Salvage Chemotherapy Using Gemcitabine for Taxane/ Platinum-resistant Recurrent Ovarian Cancer: A Single Institutional Experience

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Abstract. *Background: The purpose of this study was to report on the safety and efficacy of gemcitabine used as salvage chemotherapy for ovarian cancer. Patients and Methods: From January 2002 to October 2011, 27 patients were treated with gemcitabine for platinum-resistant recurrent ovarian cancer. Gemcitabine (800 mg/m^2) was given on days 1, 8, and 15 of every 28 days. The patients' medical records were retrospectively reviewed. Results: All 27 patients had previously received paclitaxel/carboplatin doublet and their disease had become platinum-resistant. The median number of previous chemotherapy regimens was 2 (range 1-7). A total of 114 cycles of single-agent gemcitabine were administered, with a median of 3 (range 1-10). No complete responses were observed. Partial response (PR) was observed in five patients (18.5%). Eight patients demonstrated stable disease (SD). The median duration of response for 5 responders was 4 months (range 2-6 months). The median survival time was 15 months. Patients with PR or SD (n=13) had significantly better survival compared with the group with progressive disease (n=14) (p=0.03, by univariate analysis). In addition, multivariate Cox proportional hazards analysis revealed that responses to gemcitabine were a significant factor for survival (hazard ratio=0.08, 95% confidence interval=0.0138 to 0.5614, p=0.01). Cases with hematological toxicity included 10 patients (37.0%) with grade 3/4 neutropenia, 3 patients (11.1%) with grade 3 thrombocytopenia, and 3 patients (11.1%) with grade 3 anemia. Non-hematological toxicity was well-tolerated. Conclusion: Gemcitabine (800 mg/m^2) used for recurrent ovarian cancer possesses a modest activity and a well-tolerated toxicity.*

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The golden-standard of therapy for epithelial ovarian cancer (EOC) includes maximal surgical debulking followed by chemotherapy with a taxane/platinum doublet. Although this therapy has resulted in some improvement in survival rates of patients with advanced ovarian cancer, the majority (70%) will eventually experience disease relapse and succumb to their disease (1). The recurrence of ovarian cancer remains the foremost formidable clinical problem, which will have to be resolved by better control of this malignant disease in order to improve survival. It is therefore critically important to develop new non-cross-resistant drugs for use after taxane/platinum doublet failure.

Gemcitabine (2', 2'-difluorodeoxycytidine), a synthetic nucleoside analog of cytidine, has been demonstrated to be an active agent for various types of solid tumors, such as non-small cell lung cancer and pancreatic, genitourinary, and breast cancers (2). As described in the pioneering work of Plunkett *et al*., gemcitabine is a pro-drug, which is metabolized to gemcitabine diphosphate and triphosphate, whose incorporation into DNA results in chain termination by inhibiting DNA polymerase activity (3). Consequently, tumor cells are blocked in the G_1 phase of the cell cycle. The gemcitabine triphosphate metabolite can also be incorporated into RNA, thus inhibiting RNA production (4).

Clinical use of gemcitabine for ovarian cancer was first reported in 1994 by Lund *et al*. (5). In their report, gemcitabine (800 mg/m^2) was given to patients with recurrent ovarian cancer, intravenously, once a week for three consecutive weeks, followed by one week of rest. A partial response was observed in 8 out of the 42 patients (19%), with a median response duration of 8.1 months. Seven out of the eight responders were resistant to first-line platinum-containing combination chemotherapy. Median overall time to progression was 2.8 months, and median overall survival (OS) was 6.2 months.

Leukocytopenia and thrombocytopenia were the main toxic effects that caused dose omissions (27% and 14%, respectively) and dose reductions (37% and 21%, respectively). Non-hematological toxicity was mild and tolerable.

