A Phase I/II Study of Docetaxel and Gemcitabine Combination for Chemotherapy-resistant Ovarian Cancer

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Abstract. *Background: A phase I/II study of docetaxel (DOC) and gemcitabine (GEM) combination for treatment-resistant ovarian cancer (OC) was conducted. Materials and Methods: Eligible patients exhibited recurrent OC within 12 months after initial treatment, or after more than 2 chemotherapy regimens. Planned dose levels (DL) were as follows: DOC 70 mg/m^2, GEM 800 mg/m^2 (DL1); DOC 70 mg/m^2, GEM 1000 mg/m^2 (DL2). DOC was administered on day 1 combined with GEM on days 1 and 8 every 3 weeks. Adverse events were assessed by NCI-CTC2.0J. Response was evaluated by RECIST or Rustin's criteria. Results: The recommended dose was DL1. For all enrolled patients, the median interval from last chemotherapy was 2.5 (1-11) months and 32 patients were assessable for response. One complete response, 6 partial responses and 6 stable disease were noted. Median time to progression was 4.8 months. Toxicities were mainly hematological and manageable. Conclusion: This combination could be an acceptable treatment option before palliation.*

The current standard of care for advanced ovarian cancer (OC) is maximum debulking surgery and combination chemotherapy of paclitaxel and platinum. Although the paclitaxel and platinum combination shows a 70-80% response rate, over 50% of patients have recurrent disease (1). Recurred OC (ROC) patients who have a long duration after first-line chemotherapy respond to a re-challenge of platinum containing regimens (2-4). However, there are no standard chemotherapy regimens for those who recur with short duration after first-line treatment or recur after second-line treatment.

Docetaxel (DOC) disrupts mitosis by the promotion of abnormal microtubular assembly and suppression of the depolymerization of microtubular bundles to free tubulin (5). Gemcitabine (GEM) is an S-phase-specific, fluorine-substituted pyrimidine analog, which is phosphorylated by deoxytidine kinase to the active diphosphate and triphosphate metabolites. This metabolite inhibits ribonucleotide reductase and DNA synthesis (6). Single DOC (7-10) and single GEM (11-13) have shown efficacy for ROC. Distinct mechanisms of action, different intracellular targets and high levels of single-agent activity support a rationale for combining the two drugs. The promotion of apoptosis by DOC in combination with DNA synthesis termination by GEM may lead to more than an additive effect (14). A combination of DOC and GEM was reported to present a synergistic effect for platinum and paclitaxel pre-treated non-small cell lung cancer (NSCLC) and other malignancies (14-17).

Materials and Methods

This study was designed as a multi-institutional, open-labeled, phase I/II study to determine the maximum tolerable dose (MTD) of DOC and GEM combination therapy for the treatment of resistant ROC, and to evaluate the response rate and toxicities of patients enrolled in the study. This protocol was approved by the ethical review boards of Kansai Clinical Oncology Group and of each participating institution. Eligibility

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criteria were as follows: histologically confirmed OC; refractory disease or relapse within 12 months after completion of platinum based first-line chemotherapy, or relapse after more than 2 chemotherapy regimens; patients had at least a 4-week interval after completion of prior chemotherapy administration; patients had measurable disease or were assessable by CA125. Without measurable disease, serum CA125 elevation (>100 U/mL) was determined to be evidence of disease progression and deemed suitable for assessing response; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; age 16-75 years; adequate bone-marrow function as follows: white blood cell count >3,000/mm^2, absolute neutrophil count >2,000/mm^2, platelet count >1.000,000/mm^2, and hemoglobin >9.0 g/dL; adequate hepatic function as follows: serum AST or ALT <2.5 times institutional upper limit of normal and total bilirubin <2.0 mg/ dL; and renal function as follows: serum creatinine <1.5 mg/dL, BUN <25 mg/dL and 24 hours of creatinine clearance >50 mL/min; life expectancy of more than 3 months; written informed consent. Exclusion criteria were as follows: active, uncontrollable cardiac disease; interstitial pneumonitis; uncontrollable pleural effusion or ascites; active inflammatory or collagen disease; other active malignancy.

