Original Article

Phase I study on pegylated liposomal doxorubicin in combination with docetaxel for patients with platinum-resistant or partially platinum-sensitive epithelial ovarian cancer: The Kansai Clinical Oncology Group study

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ABSTRACT

Context: In platinum-resistant ovarian cancer, single-agent chemotherapy is recommended for the reduction of adverse events. However, in clinical practice, some patients can tolerate drug-specific adverse events.

Aims: We assessed the safety of pegylated liposomal doxorubicin (PEG-LD) and docetaxel regimen in the first cycle of ovarian cancer.

Settings and Design: We performed a phase I study to evaluate the combination therapy of PEG-LD and docetaxel.

Materials and Methods: We recruited five patients with recurrent ovarian cancer within 12 months of first-line platinum-based chemotherapy. All patients had measurable disease severity. PEG-LD and docetaxel were intravenously administered on day 1 and every 21 days using three dose levels: 25 mg/m^2 PEG-LD and 50 mg/m^2 docetaxel; 30 mg/m^2 PEG-LD and 50 mg/m^2 docetaxel; and 30 mg/m^2 PEG-LD and 60 mg/m^2 docetaxel.

Statistical Analysis Used: We defined the maximum tolerated dose of the combination therapy based on the modified Fibonacci method.

Results: Five patients were enrolled in this study. The median treatment-free interval was 5.5 months. Two dose-limiting toxicities (Grade 4 neutropenia) were observed in two patients. One complete response, one partial response, one stable disease, and two progressive disease cases were observed. The overall response rate was 2/5, and the disease control rate was 3/5. The median overall survival was 7.4 months.

Conclusions: We determined that 25 mg/m^2 of PEG-LD and 50 mg/m^2 of docetaxel were safe and effective doses. This preliminary efficacy and safety data should be further investigated in a Phase II trial.

KEY WORDS: Docetaxel, ovarian cancer, pegylated liposomal doxorubicin, platinum resistance, platinum sensitivity, therapeutic dose

INTRODUCTION

Combined chemotherapy using taxane and platinum is currently the standard initial treatment for recurrent ovarian cancer. The time to recurrence after the completion of initial chemotherapy, i. e., treatment-free interval (TFI) can be correlated with the response rate (RR). In general, TFI for drug susceptibility is <1 month, whereas TFI of 6 months indicates drug resistance. In addition, cases with TFI of ≤12 months were less sensitive to chemotherapy compared with those with TFI of ≥12 months.[1]

The addition of platinum-based regimen to standard chemotherapy has been recommended

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for the relapse of platinum-sensitive ovarian cancer. In cases of platinum resistance, no significant difference between a multidrug and single-agent regimen was observed in prolonging life or RR in past trials. In addition, single-agent chemotherapy is the treatment of choice when aiming for the reduction of adverse events. The selection of an agent for platinum-resistant cases is dependent on the absence of cross-resistance to the initial treatment.[2-4] However, in clinical practice, some patients can tolerate drug-specific adverse events. The agents recommended for platinum-resistant epithelial ovarian cancer relapse are paclitaxel, docetaxel, irinotecan, pegylated liposomal doxorubicin (PEG-LD), topotecan, gemcitabine, and oral etoposide in the United States and Japan.[5-14]

The addition of PEG-LD to standard chemotherapy is recommended by the British Ovarian Cancer Treatment Guidelines not only for platinum-resistant cases but also for those with intermediate sensitivity. PEG-LD is an anthracycline agent that selectively targets the tumor organizational liposome. Conventional doxorubicin is no longer used for chemotherapy because of its alopecia effect and toxicity to the heart, digestive organs, and blood.[15,16] Previous clinical trials have reported that PEG-LD has no cross-tolerance with other chemotherapeutic agents for recurrent epithelial ovarian cancer. In addition, PEG-LD is not significantly different from paclitaxel, topotecan, and gemcitabine in terms of overall survival (OS) and progression-free survival (PFS). Furthermore, the management of adverse events, such as hand–foot syndrome (HFS) and stomatitis, is relatively easy. The toxicity profile of PEG-LD does not overlap with that of other agents that are currently used in Japan.[16,17]