Matsuo *et al*., recently carried out a systematic literature review of clinical studies published between January 2005 and March 2010 to analyze which systemic agents were being employed for platinum-resistant ovarian cancer. They found that gemcitabine was the most common drug used in the clinical trials reporting the highest response rates. Gemcitabine-based combination therapy had an average response rate of 27.2%, with relatively better progression-free survival (more than 4.1 months) (6).

In the present retrospective study, we evaluate the antitumor response and toxicity profile of single-agent gemcitabine (800 mg/m^2) and report our experience in using it for taxane/platinum-resistant recurrent ovarian cancer.

Patients and Methods

Patients. We retrospectively reviewed the medical records of all patients with recurrent ovarian cancers treated with the single agent gemcitabine, who underwent such a treatment between January 2002 and October 2011 while at the Osaka University Hospital, Japan. Eligible patients were required to have histologically confirmed EOC.

Gemcitabine therapy. Gemcitabine (800 mg/m^2) was given on days 1, 8, and 15 of every 28 days. Courses were repeated until either the disease progressed or an unacceptable toxicity appeared. The initial doses of gemcitabine were reduced in subsequent courses, depending on toxicity. The minimum dose of gemcitabine was 650 mg/m^2.

Response criteria. Patients were evaluated for their response to treatment after they completed at least one 28-day treatment cycle. Reevaluation procedures included serial computed-tomography (CT) visualization of measurable disease. Response categories were assigned when patients had measurable disease fulfilling the revised RECIST guidelines (version 1.1) (7).

Safety assessment. All patients who received at least one cycle of gemcitabine were included in the toxicity analysis. Both hematological and non-hematological toxicities were assessed through review of laboratory reports, including standard variables, such as hemoglobin, hematocrit, neutrophil, leukocytes and platelet counts, and medical records for clinical history. Toxicity was assessed using the National Cancer Institute's Common Toxicity Criteria (v. 4.0, Common Terminology Criteria for Adverse Events, 2009) (8).

Statistical analysis. The treatment-free interval (TFI) was defined as the time (months) from completion of the previous therapy to the start of gemcitabine treatment. OS was defined as the time elapsed between the start of gemcitabine treatment and date of death, or the date of last follow-up. The Kaplan and Meier statistical method was used for the calculation of overall survival times. The log-rank test was employed to assess the statistical significance; *p*-values less than 0.05 were considered to indicate statistical significance.

Table I. *Patients' characteristics*.

Characteristic	No. (n=27)	%
Median age (range), years	57 (26-75)	
FIGO stage		
I	3	11.1
II	5	18.5
III	17	62.9
IV	2	7.4
Histology		
Serous	13	48.1
Clear cell	7	25.9
Endometrioid	3	11.1
Other	4	14.8
Number of prior chemotherapy regimens		
1	1	3.7
2	14	51.6
3	7	25.9
4	4	14.8
7	1	3.7
Median TFI (months, range)	1 (1-11)	

TFI, Treatment-free interval; FIGO, International Federation of Gynecology and Obstetrics.

The Mann-Whitney *U*-test was used to compare toxicity and efficacy. Univariate and multivariate proportional-hazards models (Cox) were fitted to the data to determine the importance of recognized explanatory variables. Selected factors were included in the multivariate Cox proportional-hazards analysis, namely, age (≤57 *vs*. >57 years), FIGO stage (I/II *vs*. III/IV), type of histology (clear cell *vs*. non-clear cell), TFI (<3 *vs*. ≥3 months), number of gemcitabine courses (≤3 *vs*. >3), the number of previous regimens (≤2 *vs*. >2), maximum response to gemcitabine [(PR) + (SD) *vs*. (PD)] and hematological toxicity (grade 1/2 *vs*. 3/4). Statistical analyses were performed using MedCalc for Windows (version 11.3.3.0; MedCalc Software, Mariakerke, Belgium).

