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Retrospective analysis of the survival benefit of chemotherapy for recurrent or advanced epithelial ovarian carcinoma in patients previously treated with paclitaxel plus platinum-based chemotherapy

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Summary

Aim: The outcomes of treatment for women with recurrent or advanced epithelial ovarian carcinoma previously treated with paclitaxel plus platinum-based chemotherapy were analyzed. *Materials and Methods:* Retrospective analysis was performed in a total of 65 series of treatments provided for 35 patients with a history of paclitaxel plus platinum-based chemotherapy. The chemotherapy regimens used were classified into the following four types for analysis: conventional paclitaxel plus carboplatin therapy (TC arm), pegylated liposomal doxorubicin-containing regimens (PLD arm), CPT-11-containing regimens (CPT-11 arm), and others. Disease-control rates (DCRs) were compared and subjected to univariate analysis. Progression-free survival (PFS) was determined from the date of the first cycle of each chemotherapy with the Kaplan-Meier method, and comparisons were performed using the log-rank test. *Results:* DCR was 80%, 71%, and 26% for the TC, PLD, and CPT-11 arms, respectively. The median PFS was 286, 372, and 76 days for the TC, PLD, and CPT-11 arms, respectively. There was no discernible difference in PFS between the TC and the PLD arm. In contrast, PFS of the CPT-11 arm was significantly shorter than that of the TC and PLD arms. In addition, three of seven (42.9%) treatments in the PLD arm maintained a progression-free period for longer than one year, while only one of 25 (4%) treatments in the TC arm maintained a progression-free period for more than one year. *Conclusions:* The PFS of PLD is similar to that of TC. PLD-containing regimens might have a potential benefit with a higher PFS over one year than the TC regimen.

Key words: CPT-11; Disease control rates; Ovarian carcinoma; Pegylated liposomal doxorubicin; Progression-free survival.

Introduction

Recurrent ovarian carcinoma is generally incurable [1], and, therefore, several treatments including chemotherapies, selected surgery, and radiation are combined for each patient. However, the effects of these treatments on progression-free survival (PFS) have not been evaluated. Therefore, the outcomes of each treatment for women with recurrent or advanced epithelial ovarian carcinoma previously treated with paclitaxel plus platinum-based chemotherapy were evaluated.

Materials and Methods

All women with a histologically confirmed diagnosis of epithelial ovarian cancer who were referred to the present center from January 2007 to December 2011 were included in a database of treatment and outcome variables. The charts of patients who progressed while receiving or after completion of at least three cycles of paclitaxel plus platinum-based chemotherapy or discontinued treatment early because of toxicity were reviewed to update their follow-up. The follow-up period was ended in December 2012. All patients had measurable lesions that conformed to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and tumor response evaluation was performed according to the RECIST v1.0 guidelines [2].

Whether and how a patient should be treated in cases of relapse were up to the investigator's discretion, and the documented therapies were independently assigned to the following groups. For platinum-resistant patients whose recurrence was documented within six months of platinum-based therapy, the regimen of chemotherapy was a non-platinum regimen as second-line treatment. The chemotherapeutic choices included pegylated liposomal doxorubicin (PLD), irinotecan (CPT-11), gemcitabine, and docetaxel. For platinum-sensitive patients whose recurrence was documented for more than six months after the completion of platinum-based therapy, platinum-based chemotherapy was used again. Among carefully selected patients, secondary surgery with complete cytoreduction (no visible residual disease) or irradiation was also performed.

