125 [14]. Briefly, sample 1 = x and ≥ 40 U/ml; sample 2 = y; sample 3 ≤ 50% of both x and y; and sample 4 ≤ 110% sample 3 and ≥ 28 days after sample 3. If samples 3 and 4 are less than the upper limit of normal, intervening samples between 2 and 3, or 3 and 4, that are within the normal range must be ≤ 150% of sample 2 or 3, respectively. Intervening samples between 2 and 3, or between 3 and 4, that are outside the normal range must be ≤ 110% of sample 2 or 3, respectively, and ≤ 110% of the preceding sample. For progressive disease, the serum CA-125 level must have been at least 70 U/ml and have doubled from the previous value. This had to be repeated 28 days later and met the same criteria. The date of progression was the date of the level confirming the doubling of the CA-125 value and at least 70 U/ml.

Results

From January 2003 to February 2005, a total of 16 patients with a median age of 58 years (range; 40-71) were treated by weekly PTX/5FU. The chemotherapy-free interval ranged from one to ten months. Five patients showed sensitive disease and 11 revealed resistant disease. A median of time to recurrence/progression after initial platinum treatment was three months (range; 0-16 months) (Table 1).

Table 1. — *Clinical characteristics of the patient cohort (n = 16).*

Variable	No.	%
Age at first surgery (years); median (range)	58.0 (40-71)	
Stage at diagnosis		
IIc	1	6.3
IIIb	1	6.3
IIIc	14	87.4
Response to initial platinum treatment		
sensitive	5	31.3
resistant/refractory	11	68.7
Time to recurrence or progression after last platinum treatment; median (range)	3 months (0-16)	
Cycles of platinum treatment before weekly PTX/5-FU; median (range)	8.8 months (3-12)	

Toxicity of weekly PTX/5-FU (Table 2)

All patients were fully evaluable for toxicity of weekly PTX/5-FU. Table 2 summarizes the incidence of certain toxic effects. Leukopenia was the most frequent form with this combination regimen. Although seven patients revealed grade 3 toxicity on leukopenia, G-CSF administration was effective for all patients.

Non-hematological toxicity was modest. One patient complained of febrile neutropenia (grade 3). Elevation of total bilirubin grade 3 was observed in one patient with a maximum value of 4.7 mg/dl and grade 2 for one patient with a maximum value of 2.4 mg/dl. Nine patients experienced nausea/vomiting grade 1 and one grade 2. One patient experienced arthralgia/myalgia grade 1. Peripheral neuropathy grade 1 was observed in two patients. One patient experienced nail disorder grade 1.

Table 2. — *Hematological and non-hematological toxicity of weekly PTX/5FU.*

Toxic effect	No. of patients				
	NI-CTC grade				
	1	2	3	4	5
Hematological					
leukopenia	0	7	9	0	0
thrombocytopenia	1	0	0	0	0
anemia	4	8	2	0	0
Non-hematological					
arthralgia/myalgia	2	0	0	0	0
nausea/vomiting	15	1	0	0	0
fever	0	0	1	0	0
allergy	0	0	0	0	0
total bilirubin	0	1	1	0	0
peripheral neuropathy	7	0	0	0	0
nail disorder	1	0	0	0	0

Efficacy of weekly PTX/5FU (Table 3)

All patients were assessable for response of weekly PTX/5-FU. Five patients with sensitive disease and 11 with resistant disease received weekly PTX/5-FU. Median of platinum-free interval prior to weekly PTX/5-FU was ten months for sensitive disease and three months for resistant disease. Among five patients with sensitive disease, one of four patients with measurable tumor and one without measurable tumor responded to weekly PTX/5-FU. Among 11 patients with resistant disease, none of five patients with measurable tumor and three of six patients without measurable tumor responded to weekly PTX/5-FU. Notably, six patients (75.0%) with measurable disease revealed stable disease without remission of measurable tumor and appearance of a new lesion. Overall objective response rate by weekly PTX/5-FU was 31.3% (5/16).

Platinum retreatment after weekly PTX/5-FU (Table 3)

Among 16 patients, 13 patients who showed stable disease or progressive disease (three with sensitive disease, ten with resistant disease) received platinum retreatment including CPT-11/CDDP (10 cases), DTX/CDDP or CBDCA (3 cases) after weekly PTX/5FU. Among three patients who were not retreated with platinum, one was treated with cytoreductive surgery followed by radiotherapy, one received non-platinum treatment (liposomal doxorubicin), one continued weekly PTX/5-FU. A median of platinum-free interval after weekly PTX/5-FU was 19 months for sensitive disease, five months for resistant disease. All three patients with sensitive disease and three of ten patients with resistant disease revealed response to platinum retreatment. Overall objective response rate by platinum retreatment after weekly PTX/5-FU was 46.2% (6/13).