In other countries, PEG-LD has been identified as the standard therapeutic agent for recurrent platinum-resistant epithelial ovarian cancer; however, its use in Japan was only authorized in April 2009. The recommended dose (RD) of PEG-LD is 50 mg/m^2 given intravenously every 4 weeks. However, HFS (Grades 1–3), which was the main adverse event, occurred in 48%.[18] In the only retrospective study available for PEG-LD, the effective dose was found to be 30–40 mg/m^2. Moreover, compared with the 50 mg/m^2 dose, the 40 mg/m^2 dose had similar OS and PFS but fewer adverse events.[18] Since the year 2000, few clinical trials comparing the anticancer spectrum and toxicity profile of combination therapy with PEG-LD and docetaxel have been conducted, mainly for breast cancer. Kouroussis *et al.* reported that the maximum tolerated dose (MTD) was 35 mg/m^2/week for docetaxel and 14 mg/m^2/week for PEG-LD in a Phase I study of patients with solid tumor. The combination therapeutic overall response in that study was reported to be 22.7%.[20,21] Recently, Sparano *et al*. performed a Phase III clinical trial on 751 patients with progressing breast cancer. They reported that a combination therapy of 60 mg/m^2 docetaxel and 30 mg/m^2 PLD→PEG-LD given every 3 weeks improved the time to progression (TTP) and RR compared with 75 mg/m^2 docetaxel given as a single agent every 3 weeks.[22,23]

On the basis of the hypothesis that the toxicity profile and anticancer spectrum of docetaxel differ from those of PEG-LD, we aimed to perform a Phase I trial on the efficacy of combination therapy with PLD and docetaxel, compared with single-agent PEG-LD regimen, for patients with platinum-resistant ovarian cancer in Japan.

MATERIALS AND METHODS

Study protocol, ethics committee approval, and informed consent

For the purpose of evaluating the combination therapy of PEG-LD and docetaxel, the member institutions of the Kansai Clinical Oncology Group (KCOG) assigned patients with recurrent epithelial ovarian and peritoneal carcinomas between January 2010 and March 2011 into the KCOG protocol (KCOG-G0901). Approval for this study was granted by the Local Ethics Committees of KCOG, Kansai Rosai Hospital, Shizuoka Cancer Center, Nara Medical University, Hyogo Medical College, and Nagoya Municipal University. All patients who participated in this study provided written informed consent after a thorough explanation of the contents of the study and provision of other explanatory documents.

Patient eligibility

All patients were required to meet the following criteria: (1) histologic or cytologic diagnosis of Mullerian carcinoma (epithelial ovarian carcinoma, fallopian tube carcinoma, or primary peritoneal carcinoma); (2) recurrence within 12 months after the final course of the first-line platinum-based chemotherapy (including recurrence identified by tumor markers); and (3) ECOG performance status of 0–2. To be eligible to receive first-line platinum-based chemotherapy, patients had to be at least 20 years old and not older than 75 years old at the time of enrollment. In addition, patients who met the following criteria were included: hemoglobin >9.0 g/dL, white blood cell count 3000–12,000/mm^3, absolute neutrophil count (ANC) ≥1500/mm^3, platelet count ≥100,000/mm^3, aspartate transaminase/alanine transaminase ≤2.5 times the upper limit of normal (ULN), alkaline phosphatase ≤2.5 times ULN, bilirubin <1.2 mg/dL, serum creatinine ≤1.5 times ULN, cardiac function with left ventricular ejection fraction (LVEF) ≥50% and electrocardiogram within normal limits, and no symptoms requiring treatment. The patients were expected to survive for at least 3 months and should not have received chemotherapy for more than 4 weeks.

The principal investigator or subinvestigator excluded the following patients: (1) patients with severe complications or active systemic infection that may affect the administration

and proper assessment of the drugs; (2) patients with multiple synchronous and metachronous cancers within 5 years of disease-free interval, with the exceptions of basal and squamous cell carcinoma, carcinoma *in situ*, and intramucosal carcinoma-like lesions, which are curable by local treatment; (3) patients with angina or myocardial infarction within the last 90 days (day 1 was defined as the day before enrollment); (4) patients who had symptomatic brain metastases that required the administration of steroids or anti-inflammatory agents; (5) patients who have received bone marrow transplant, hematopoietic stem cell transplant, or high-dose chemotherapy; (6) patients who have received prior chemotherapy consisting of anthracycline, including PLD, or docetaxel; (7) patients with a history of hypersensitivity to the components of anthracycline, taxane, or liposomal doxorubicin (mPEG-DSPE, hydrogenated lecithin, cholesterol, ammonium sulfate, histidine, sucrose, hydrochloric acid, and sodium hydroxide); and (8) patients who were or suspected to be pregnant or lactating.