The treatment consisted of DOC on day 1 by 60-minute infusion and GEM on days 1 and 8 by 30-minute infusion within a 21-day cycle. The dose-escalation scheme was as follows: dose level 0 (DL0); DOC 60 mg/m^2, GEM 800 mg/m^2; DL1, DOC 70 mg/m^2, GEM 800 mg/m^2; and DL2, DOC 70 mg/m^2, GEM 1,000 mg/m^2. The starting dose level was DL1. According to the modified Fibbonacci's scheme, DL was escalated unless patients had dose-limiting toxicity (DLT) by the end of the first cycle, in which case dose escalation was stopped. This regimen was discontinued in the case of disease progression, unacceptable adverse events, or at the discretion of the investigator. No dose escalation was permitted in individual patients. After confirming MTD, patients were continued to be entered into the phase II study at the MTD level as the recommended dose. Definition of DLT: Chemotherapy-induced toxicity was graded according to the National Cancer Institute's common toxicity criteria version 2.0J (18). DLT was defined as grade 3 or 4 thrombocytopenia, grade 3 or 4 febrile neutropenia or persistent grade 4 neutropenia for more than 4 days, and grade 3 or 4 non-hematological toxicities excluding nausea and vomiting. Dose modification: Patients who developed DLT at the planned DL were required to reduce their dose by one level in the subsequent cycles of chemotherapy. In phase II it was amended that patients who had received more than 2 prior regimens were allowed to reduce their DL by one level from the recommended dose at the first administration. If patients did not recover from the prescribed adverse events within 3 weeks from the planned date, they were withdrawn from the study.

Response for measurable disease was assessed by RECIST (19) and response for CA125-elevated-only patients was assessed by Rustin's Criteria (20). Patients with stable (SD) or responsive disease continued chemotherapy for at least 3 cycles and patients with progressive disease (PD) were withdrawn from the study. In responsive disease, the period between enrollment and confirmed PD or sustained response was defined as progression-free survival time (PFS).

Results

Between October 2000 and April 2004, 34 patients were entered in this phase I/II study. The median age was 56 years old (range 21-72) (Table I). Median interval from the latest chemotherapy was 2.5 months (range 1-11) and median interval from the latest platinum administration was 3.5 months (range 1-16). Thirty-two patients (94%) were treated primarily with a combination of carboplatin and paclitaxel. In one-half of the cases (17/34), more than 3 regimens had been administered at the time of enrollment. The percentage of patients with measurable disease was 59% (20/34). Patients with only CA125 elevation and no measurable lesions accounted for 38.2% (13/34). One patient had no assessable disease in terms of eligibility criteria. A total of 103 courses were evaluable for toxicity. Seven patients were enrolled in phase I, and the remaining patients were enrolled in phase II. One patient who entered phase I with CA125 elevation revealed dermatomyositis, which was diagnosed soon after study enrollment. She was determined ineligible and withdrawn from the study and excluded from toxicity, response and survival evaluation.

In the phase I study, three eligible patients entered at DL1 did not develop DLT. Although non-hematological toxicity did not reach DLT, the other 3 patients at DL2 developed grade 4 neutropenia which continued for more than 4 days. Therefore, the recommended dose for phase II was defined as DL1. Among twenty-seven patients enrolled in phase II, three were found to violate protocol requirements as follows: having no assessable disease, anemia (low hemoglobin, 8.6 g/dL) and poor PS (PS 3). All three patients were included in toxicity rating and two of them with measurable disease in response evaluation.

Toxicities in phase I/II were graded (Table II). Grade 4 neutropenia was observed in 57% (19/33). Three patients developed febrile neutropenia and another patient developed Grade 3 infection. They were intensively treated with antibiotics and G-CSF and recovered. Grade 4 anemia was observed in 6% (2/33) after three cycles of treatment. G-CSF was used in 23 patients and the median use was twice (95% confidence interval (CI): 1.3-2.5). The other non-hematological toxicities were not of major clinical relevance. The rate of dose-modified patients during treatment was 48% (16/33). Treatment delay occurred for 48% (16/33) of patients and 25.5% (28/110) of courses. Median delayed time to subsequent cycles was 7 days (1-21 days). The reasons for the delay included neutropenia (5/33); infection, fever, febrile neutropenia (4/33); fatigue (1/33); ileus (1/33); and patients' request (5/33). There were no treatment-related deaths in this trial. One patient died 6 weeks after entry due to disease progression.