The disease-control rate (DCR) was defined as either tumor response (CR/PR) or stable disease (SD). DCR was compared and subjected to univariate analysis. PFS was determined from the

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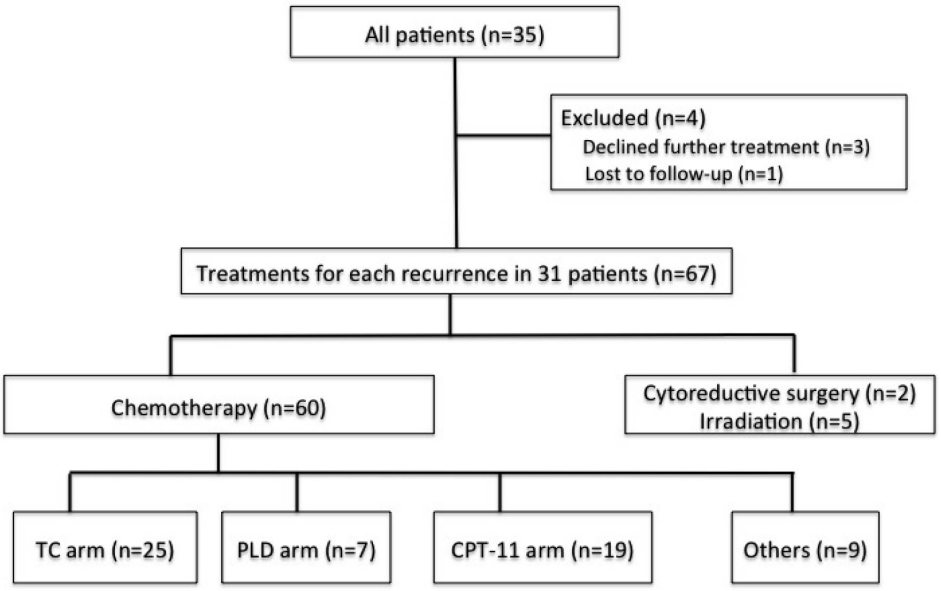

Figure 1. — Study design. TC arm, carboplatin and paclitaxel; PLD arm, pegylated liposomal doxorubicin-containing regimens; CPT-11 arm, CPT-11-containing regimens.

Table 1. — *Patients' clinical characteristics (n=35).*

Characteristic			No. (%)
Mean age	Years		60.9
	Range		(41-83)
Stage	I		5 (14)
	II		1 (3)
	III		22 (63)
	IV		7 (20)
Tumor histology/cytology		Serous	24 (69)
		Mucinous	3 (9)
		Endometrioid	0 (0)
		Clear cell	6 (17)
		Others	2 (6)

Table 2. — *Treatment response, duration of exposure, and discontinuation of treatment.*

	TC (n=25)	CPT-11 (n=19)	PLD (n=7)	Others (n=9)
DCR	80%	26%	71%	33%
Median PFS (days)	286	71	372	78
PFS > 1 year	4%*	0%	42.9%*	0%
Duration of exposure (days)	117 (3-175)	62 (5-210)	167 (42-372)	74 (19-127)
Discontinuation due to AE	2 (8%)	2 (10.5%)	0	0

TC: carboplatin and paclitaxel;
PLD: pegylated liposomal doxorubicin-containing regimens;
CPT-11: CPT-11-containing regimens;
DCR: disease-control rate; PFS: progression-free survival; AE: adverse event.
*$p < 0.05$.

date of the first cycle of each chemotherapy to first disease progression and, thereafter, from one progression to the subsequent one or the last contact date that the patient was still known to be progression-free. The Kaplan-Meier method and the log-rank test were used to analyze PFS, and a Bonferroni correction was then used for comparisons of multiple groups. Differences were considered significant if the *p*-value was < 0.05. Statistical analysis was performed using MedCalc version 12.7.5.