Results

Patients' characteristics. Twenty-seven patients treated with gemcitabine for recurrent ovarian cancer were identified in our hospital archive. Clinical characteristics of the 27 patients are summarized in Table I. The median age was 57 years (range 26-75). FIGO stage for these patients were: 3 patients (11.1%) at stage I, 5 patients (18.5%) at stage II, 17 patients (62.9%) at stage III and 2 patients (7.4%) at stage IV. Histological diagnoses revealed serous adenocarcinoma in 13 (48.1%), clear cell carcinoma in 7 (25.9%), endometrioid adenocarcinoma in 3 (11.1%), and other types in 4 (14.58%). The median number of prior chemotherapy regimens was 2 (range 1-7). All 27 patients had platinum-resistant recurrences and all had received paclitaxel/ carboplatin doublet previously. Their median TFI was one month (range 1-11 months).

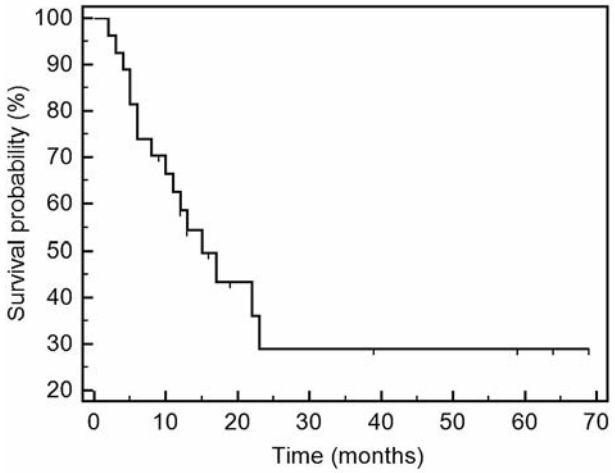

Figure 1. *Kaplan–Meier curve showing overall survival time of 27 patients with recurrent ovarian cancer treated with gemcitabine. The median survival time was 15 months.*

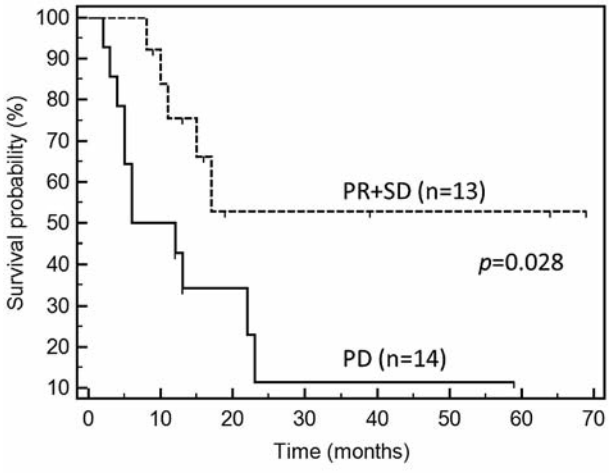

Figure 2. *Kaplan–Meier curve showing overall survival time stratified by maximum responses to gemcitabine. OS was significantly better in the group of patients who had PR or SD when compared with the group of PD (p=0.028).*

Efficacy. The responses of the platinum-resistant recurrences to gemcitabine are summarized in Table II. Twenty-seven patients received at least two cycles of gemcitabine treatment and all of them fulfilled the RECIST criteria. The overall response rate was 18.5% [no CRs; 18.5% (5/27) PRs] and SD was found in 29.6% (8/27), whereas PD was noted in 51.9% (14/27) patients. When comparing between different histologies, PR was observed more frequently in clear cell carcinoma and endometrioid adenocarcinoma. However, there was no significant difference between the groups (p=0.66, chi-square test). The disease control rate (CR+PR+SD) was 53.8% (7/13) for serous adenocarcinoma, 57.1% (4/7) for clear cell carcinoma, 33.3% (1/3) for endometrioid adenocarcinoma and 25.0% (1/4) for other histologies. Figure 1 shows the OS, which was a median of 15 months. As shown in Figure 2, OS was significantly better in the group of patients who had PR or SD when compared with the group of PD (p=0.028). Meanwhile, age (≤57 *vs*. >57 years), FIGO stage (I/II *vs*. III/IV), type of histology (clear cell *vs*. non-clear cell), TFI (≤3 *vs*. >3 months), number of gemcitabine courses (≤3 *vs*. >3), the number of previous regimens (≤2 *vs*. >2) and hematologic toxicity (grade 1/2 *vs*. 3/4) had no impact on OS by univariate analysis.