Treatment

The patients were required to undergo medical history interview, physical examination, and laboratory tests within 14 days of starting the treatment. Toxicity assessment using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v. 3.0) and complete blood count were obtained weekly. Tumor measurements and tumor markers, when applicable, were examined after one or two cycles of chemotherapy. Adverse events were reported and recorded as they occurred.

On day 1 of a 21-day cycle, PEG-LD and docetaxel were given in combination as an intravenous infusion for 1 h. This study arm was created to assess the toxicity of each sequential dose setting [Table 1]. This design began with the treatment of the first patient at a Level 1 dose. If the next three patients did not experience (DLT), dose escalation continued. Additional patients were enrolled at the same dose level on the basis of the classic modified Fibonacci scheme.[24]

DLT was defined as (1) Grade 4 neutropenia lasting longer than 7 days; (2) Grade 4 thrombocytopenia; (3) any Grade 3 or Grade 4 nonhematologic toxicity, except nausea, emesis, anorexia, alopecia, anaphylaxis, and infusion reaction; (4) serum bilirubin of ≥3.0 mg/dL; or (5) any episode of febrile neutropenia.

Treatment was delayed by 1 week for patients with ANC ≤1500 cells/mm^3, at least Grade 2 stomatitis, at least Grade 2 HFS, or platelet count ≤100,000 cells/mm^3. Both PEG-LD and docetaxel doses were reduced by 25% if a patient's nadir values for ANC were <500 cells/mm^3 and for platelet count were <25,000 cells/mm^3 as well as for those with Grade 3/4 nonhematologic toxicities, except for fatigue, nausea, emesis, anorexia, alopecia, hypokalemia, hyponatremia, and infusion reaction. PEG-LD dose was reduced by 25% for Grade 3 palmar-plantar erythrodysesthesia (PPE) and Grade 3/4 stomatitis. Therapy was discontinued in cases of voluntary patient withdrawal, development of clinical congestive heart failure (LVEF of <45% or a decrease of 20% or more from pretreatment value), two dose reductions, cumulative anthracycline level of ≥500 mg/m^2 with PEG-LD, prolonged Grade 2 infusion reaction within 24 h of administration, or disease progression or at the discretion of the treating physician.

Table 1: Accelerated dose escalation schema

Level	PLD (mg/m^2, day 1)	DXT (mg/m^2, day 1)
0	25	50
1	30	50
2	30	60

PLD=Pegylated liposomal doxorubicin, DXT=Docetaxel

Response criteria

Response assessment was based on guidelines set forth in the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. For the assessment of safety and toxicity, we used CTCAE (version 3.0). The primary objective was to determine RD of PEG-LD in combination with docetaxel. MTD was used to determine RDs of PEG-LD and docetaxel. The secondary objective was to evaluate the best overall response (RR) and safety of PEG-LD in combination with docetaxel.

RESULTS

Six patients were enrolled in the study between January 2010 and March 2011. The baseline characteristics, dose levels, total number of cycles, and OS are listed in Table 2. One patient, designated as patient 5, dropped out because of an improper regimen administered by the treating physician. Two patients who were enrolled at dose Level 1 experienced DLTs, such as Grade 4 neutropenia, whereas three patients who were enrolled at dose Level 0 did not experience DLT. MTD for this study arm was dose Level 0.

Table 3 presents the severity of hematologic toxicities for all patients in the entire study arm. There were no Grade 2–4 thrombocytopenia and Grade 3–4 anemia observed in any patient. Table 4 shows the most common nonhematologic toxicities for each patient. Grade 2 toxicities were uncommon, and no Grade 3–4 toxicities occurred. The antitumor response of patients in this study arm is shown in Tables 2 and 5. One complete response was documented in a patient who was enrolled at dose Level 1. One partial response was documented in a patient who was enrolled at dose Level 0. RR was 2/5 (40%), the disease control rate was 3/5 (60%), and the median OS time was 7.4 months (range, 4.5–15.4 months). After experiencing DLT and dropping out of this study, two patients who were enrolled at dose Level 1 continued to undergo treatment at reduced doses for nine or four cycles.

