Retrospective study comparing irinotecan and pegylated liposomal doxorubicin in treatment of recurrent platinum-refractory/resistant epithelial ovarian cancer

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Summary

Purpose: The standard regimen for platinum-resistant/refractory recurrent epithelial ovarian cancer (EOC) remains to be determined. In this study, we retrospectively compared the effect of irinotecan (CPT-11) and pegylated liposomal doxorubicin (PLD) in the treatment of platinum-resistant recurrent EOC. *Methods:* Thirty patients who received salvage chemotherapy with CPT-11 or PLD were included in the study. CPT-11 (100 mg/m^2) was administered intravenously on days 1, 8 and 15 every four weeks. PLD (50 mg/m^2) was administered on day 1 every four weeks. Treatment was repeated, provided that no disease progression or intolerable toxicity occurred. *Results:* Response rate in the CPT-11 group and PLD group showed no difference at 26.7% ($p = 0.66$) in both, while non-PD rate was 73.3% vs 33.3% ($p < 0.05$), respectively. Progression-free survival after CPT-11 treatment and PLD treatment was 28.4 weeks and 16.8 weeks ($p = 0.07$), respectively. Hand-foot syndrome and mucositis were more common in the PLD group than in the CPT-11 group ($p < 0.05$). *Conclusions:* The results indicate that CPT-11 is a promising drug for the treatment of platinum-resistant recurrent EOC.

Key words: Ovarian cancer; Recurrence; Platinum-resistant; Irinotecan; Liposomal doxorubicin.

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, accounting for approximately 8,000 new diagnoses and 4,000 deaths annually in Japan [1]. Patients are usually treated with cytoreductive surgery, followed by platinum/taxane chemotherapy, and the initial response rate for these treatments exceeds 70% [2]. Despite such a good initial response, however, the majority of patients experience a relapse, with a median disease-free interval of 18 to 24 months. Recurrent cases are classified into three categories: platinum-sensitive (relapse after ≥ 6 months of initial platinum therapy); platinum-resistant (relapse within 6 months of initial platinum therapy); or platinum-refractory (stable disease or progressive disease during initial platinum therapy). According to guidelines issued by the National Comprehensive Cancer Network (NCCN), while platinum-based combination therapy should be considered in recurrent cases classified as platinum-sensitive, non-platinum monotherapy is recommended in recurrent cases classified as platinum-resistant/refractory [3]. The standard regimen, however, remains to be determined. Pegylated liposomal doxorubicin (PLD) is approved by the US Food and Drug Administration for use in patients with EOC whose disease has progressed or recurred after platinum-based chemotherapy, and PLD has become a commonly used treatment option for patients with recurrent platinum-resistant/refractory EOC. Irinotecan (CPT-11), a semi-synthetic derivative of camptothecin and topoisomerase I inhibitor, is widely used for platinum-resistant EOC in Japan [4]. In this retrospective study, we compared the effect of CPT-11 and PLD in the treatment of platinum-resistant recurrent EOC.

Materials and Methods

Patients

We retrospectively reviewed the medical records of women with platinum-refractory/resistant recurrent EOC who received CPT-11 or PLD.

Thirty patients in whom salvage chemotherapy was commenced between May 2006 and May 2010 were included in the study. All patients underwent initial surgery and primary chemotherapy consisting of a platinum/taxane regimen, and were followed-up at the Department of Obstetrics and Gynecology, Keio University Hospital, Tokyo. All treatments were performed by staff of the same gynecologic oncology group. Decisions with regard to the salvage chemotherapy were usually made by the attending clinician. Any regimen that contained a platinum or taxane drug was counted as one regimen. For example, if a patient received a platinum/taxane regimen as first-line chemotherapy and then, after recurrence, received another platinum/taxane regimen as second-line chemotherapy, the number of regimens was counted as two. Except one patient, none of the patients in the CPT-11 group had received prior treatment with CPT-11, topotecan (TOP) or some other topoisomerase I inhibitor, and none of the patients in the PLD group had been treated with anthracyclines, including PLD. Data were collected on age, International Federation of Gynecology and Obstetrics (FIGO) staging, histologic type, histologic grade, prior chemotherapeutic treatment, site of recurrence, interval between prior chemotherapy and date of recurrence and progression-free survival (PFS) after recurrence.