Table III shows the results of multivariate analysis, in which maximum response to gemcitabine (PR+SD *vs*. PD) has been defined as the independent prognostic factor for OS in patients with recurrent ovarian cancer treated with gemcitabine (hazard ratio=0.08, 95% confidence interval=0.0138-0.5614, p=0.01); whereas as observed in univariate analysis, none of the other parameters had any impact on OS.

Table II. *Antitumor effect of single-agent gemcitabine for recurrent ovarian cancer.*

Histology	PR	PR+SD
Serous	15.3% (2/13)	53.8% (7/13)
Clear cell	28.5% (2/7)	57.1% (4/7)
Endometrioid	33.3% (1/3)	33.3% (1/3)
Other	0/4	25.0% (1/4)
Total	18.5% (5/27)	48.1% (13/27)

PR, Partial response; SD, stable disease.

Toxicity. All 27 patients were evaluated for safety and tolerability. Collectively, a total of 118 cycles of gemcitabine were administered. The starting dose for all patients was 800 mg/m^2 of gemcitabine, which was given on days 1, 8, and 15 of every 28 days. The median number of cycles of gemcitabine was 3 (range 1-10). In 3.7% (1/27) of patients, a dose reduction, to 650 mg/m^2 was necessary due to hematological toxicity. Discontinuation of the gemcitabine chemotherapy was required for two patients (7.4%) due to thrombocytopenia and neutropenia. There was no death associated with the gemcitabine treatment. The main toxicities are shown in Table IV. Hematological toxicity included 10 patients (37.0%) with grade 3/4 neutropenia and three patients (11.1%) with grade 3 thrombocytopenia and three patients (11.1%) with grade 3 anemia. Non-hematological toxicity was well-tolerated, with the exception of a grade 3 urticaria observed in one patient, which disappeared within three days.

Table III. *Multivariate Cox proportional hazards-analysis for recurrent ovarian cancer treated with gemcitabine.*

Variables	Hazard ratio	95% CI	*p*-Value
Age, years			
≤57 (n=15)	1		0.14
>57 (n=12)	0.17	0.0171-1.7481	
Stage			
I/II (n=8)	3.57		0.09
III/IV (n=19)	1	0.8165-15.6056	
Histology			
Clear cell (n=7)	0.60		0.52
Non-clear cell (n=20)	1	0.1328-2.7509	
Treatment-free interval			
<3 months (n=16)	0.59	0.0781-4.5217	0.62
≥3 months (n=11)	1		
Number of courses of gemcitabine			
≤3 (n=13)	1	0.4246-10.4723	0.36
>3 (n=14)	2.11		
Number of previous regimens			
≤2 (n=15)	4.02	0.9098-17.7512	0.07
>2 (n=12)	1		
Maximal response to gemcitabine			
PR or SD (n=13)	0.08	0.0138-0.5614	0.01
PD (n=14)	1		
Hematological toxicity			
Grade 1/2 (n=17)	1	0.1917-4.5447	0.93
Grade 3/4 (n=10)	0.93		

PR, Partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

Discussion

It is well-recognized that salvage therapy in ovarian cancer strongly depends upon the primary chemotherapy results. When the recurrence occurs more than 6 months after completion of the initial therapy, a re-administration of the platinum-containing doublet can be effective in many cases, resulting in extended survival times. However, if the recurrence occurs before 6 months pass, most chemotherapeutic agents are no longer effective (9, 10). Second-line treatment for patients with platinum-resistant disease relies on medication with a single-agent of chemotherapy, such as topotecan, liposomal pegylated doxorubicin, oral etoposide, paclitaxel and gemcitabine. All of these agents have a similar response rate of 10%. Among these agents, gemcitabine is currently the most commonly used drug because of its tolerable toxicity, although the antitumor activity of all these second-line agents is quite similar (6).