Results

Eighty-nine patients with histologically confirmed epithelial ovarian cancer were referred to the present center from January 2007 to December 2011. In 35 patients, at least one relapse was reported after first-line therapy (Figure 1). Three patients refused further treatment, and one patient was lost to follow-up. Information on subsequent therapies after the first recurrence was evaluable in 31 patients. The patients' characteristics are shown in Table 1. A total of 67 treatments was documented. These treatments comprised of different modalities such as chemotherapy (n=60, 89.6%), surgery (n=2, 3.0%), and radiotherapy (n=5, 7.5%). The most commonly used chemotherapeutic regimen was a combination of paclitaxel plus platinum-based chemotherapy (n=25, 41.7%; TC arm), followed by CPT-11 containing regimens (n=19, 31.7%: monotherapy with CPT-11 n=2, combination of CPT-11 and docetaxel n=16, combination of CPT-11 and platinum n=1; CPT-11 arm), and PLD-containing regimens (n=7, 11.7%: monotherapy with PLD n=5, combination of PLD and carboplatin n=2; PLD arm). Two patients with platinum-resistant recurrent ovarian cancer underwent secondary cytoreductive surgery. In one case, splenectomy was performed for isolated splenic metastasis. The patient had a 179-day remission before the next recurrence of her disease. In the other case, for a local recurrence in the right retroperitoneal space and brain metastasis in the cerebel-

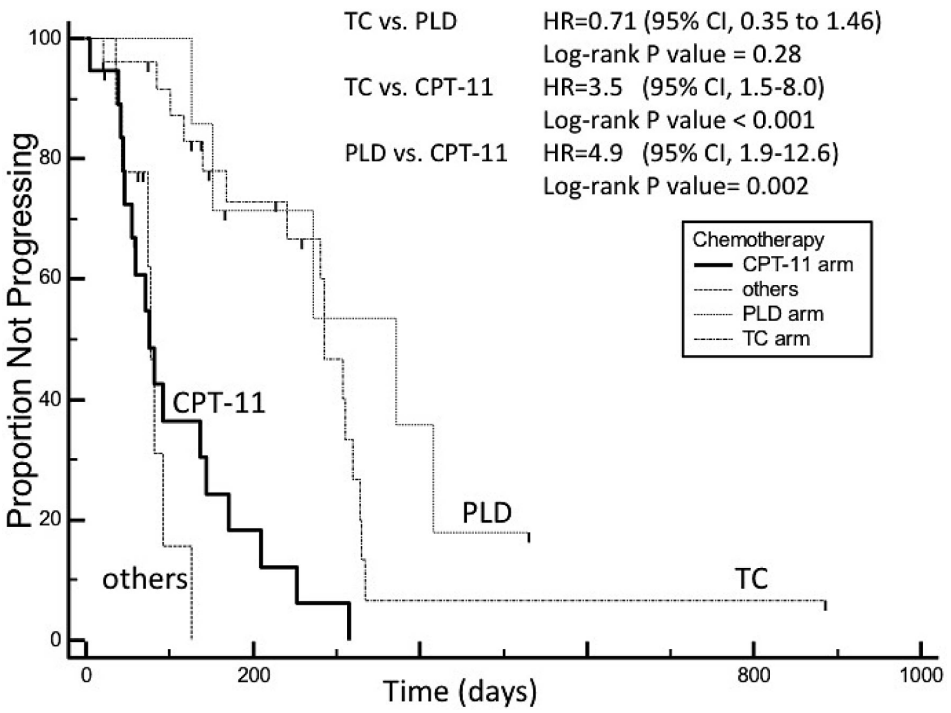

Figure 2. — Kaplan-Meier estimates of progression-free survival (PFS). HR: hazard ratio; TC arm: carboplatin and paclitaxel; PLD arm: pegylated liposomal doxorubicin-containing regimens; CPT-11 arm: CPT-11-containing regimens.

lum, excision of tumor from the pelvic peritoneum and of the brain metastasis was performed. She survived with no evidence of recurrent disease (CR) for about 32 months. These two cases of cytoreductive surgery were excluded from the analysis due to their small number. Five cases of irradiation due to palliative administration for recurrent ovarian cancer were also excluded.