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Definition of chemotherapy sensitivity of prior chemotherapy

"Refractory," "resistant," and "sensitive" at first recurrence were defined as follows: refractory: progression, partial remission, or stable disease during primary chemotherapy; resistant: complete remission and relapse < 6 months of termination of primary chemotherapy; sensitive: complete remission and relapse ≥ 6 months after termination of primary chemotherapy.

Treatment schedule, response evaluation and toxicity assessment.

The treatment cycle consisted of four weeks. Irinotecan (100 mg/m^2) was administered intravenously over 90 min on days 1, 8 and 15 every four weeks. Pegylated liposomal doxorubicin (50 mg/m^2) was administered on day 1 every four weeks. Treatment was repeated for up to eight cycles, provided that no disease progression or intolerable toxicity occurred.

Response was based on 2-dimensional measurement of lesions based on computed tomography (CT) or magnetic resonance imaging (MRI). Complete response (CR) was defined as no evidence of disease on images obtained, with normalization of serum CA125 level. Partial response (PR) was defined as a > 50% decrease in tumor size. Progressive disease (PD) was defined as a > 25% increase in tumor size or the appearance of a new lesion. Stable disease (SD) was defined as neither sufficient shrinkage to qualify as PR, nor sufficient increase to qualify as PD. The CA125 response criteria were not used; however, the patients were considered as showing no PR or change if there was an increase in CA125. CT or MRI were performed every two to three cycles during chemotherapy and every three to six months after chemotherapy. Progression-free survival (PFS) was defined as the interval from the first day of administration of salvage chemotherapy to the day of disease progression.

All adverse effects were classified according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTC), version 3.

Statistical analysis

The Fisher exact test or chi-square test was used to compare clinical background and toxicity between the CPT-11 and PLD groups. The relationships between response rate or non-PD rate and age, histology, number of prior regimens and treatment-free interval (TFI) were analyzed with the Fisher exact test. Patients were categorized by age (< median vs ≥ median), histology (serous vs non-serous), regimen (CPT-11 vs PLD) and TFI (0-3 months vs 4-6 months). Factors influencing PFS were estimated by the Kaplan-Meier method and analyzed with the log-rank test. Statistical calculations were performed using the SPSS Statistics software package, version 17.0 for Windows (SPSS, Chicago, IL).

Results

Patients

Median age at time of salvage chemotherapy was 63 years (range: 37-77 years). Clinical stage and histology were as follows: clinical stage (IIIa, 1; IIIb, 1: IIIc, 14; IV, 14); histology (serous, 18; clear cell, 4; endometrioid, 2; mucinous, 2; other, 4). Median TFI after prior chemotherapy was 3.3 months. Recurrent disease was solitary in five cases and multiple in 25. No patient underwent interval debulking surgery or secondary debulking surgery. Fifteen patients received monotherapy with CPT-11 and 15 with PLD. The clinical background in each regimen is shown in Table 1. No significant differences were observed between the CPT-11 group and the PLD group. The median number of prior chemotherapy regimens was 2.1 (range: 1-4) for CPT-11 and 2.1 (range: 1-5) for PLD. The median number of salvage chemotherapy cycles was 3.9 (range: 2-7) for CPT-11 and 4.1 (range: 2-8) for PLD.

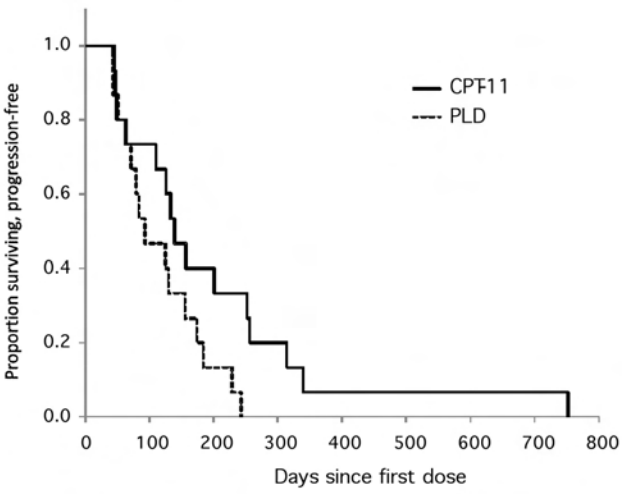

Figure 1. — Kaplan-Meier curve of estimated progression-free survival.