The use of gemcitabine for ovarian cancer was first reported by Silver *et al*. (11), where it was used at a dose of 800 mg/m^2 on days 1, 8, and 15 of every 28 days. Gemcitabine has been subsequently used at up to 1250 mg/m^2, as reviewed by Lorusso *et al*. (12). In Japan, Watanabe *et al*. (13) reported on 27 patients with recurrent ovarian cancer of similar condition to the ones of the present study. In their report, gemcitabine was used at 1000 mg/m^2 on days 1, 8 and 15, every 28 days. In contrast, we administered 800 mg/m^2 of gemcitabine for days 1, 8 and 15, every 28 days. The antitumor effects of our treatment course (800 mg/m^2) and that of Watanabe *et al*. (1000 mg/m^2) was similar, as response rates were 18.5% and 17.9%, respectively. The median survival times were 15 and 11 months, respectively. Regarding hematological toxicity, grade 3/4 neutropenia was observed in 37.0% and 39.3% of the patients, respectively, and grade 3/4 thrombocytopenia was observed in 11.1% and 46.4% of patients, respectively. Non-hematological toxicities were mild and tolerable in both studies.

Table IV. *Adverse events of gemcitabine therapy (n=27).*

Toxicity	Grade 2	Grade 3	Grade 4
Hemoglobin	8 (29.6%)	3 (11.1%)	0
Neutropenia	7 (25.9%)	9 (33.3%)	1 (3.7%)
Platelet reduction	2 (7.4%)	3 (11.1%)	0
Urticaria	0	1 (3.7%)	0

The results of both univariate and multivariate analyses showed that our patients with a response to gemcitabine of SD or PD had better OS compared with these with PD. This result supports the idea that the survival benefit following second-line chemotherapy for platinum-resistant disease, if a complete remission is not obtained, is similar for PR and SD, as described by Cesano *et al*. (14). Thus, disease stabilization is important for patients whose life expectancy is generally short.

It should be noted that having a histology of clear cell carcinoma was not a significant factor for OS. Extremely low response rates for first-line platinum-based (15) and platinum/taxane doublet (16) chemotherapy for ovarian cancer have been reported. In addition, recurrent clear cell carcinoma has been reported by Takano *et al*. (17) and Yoshino *et al*. (18) to be particularly chemoresistant.

Although not statistically significant in our series, clear cell carcinoma had a better response rate compared to serous adenocarcinoma. The disease control rate and OS were similar between these groups. Thus, patients with recurrent clear cell carcinoma did not have an inferior prognosis when gemcitabine was used. Benefits of gemcitabine administration for recurrent ovarian cancer have been reported by other groups. Ferrandina *et al*. described a case of multidrug-resistant clear cell carcinoma of the ovary showing a selective susceptibility to gemcitabine at first administration and again at re-challenge. Moreover, they showed that the tumor expressed a certain molecular profile that likely made it highly sensitive to gemcitabine (19). Komiyama *et al*. reported successful control of massive

ascites due to *peritonitis carcinomatosa* with gemcitabine in a patient with recurrent clear cell carcinoma (20).

In conclusion, our results suggest that administration of gemcitabine at 800 mg/m^2 to platinum-resistant disease is as valuable as the commonly used 1000 mg/m^2 dose, irrespectively of tumor histology. However, our data include only a relatively small number of patients in this retrospective study, whereas the importance of this subject warrants a prospective randomized trial for full validation. In addition, due to its low toxicity, gemcitabine might be useful in combination chemotherapy, to overcome platinum-resistant recurrent ovarian cancer.

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