DISCUSSION

This small preliminary Phase I study evaluated the safety profile and MTD of combination therapy with PEG-LD and

Table 2: Patient characteristics, dose level, total cycles, and overall survival

Patient number	Level	Age (years)	Histology	TFI (months)	PS	Measurable disease	Nonmeasurable disease	DLT	Total cycles	Overall survival (months)
1	1	61	Serious	9.1	0	None	CA125	Neutropenia G4	9	15.4 AWD
2	1	47	Serious	3.7	2	None	Pleural effusion	Neutropenia G4	4	14.0 DOD
3	0	71	SSPC	1.0	0	Peritoneal dissemination	Ascites	None	7	7.4 DOD
4	0	53	Serious	11.0	0	Peritoneal dissemination	Ascites	None	3	4.5 DOD
6	0	66	High-grade adenocarcinoma	5.5	2	Peritoneal dissemination	Ascites	None	7	6.2 AWD

One patient enrolled as "number 5" dropped out because of improper regimen by the treating physician. Two patients enrolled at dose Level 1 experienced DLT (Grade 4 neutropenia). Three patients enrolled at dose Level 0 experienced no DLT. The maximum tolerance dose for this study arm was dose Level 0. No Grade 2–4 thrombocytopenia was observed in any patient. No Grade 3–4 hemoglobin decrease was observed in any patient. AWD=Alive with disease, DOD=Death of disease, SSPC=Serous surface papillary carcinoma, TFI=Treatment-free interval, PS=Platinum-sensitive, DLT=Dose-limiting toxicity

Table 3: The worse grade of hematological toxicities for each patient

Patient number	Level	Neutropenia	Hemoglobin decreased	Thrombocytopenia
1	1	4	2	-
2	1	4	-	1
3	0	4	1	-
4	0	3	1	-
6	0	3	2	1

Grade 2 toxicities were uncommon, and no Grade 3–4 toxicities occurred

docetaxel administered every 21 days to patients with recurrent epithelial ovarian and peritoneal carcinomas. We demonstrated that this combination regimen was feasible with minimal hematologic and nonhematologic toxicities. Grade 4 neutropenia was considered DLT. MTD was 25 mg/m^2 PEG-LD, followed by 50 mg/m^2 docetaxel on day 1 and every 21 days thereafter.

Studies on the combination of PEG-LD and docetaxel for other malignancies, including breast cancer, have been published since 2000. In 2003, Fracasso *et al*. reported their Phase I study on advanced malignancy in 22 patients who were enrolled in two treatment arms. In their accelerated, dose escalation trial, Arm A comprised PEG-LD followed by docetaxel on days 1 and 15 every 28 days, whereas Arm B comprised docetaxel followed by PEG-LD on days 1 and 15 every 28 days.[20] Patients enrolled in that study had malignancies other than ovarian cancer, whereas all patients in our study had only ovarian cancer. Our study was conducted in only one arm, which was PEG-LD followed by docetaxel; this is because myelosuppression when doxorubicin is followed by paclitaxel is less severe compared with that when paclitaxel is followed by doxorubicin. Moreover, paclitaxel may increase the concentration of unchanged doxorubicin.

Recently, Sparano *et al*. reported a Phase III trial in which they compared docetaxel (75 mg/m^2) given as a single agent every 3 weeks with a combination of docetaxel (60 mg/m^2) and PEG-LD (30 mg/m^2) given every 3 weeks. Their results indicated that the addition of PEG-LD to docetaxel was superior to docetaxel alone in terms of TTP and RR. The percentage of Grade 3/4 neutropenia in patients who received combination treatment and docetaxel alone was 66% and 65%, respectively. Grade 3/4 PPEs occurred in 24% patients enrolled in this trial. On the basis of previous studies, we concluded that the toxicities were acceptable.[22,23]