Clinical effect of CPT-11 and PLD

The relationships between clinical factors and response rate or non-PD rate with salvage chemotherapy are shown in Table 2. In total, response rate and non-PD rate in all cases were 26.7% (95% CI: 10.9%-42.5%) and 53.3% (95% CI: 35.4%-71.2%), respectively. PFS after salvage chemotherapy was 22.6 weeks (range: 6.0-107.4 weeks). Age, histology, disease site or TFI showed no association with response rate or non-PD rate in any case.

Response rate in the CPT-11 group and PLD group showed no difference at 26.7% (95% CI: 4.3%-49.1%) (p = 0.66) in both, while the non-PD rate was 73.3% (95% CI: 50.9%-95.7%) vs 33.3% (95% CI: 9.5%-57.1%) (p < 0.05), respectively. Non-PD rate was significantly better in the CPT-11 group than in the PLD group. PFS after CPT-11 treatment and PLD treatment was 28.4 weeks (range: 6.4-107.4 weeks) and 16.8 weeks (range: 6.0-34.7 weeks) (p = 0.07), respectively (Figure 1).

Toxicity

A total of 59 cycles of CPT-11 was administered, and the CPT-11 dose on days 8 and 15 was skipped in 19% and 19% of patients, respectively. Forty-four cycles of CPT-11 were administered after the first cycle. In the

Table 1. — *Clinical background of salvage chemotherapy*.

Factors	CPT-11 (n = 15)	PLD (n = 15)	*p* value
Median age in years	63 (range: 42-71)	62 (range: 37-77)	ns
Histology			ns
Serous	9	9	
Non-serous	6	6	
Endometrioid	2	0	
Mucinous	1	1	
Clear cell	3	1	
Other	0	4	
Disease			ns
Solitary	3	2	
Multiple	12	13	
TFI			ns
0-3 months	9	4	
4-6 months	6	11	
Prior regimen	2.1 (range: 1-4)	2.1 (range: 1-5)	ns

TFI: treatment-free interval; ns: not significant.

Table 2. — *Effect of CPT-11 treatment and PLD treatment*.

Clinical factor		CR+PR (8 cases)	CR+PR+SD (16 cases)
All cases (n = 30)			
Age	< Median	3	9
	≥ Median	5	7
Histology	Serous	3	8
	Non-serous	5	8
Disease site	Solitary	0	1
	Multiple	8	15
TFI	0-3 months	3	8
	4-6 months	5	8
CPT-11 (n = 15)		(4 cases)	(11 cases)
Age	< Median	1	6
	≥ Median	3	5
Histology	Serous	1	6
	Non-serous	3	5
Disease site	Solitary	0	1
	Multiple	4	10
TFI	0-3 months	2	7
	4-6 months	2	4
PLD (n = 15)		(4 cases)	(5 cases)
Age	< Median	2	3
	≥ Median	2	2
Histology	Serous	2	2
	Non-serous	2	3
Disease site	Solitary	0	0
	Multiple	4	5
TFI	0-3 months	1	1
	4-6 months	3	4

TFI: treatment-free interval.

CPT-11 group, 12 of 44 (27%) cycles were delayed, and median delay per one cycle was 3.8 days. Forty-six cycles of PLD were administered after the first cycle. In the PLD group, 17 of 46 (37%) cycles were delayed, and median delay per one cycle was 4.4 days.

The adverse events in the CPT-11 and PLD groups are shown in Table 3. No significant differences were observed in hematologic toxicities between the two groups. Hand-foot syndrome (HFS) and mucositis were significantly more common in the PLD group ($p < 0.05$). Although diarrhea and nausea were more common in the CPT-11 group than in the PLD group, the differences were not significant.