Thirty-two patients were assessed for response (Table III). Of the 20 patients with measurable disease, 3/20 (15% : 95% CI; 4.9, 34) experienced objective response (1 complete response (CR), and 2 PR. Twelve out of 20 patients with measurable disease also had CA125 elevation of more than 100 U/mL. The overall objective response rate in this phase I/II study was 21.9% (7/32) (95% CI: 10.6-37.7). There were no differences in overall response rates among 3 groups divided by treatment-free intervals (Chi-square test, p=0.475), platinum-free interval (Chi-square test, p=0.256) and formerly

Table I. *Patient characteristics*.

Characteristics		No. of patients (n=34)
Age (years)		
Median (range)		56 (21~72)
Performance status (ECOG*)		
0		22
1		8
2		3
3		1
Histology		
Serous		18
Endometrioid		6
Mucinous		5
Clear cell		3
Undifferentiated		2
Interval since prior chemotherapy (months)		
median		2.5
1-3		21
4-6		5
7-11		8
Interval since prior platinum administration (months)		
median		3.5
1-3		17
4-6		8
7-16		9
Number of prior chemotherapy regimens		
median		2.5
1		9
2		8
3		6
≥4		11
Paclitaxel and platinum regimens previously administered		32
Measurable disease		20
Metastatic site		
Abdominal cavity		5
Liver parencymal**		3
Lymph nodes**		7
Pelvic cavity**		5
Lung		2
CA125 elevation (>100 IU/mL)***		25
Number of DOC+GEM cycles administered		
1		7
2		7
3		5
≥4		15
Administered dose level at first cycle	Enrolled phase	
0	II	6
1	I	4
	II	21
2	I	3
Inevaluable for toxicity		1
Inevaluable for response		2

*Eastern Cooperative Group performance status. **Metastatic sites were duplicated. ***There were 13 patients with elevated CA125 levels alone.

Table II. *Toxicities (n=33)*.

NCI-CTC ver2.0J	grades 1 & 2	grade 3	grade 4
Hematological toxicity			
White blood cells	6	19	6
Neutrophils	2	9	19
Febrile Neutropenia/Infection	0	4	0
Platelets	19	8	0
Anemia (Hemoglobin)	20	5	2
Non-hematological toxicity			
Nausea/vomiting	15	3	0
Neurotoxicity	8	0	0
Fatigue	12	0	0
Diarrhea	1	0	0
Pulmonary	3	0	0
Nail changes	1	0	0
Myalgia	2	0	0
Alopecia	17	0	0
Ileus	0	1	0

Adeverse events occurring in phase I/II study were listed according to NCI-CTC ver2.0J.

administered regimens (Chi-square test, p=0.626) (Table III). The combined rate of CR, PR and SD was 13/32 patients, or 40.6% (95% CI: 24.6-56.3). The median time to progression for the 33 patients was 4.8 months with a median follow-up period of 10 months (range 1-36 months) by Kaplan-Meier estimation. The median survival time was 13 months with a 2-year survival rate of 25.8% .

Discussion

For recurred platinum-sensitive OC, combination chemotherapy of carboplatin plus paclitaxel or carboplatin plus GEM provided longer PFS than carboplatin alone and has become a standard of care (22, 23). However there are still no standard regimens for those patients with platinum-resistant or -refractory disease. DOC, topotecan, liposomal-doxorubicin, GEM, tamoxifen and oral etoposide are agents which have shown activity in such patients (3). ROC patients who respond to initial platinum-based chemotherapy and have more than six months relapse-free interval are thought to be platinum sensitive (3). However, Gore *et al*. (4) reported that ROC with a treatment-free interval of less than 18 months had a low response rate (17%), and Parmar *et al*. used a treatment-free interval of more than 12 months as an indication of platinum sensitivity in a large phase III study (ICON-4) (23). Treatment-resistant OC was defined as recurrent with a treatment-free interval of less than 12 months or recurrent after more than 2 chemotherapy regimens. In this phase I/II study, 27 patients had less than 6 months duration from their most recent chemotherapies, and 23 of these had treatment-free intervals of only 1 to 3 months. Moreover, 25 patients enrolled in this trial experienced more than 2 prior