Table 3. — *Outcome of weekly PTX/5-FU followed platinum retreatment.*

	Platinum-sensitive	Platinum-resistant	Total
Received PTX/5-FU	5	11	16
Median platinum-free interval (months, prior to PTX/5-FU)	10	3	3
Response (measurable)	1/4	0/5	1/9
Response (CA 125)	1/1	3/6	4/7
Response (overall)	2/5	3/11	5/16
Platinum retreatment after PTX/5-FU	3	10	13
Median platinum-free interval (months, prior to PTX/5-FU)	19	5	6
Response (measurable)	3/3	1/4	4/7
Response (CA 125)	0	2/6	2/6
Response (overall)	3/3	3/10	6/13

Discussion

As far as we know, this is the first report on the toxicity and efficacy of weekly PTX/5-FU for ovarian cancer. In this preliminary report, we confirmed that PTX/5-FU in a weekly cycle is largely tolerable for patients with recurrent ovarian cancer and even for heavily pretreated patients.

In an effort to improve response rates of chemotherapy, taxanes have been combined with other cytotoxic agents such as antimetabolites including 5-FU. Combination of PTX and 5-FU has been reported to be effective in gastric cancer and breast cancer. If 5-FU is administered prior to PTX, it can induce a G-S block in cell lines, potentially limiting the efficacy of subsequent taxane exposure. Indeed, Kano *et al*. investigated various schedules of paclitaxel and 5-FU in vitro in four human cancer cell lines, evaluating dose-response effects with isobolograms. They found that sequential exposure to 5-FU for 24 hours followed by PTX for 24 hours showed an antagonistic interaction, while reversal of the sequence revealed an additive effect [15]. Therefore, to optimize antitumor effects, it would appear that 5-FU should be administered after PTX treatment for 24 hours, which can block the cell cycle at the G2-M phase. In previous reports on PTX/5-FU, 5-FU was continuously administered for 24 hours. In this study, we administered 5-FU by bolus injection. Although the opitmal duration of 5-FU infusion following PTX is unknown, preclinical models suggest similar toxicity from 5-FU irrespective of

duration. We treated two human ovarian cancer cell lines (OVCAR-3 and PA-1) with the combination of PTX/5-FU and found that sequential exposure to PTX for 24 hours followed by 5-FU for one hour with higher dose has a similar synergistic cytotoxic effect as 24-hour treatment by 5-FU with lower dose (unpublished observation).

Concerning the quality of life of patients with recurrent ovarian cancer, bolus injection is superior to a 24-hour continuous infusion, because we can administer this combination chemotherapy in the outpatient clinic without the need for ambulatory infusion pumps. Four studies investigating paclitaxel and 5-FU in weekly cycle noticed tolerable side-effects of mainly leucocytopenia and mild neurotoxicity [10, 16, 17]. Indeed, we found that hematological side-effects were easily manageable with G-CSF as previously reported [17].

In this preliminary report, we obtained an objective response rate of 31.3% by weekly PTX/5-FU for patients with recurrent ovarian cancer. It is unclear if 5-FU showed synergistic effect with weekly PTX in this study, because the response rate of weekly PTX has been reported to be 20-25% for patients with resistant disease [3, 4]. However, we might expect a better response rate for ovarian cancer if we employed this regimen as the first-line treatment or for patients with sensitive disease since 11 patients showed resistant disease to PTX or DTX + CBDCA in our cohort.

It is notable that we found only two cases of rapid disease progression (2/16 = 12.5%) during weekly PTX/5-FU in this study. The clinical value of prolonged stable disease in ovarian cancer has been established [18]. Survival among patients who achieved stable disease was statistically comparable with those who experienced a partial response to topotecan. Thus, stable disease may offer equal clinical benefits compared with partial tumor responses in patients with relapsed ovarian cancer. In the context of maintaining stable disease, weekly PTX/5-FU must be considered as the second-line chemotherapy for recurrent ovarian cancer since this regimen is less toxic and effective to keep at least stable disease for the third-line chemotherapy.

We obtained an objective response rate of 46.2% by platinum retreatment after weekly PTX/5-FU for patients with recurrent ovarian cancer. According to current dogma in ovarian cancer treatment, the potential for patient sensitivity to platinum might be the most important factor in planning subsequent treatment. Tumor response rates are directly related to the platinum-free interval among all the novel agents currently used in second-line therapy [5-7, 19]. An important goal of treatment, therefore, is to extend the platinum-free interval for all patients, regardless of platinum sensitivity. The use of a non-platinum agent at first relapse, for instance, can lower the probability that tumors will become increasingly resistant to the platinum retreatment. In terms of platinum-free interval, we can use weekly PTX/5-FU as the second line regimen for prolongation of platinum-free interval. Indeed, the median platinum-free interval was six months after weekly PTX/5-FU in this study. Possible third line chemotherapy after weekly PTX/5-FU should be the regimen containing platinum such as CPT-11/CDDP for patients with recurrent disease.

In summary, weekly PTX/5-FU is a useful treatment as the second-line regimen at least to maintain stable disease and to prolong the platinum-free interval, which might result in better response to platinum retreatment as the third-line chemotherapy, and in improvement of survival of patients with recurrent ovarian cancer with poor prognoses.

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