Discussion

Despite a high clinical complete remission rate, EOC patients still exhibit a high rate of recurrence and require chemotherapy. According to guidelines issued by the NCCN, while platinum-based combination therapy should be considered in recurrent cases classified as platinum-sensitive, non-platinum monotherapy is recommended in recurrent cases classified as platinum-resistant/refractory [3]. A number of randomized phase III studies on PLD, TOP, gemcitabine (GEM) and paclitaxel (PTX) for recurrent EOC have been reported [5-8]. Ten Bokkel *et al*. compared TOP and PTX in 235 recurrent EOC cases and reported that TOP showed a level of efficacy at least equivalent to that of PTX, as manifested by an increased response rate and significantly longer time to progression [8]. Gordon *et al*. performed a randomized phase III study to compare the effect of TOP and PLD in 474 recurrent EOC cases and concluded that PLD yielded comparable efficacy, a favorable safety profile and convenient dosing, thus supporting its candidacy as a valuable treatment option in recurrent EOC [6]. However, the subset analysis of platinum-refractory/resistant EOC showed a trend in favor of TOP over PLD in terms of PFS ($p = 0.733$), with a median of 13.6 vs 9.1 weeks, respectively, and overall survival (OS) ($p = 0.455$), with a median of 41.3 vs 35.6 weeks, respectively [6]. Mutch *et al*. performed a randomized phase III trial comparing GEM with PLD in 195 platinum-refractory/resistant recurrent EOC cases and reported that median PFS was 3.6 vs 3.1 months, median OS was 12.7 vs 13.5 months and overall response rate was 6.1% vs 8.3% in the GEM and PLD groups, respectively [7]. From these results, it remains difficult to determine the standard monotherapy regimen for platinum-refractory/resistant recurrent EOC.

Irinotecan is a topoisomerase I inhibitor, and is widely used in platinum-refractory/resistant recurrent EOC in Japan. Matsumoto *et al*. retrospectively analyzed the effect of CPT-11 in 28 platinum-refractory/resistant recurrent EOC patients and reported that response rate (CR+PR) was 29% and that median time to progression was 17 weeks [4]. These results are believed to be promising.

In this study, we compared the effect of CPT-11 and PLD in platinum-refractory/resistant recurrent EOC, retrospectively. Although the response rate was comparable, both non-PD rate and PFS were better in the CPT-11 group than in the PLD group at 73.3% vs 33.3% ($p < 0.05$) and 28.4 weeks vs 16.8 weeks ($p = 0.07$), respectively. Both CPT-11 and TOP are topoisomerase I inhibitors, and this type of drug may be effective for platinum-refractory/resistant recurrent EOC.

Table 3. — *Toxicity of CPT-11 treatment and PLD treatment.*

	CPT-11 (n = 15)						PLD (n = 15)					
	G1	G2	G3	G4	All grades	G3 + 4	G1	G2	G3	G4	All grades	G3 + 4
Hematologic												
WBC	3	9	2	0	14 (93%)	2 (13%)	2	6	6	1	15 (100%)	7 (47%)
ANC	1	5	6	0	12 (80%)	6 (40%)	1	3	6	4	14 (93%)	10 (67%)
Hb	4	6	3	0	13 (87%)	3 (20%)	4	6	2	1	13 (87%)	3 (20%)
Plt	3	0	0	0	3 (20%)	0 (0%)	6	1	2	0	9 (60%)	2 (13%)
Non-hematologic												
Total bilirubin	0	0	0	0	0 (0%)	0 (0%)	0	0	0	0	0 (0%)	0 (0%)
AST	2	0	0	0	2 (13%)	0 (0%)	5	0	0	0	5 (33%)	0 (0%)
ALT	1	1	0	0	2 (13%)	0 (0%)	3	0	0	0	3 (20%)	0 (0%)
Creatinine	3	1	0	0	4 (27%)	0 (0%)	3	0	0	0	3 (20%)	0 (0%)
Diarrhea	5	1	1	0	7 (47%)	1 (7%)	2	0	0	0	2 (13%)	0 (0%)
Nausea	8	3	1	0	12 (80%)	1 (7%)	7	1	0	0	8 (53%)	0 (0%)
HFS	0	0	0	0	0 (0%)*	0 (0%)	6	3	0	0	9 (60%)*	0 (0%)
Mucositis	2	1	0	0	3 (20%)*	0 (0%)	6	4	0	0	10 (67%)*	0 (0%)

* $p < 0.05$.

One of the important purposes of salvage chemotherapy is palliation of symptoms and maintenance of quality of life (QOL). Therefore, toxicity is an important consideration in choice of chemotherapy regimen. In this study, no significant difference was observed in hematologic toxicities or most non-hematologic toxicities between the CPT-11 and PLD groups. However, HFS and mucositis were more common in the PLD group. Finally, tolerability was equivalent between the two groups. Assessment of QOL will be an essential factor in choice of drug.

Conclusion

In conclusion, the results indicate that CPT-11 is a promising drug for the treatment of platinum-resistant recurrent EOC. Further randomized phase III studies are required to elucidate the efficacy of CPT-11 in the treatment of platinum-refractory/resistant recurrent EOC in comparison with PLD.

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