Table III. *Response to DOC+GEM combination (n=32).*

	Measurable disease	CA125 only	No. of overall responses	(%)
CR	1	0	1	3.1
PR	2	4	6	18.8
SD	4	2	6	18.8
PD	13	6	19	59.4

	Treatment-free interval from prior chemotherapy (months)					
	1-3		4-6		7-12	
	Measurable disease	CA125 only	Measurable disease	CA125 only	Measurable disease	CA125 only
CR	0	0	0	0	1	0
PR	2	2	0	1	0	1
SD	2	0	0	1	2	1
PD	11	3	1	2	1	1

	Treatment-free interval from prior platinum therapy (months)					
	1-3		4-6		7-16	
	Measurable disease	CA125 only	Measurable disease	CA125 only	Measurable disease	CA125 only
CR	0	-	0	-	1	-
PR	2	2	0	1	0	2
SD	4	2	1	1	2	1
PD	7	0	2	2	1	1

	Number of regimens before enrollment							
	1		2		3		≥4	
	Measurable disease	CA125 only	Measurable disease	CA125 only	Measurable disease	CA125 only	Measurable disease	CA125 only
CR	1	0	0	0	0	0	0	0
PR	0	0	0	1	1	1	1	2
SD	1	1	1	0	0	0	2	1
PD	4	1	5	1	2	2	2	2

Response to prior treatment was represented. CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable. One patient with CA125 elevated was excluded from evaluation for efficacy due to ineligible criteria. The other patient was not evaluable for efficacy.

chemotherapy regimens. Thus, the population of this study was weighted toward heavily pre-treated treatment-resistant OC. Single DOC as second-line chemotherapy for the treatment of resistant OC was reported to have a response rate of 20-35% with a median PFS of 3.9-5 months and a median overall survival time (OS) of 8.4-10 months (7-10). GEM had a response rate of 6.6-19% for platinum-resistant disease (11, 24). Overall median PFS was 2.8-3.6 months and median OS was 6.2 months with minimal toxicity (11, 24). There are also reports of GEM combined with liposomal doxorubicin, topotecan, or paclitaxel (25-28), liposomal doxorubicin combined with topotecan (29), and DOC combined with vinorelbine (30) for treatment-resistant OC which showed activity and tolerability. The efficacy of this trial apparently could not only exceed other combination regimens but was also less effective than even single DOC (9, 10) or GEM (11, 13). Thus, at first glance, this combination seems to offer little advantage for the treatment of resistant OC. But in a similar setting with a treatment-free interval of only 3.5 months, single GEM had a response rate of only 9.2% with a PFS of 3.6

months and a median OS of 12.7 months (22). Additionally, the response rate of single GEM for platinum and taxanes pre-treated OC was only 11-14% (31, 32). In platinum and paclitaxel pre-treated treatment-resistant OC with a progression-free interval of less than 3 months, DOC had a response rate of only 10% (33). In the current study, the reason for the low response rate of this combination was that most of the enrolled patients were heavily pre-treated and had short progression-free intervals and more than 2 prior regimens. However, a 21.9% response rate is more effective than that of each single agent. Hence, it is concluded that the combination of DOC and GEM for heavily pre-treated and treatment-resistant OC has more than an additive effect. It is also notable that 18.8% of the patients had SD and the disease-control rate (CR + PR + SD) of this trial reached 40.6% . Treatment with the GEM and DOC combination was well tolerated and had better disease-control duration in the heavily pre-treated cohort. Refractory NSCLC was treated by DOC 60 mg/m^2 on day 1 and GEM 800 mg/m^2 on days 1, 8 and 15. Adverse events were G3/4 neutropenia (33%/33%), G3/4 thrombocytopenia (17%/0%), and G3/4 febrile neutropenia (0%/0%) (16). The hematological adverse events which occurred in the present study are expected to be higher due to the pre-treated history of the cohort. Bevacizumab targets vascular endothelial growth factor A and is suggested to have an activity for platinum-resistant OC in phase II study (34). But there is still no established regimen for patients with refractory or early ROC. Until a new strategy is developed, there is no choice but to rely on cytotoxic agents or supportive care for treatment-resistant OC. A combination of DOC and GEM has a high disease control rate of SD. This could prolong the time under controlled disease with manageable toxicities and might be one treatment option for heavily pre-treated patients with prior platinum and paclitaxel regimens.

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