Since the toxicity profiles and anticancer spectrum of PEG-LD and docetaxel are considerably distinct, only Grade 4 neutropenia was observed in the trial reported by Sparano *et al*.; however, all patients continued to experience other Grade 1–2 hematologic and nonhematologic toxicities. The low incidence of adverse events observed in our study may be related to the dosage of PLD. RD of PLD alone for patients with ovarian cancer is limited to 50 mg/m^2 on day 1 and every 28 days thereafter. Grade 1–3 PPE was the main consequence of PEG-LD toxicity and occurred in 48% patients. In a Japanese Phase II trial, PPEs occurred in 78.4% patients treated with 50 mg/m^2 PEG-LD every 28 days. PPEs caused delayed PEG-LD treatment in 40.8% patients, and 4.1% patients stopped participating in the trial.[19] The efficacy of PEG-LD at a dose of 30–40 mg/m^2 every 28 days was identified in previous retrospective studies. In particular, there was no significant difference between the 40 and 50 mg/m^2 PEG-LD doses in terms of RR, PFS, and OS as well as DLT.[18] Our findings, coupled with those of previous studies, demonstrated that if PEG-LD was administered at a dose of 10 mg/m^2 per week, the efficiency of prolonging the survival is improved and toxicity is reduced.

To the best of our knowledge, this is the only Phase I trial that utilized the day 1 schedule of the administration of this combination therapy every 21 days to treat relapse of epithelial ovarian carcinoma. Sparano *et al*. conducted their Phase I study of PEG-LD and docetaxel in patients with advanced breast carcinoma using a 21-day schedule. In that study, MTD was 30 mg/m^2 PEG-LD and 60 mg/m^2 docetaxel. At these MTDs, 60% patients experienced Grade 3–4 neutropenia and 13% experienced Grade 3–4 stomatitis and PPEs; DLT of this regimen was febrile neutropenia. With the addition of granulocyte-colony-stimulating factor, MTD was 30 mg/m^2 PEG-LD and 75 mg/m^2 docetaxel every 28 days. Of 29 patients who received this regimen, 55% showed response to the

Table 4: The worse grade of nonhematological toxicities for each patient

Patient number	PPE	Stomatitis	Nausea	Emesis	Diarrhea	Anorexia	Fatigue	Alopecia	Motory neuropathy	Sensory neuropathy
1	1	1	-		-	1	-	-	-	-
2	1	1	-		-	1	1	1	-	-
3	-	2	1	1	2	1	1	-	-	1
4	-	-	-	1	-	-	-	-	-	-
6	-	1	-	-	-	1	-	1	-	1

One CR was documented in a patient enrolled at dose Level 1. One PR was documented in a patient administered at dose Level 0. Response rate was 40%, and disease control rate was 60%. The median of overall survival was 7.4 months–range, 4.5–15.4 months). Two patients enrolled at dose Level 1 continued to be administered with reducing doses for 9 and 4 cycles after experiencing DLT and dropping out this study. PPE=Palmar-plantar erythrodysesthesia, CR=Complete response, DLT=Dose-limiting toxicity, PR=Partial response

Table 5: Response to treatment for each cycle

Patient number	Dose level	Number of cycles								
		1	2	3	4	5	6	7	8	9
1	1	PD*	-	SD	SD	SD	SD	SD	SD	SD
2	1	-	CR	-	CR					
3	0	-	-	SD	-	SD	-	PD		
4	0	-	-	PD						
6	0	-	SD	-	PR in	-	PR	-		

*PD (new lesion appeared at a neck lymph node). CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease

treatment. Previous reports that used various other schedules have shown serious myelosuppression, mucositis, and skin toxicities.[22,23] MTD of our study ameliorated the hematologic and nonhematologic complications observed in these previous studies.

CONCLUSION

The administration of 25 mg/m^2 PEG-LD, followed by 50 mg/m^2 docetaxel, on day 1 and every 21 days thereafter in patients with platinum-resistant or partially platinum-sensitive epithelial ovarian cancer appeared to be a well-tolerated regimen with acceptable toxicities. RR was 40%, and the disease control rate was 60%. The median OS time was 7.4 months (range, 4.5–15.4 months). These results, coupled with those of other studies, warrant Phase II trials of this treatment combination in patients with platinum-resistant epithelial ovarian carcinoma. Based on the findings of our study, new molecular targeted drugs such as bevacizumab, veliparib, and olaparib may be effective in treating gynecological cancer. To confirm this, our group has initiated a Phase II study of cisplatin-based chemotherapy using gemcitabine and bevacizumab (KCOG-G-1601 trial; UMIN000023097).

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Conflicts of interest
There are no conflicts of interest.

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