DCR was 80% for the TC arm (CR n=7, PR n=9, SD n=4), 71% for the PLD arm (CR n=1, PR n=1, SD n=3), 26% for the CPT-11 arm (PR n=2, SD n=3), and 30% for others (PR n=1, SD n=2) (Table 2). The median PFS of each chemotherapeutic regimen is shown in Figure 2. The median PFS was 286 days for the TC arm, 372 days for the PLD arm, 71 days for the CPT-11 arm, and 78 days for others. A Kaplan-Meier analysis of patients in the PLD arm and the TC arm showed no significant difference in PFS ($p = 0.28$). On the other hand, PFS was longer in patients in the TC arm than in the CPT-11 arm ($p < 0.001$). PFS of patients in the PLD arm was also significantly longer than that of patients in the CPT-11 arm ($p = 0.002$). Exploratory analyses examining the impact on PFS of the number of previous lines of chemotherapy, histologic classification of tumor cells, and chemotherapeutic regimen were performed using Cox proportional hazards regression. PFS was significantly shorter in the TC arm and the PLD arm than in the CPT-11 arm in the multivariate Cox regression model (data not shown). In addition, with the limitation inherent from the small numbers, 42.9% (n=3 of 7) in the PLD arm significantly maintained a progression-free period for longer than one year, while only 4% (n=1 of 25) in the TC arm maintained a progression-free period for more than one year ($p > 0.05$) (Table 2). Treatment discontinuation because of adverse events (AEs) occurred with four treatments (28.6%), two of which occurred in the TC arm and the two of which occurred in the CPT-11 arm.

Discussion

Once diseases recur, patients with relapses six months after completion of initial platinum-based therapy are considered platinum/taxane-sensitive. Chemotherapy with platinum is a standard treatment, and patients were treated with TC or carboplatin and PLD [3-5].

Patients with no response or responses lasting less than six months are platinum/taxane-resistant and are best treated with agents that lack cross-resistance to the TC regimen. Most common chemotherapeutic choices for platinum/taxane resistance included PLD, CPT-11, and gemcitabine [6-10].

In this trial, PFS was similar between the PLD and TC arms, and PFS was significantly longer for the TC arm/PLD arm than for the CPT-11 regimen or other regimens. In the CALYPSO Trial, PFS for PLD with carboplatin (CD) was significantly superior to that of TC [6]. The PLD arm in this study consisted of five monotherapy and two CD regimens. In the present study, though most of the cases were monotherapy, the PLD arm had prolonged PFS, as did the

TC arm. Thus, on the basis of a median PFS of 372 days, PLD performed better than expected in terms of PFS.

Gorden *et al.* reported that a median PFS of PLD monotherapy in patients with epithelial ovarian carcinoma that recurred after or that did not respond to first-line platinum-based chemotherapy was 19.1 weeks, and the overall response rate for PLD was 19.7% [7]. In Japan, Katsumata *et al.* reported that the median time to progression of PLD monotherapy in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy was 166 days [11].

With respect to PFS of longer than one year, PLD was superior to TC. One of the reasons was that the duration of treatment was longer in the PLD arm than in the TC arm (167 *vs.* 117 days in the median duration of exposure to chemotherapy, respectively) due to lower toxicity.

As for toxicity, in the HeCOG trial, the rate of discontinuation due to toxicity was significantly higher in the paclitaxel group (13.5% in CP *vs.* 3% in CLD, $p = 0.020$) [12]. In the CALYPSO trial, fewer patients discontinued treatment early for toxicity with PLD than with TC regimens (6% *vs*. 15%; $p < 0.001$) [6]. In the present study, PLD was used for extended periods of time with very minimal toxicities. Several RCTs failed to show an improvement of survival for patients with recurrent ovarian carcinoma who received extended therapy [13]. However, some reports suggested that continuous PLD treatment in patients who achieved a response to PLD might delay time to disease progression. Collins *et al.* reported that two patients were maintained on PLD with stable disease for 18 and 34 months, respectively [14]. These cases demonstrated that PLD can be used for extended periods of time without cardiotoxicity.

Although a small number of cases was presented, the present data support the clinical efficacy and tolerability of PLD-containing regimens for the treatment of recurrent ovarian cancer. PLD can be used for extended periods of time with very minimal toxicities. These characteristics of PLD allow extended chemotherapy and might delay time to disease progression. PLD may be a promising agent in recurrent ovarian carcinoma.

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