Combination of irinotecan and platinum for platinum-resistant or refractory recurrent ovarian cancers: A preliminary case series

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Abstract. Non-platinum single agents are usually used for patients with platinum-resistant recurrent ovarian cancers (ROC). However, the efficacy of these drugs is limited. The aim of the present study was to evaluate the efficacy and adverse events (AE) of combination therapy with irinotecan and platinum (CPT-Pt) for ROC. A total of 28 platinum-resistant or refractory patients with ROC treated with CPT-Pt at the National Defense Medical College Hospital institution between 2002 and 2012 were identified. All patients received taxane and carboplatin (TC) as a first-line treatment and relapsed within 6 months after completion of TC, or progressed during TC therapy. The median age was 59 years (range, 16-78), and median number of CPT-Pt therapy cycles was 5.5 (range, 2-16). The overall response rate was 14%, with a complete response (CR) in 2 patients and partial response (PR) in 2 patients. Stable disease (SD) for >3 months was observed in 15 patients (54%), resulting in a clinical benefit rate (CBR = CR + PR + SD) of 68%. The median progression-free survival and overall survival were 8 and 15 months, respectively. Fifteen cases (68%) developed grade 3/4 hematological AE and 3 cases (11%) developed non-hematological grade 3/4 AE, which were resolved by conservative management or dose reduction. Platinum re-treatment with irinotecan for platinum refractory or resistant ROC may be a candidate in such clinical settings.

Introduction

Platinum-based agents have been key drugs for epithelial ovarian cancer during the past three decades (1). The standard treatment for ovarian cancer is debulking surgery followed by a combination of taxanes and carboplatin (TC), but more than half of cases with advanced disease relapse (2). Relapse within 6 months after the last platinum-based therapy is defined as platinum-resistant recurrence (Pt-R) (3), and non-platinum single agents such as pegylated liposomal doxorubicin, paclitaxel, topotecan and gemcitabine are commonly used for patients with Pt-R recurrent ovarian cancer (ROC) (4). Among these drugs, there appear to be no differences in response rate (10-15%), progression-free survival (PFS) (3-4 months) and overall survival (OS) (approximately 12 months) (5-10). Due to the poor prognosis of patients with Pt-R ROC by these treatments, novel agents including molecular-targeting drugs have been investigated to overcome platinum-resistance.

The efficacy of administration of platinum re-treatment for Pt-R ROC has not yet been established. Weekly paclitaxel with carboplatin for Pt-R ROC had no advantage in terms of PFS compared with weekly paclitaxel alone (11). By contrast, dose-dense weekly administration of platinum agents has been reported to extend PFS for Pt-R ROC in recent years (12,13). Additionally, patients with Pt-R ROC may benefit again from platinum-based chemotherapy following the longer interval until platinum re-treatment with non-platinum single agents (14). Therefore, by modified method or timing of platinum administration, platinum re-treatment is potentially effective for Pt-R ROC.

Irinotecan (CPT), a topoisomerase-1 inhibitor, has modest activity for patients with Pt-R ROC (15,16), and has synergic effects in combination with cisplatin (CPT-P) *in vitro* (17). Furthermore, the combination of CPT and CPT-P was reported to be effective for patients with Pt-R ROC (18,19). The present study was performed to retrospectively evaluate the efficacy and adverse events (AE) in 28 patients treated with irinotecan and platinum (CPT-Pt) for Pt-R ROC.

Patients and methods

Patients. Platinum-resistance recurrence (Pt-R) was defined as a relapse within 6 months from the last platinum-based chemotherapy. After approval by the Institutional Review Board of the institution, a total of 28 patients with Pt-R ROC treated with CPT-Pt at the National Defense Medical College Hospital (Tokorowaza, Japan) between January, 2002 and December,

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Table I. Characteristics of the patients.

Characteristic	Number of patients (%)
Total	28 cases
Age, years	57.5
Median (range)	(16-78)
PS	
0	28 (100)
FIGO stage	
I/II	3 (11)
II/IV	25 (89)
Histology	
Serous AC	17 (60)
Endometrioid AC	1 (4)
Clear cell AC	4 (14)
Mucinous AC	1 (4)
AC, NOS	5 (18)
Residual disease at primary surgery, cm	
<1	12 (43)
≥1	16 (57)
Status of platinum resistance	
Platinum-refractory	12 (43)
Primary platinum resistance	10 (36)
Secondary platinum resistance	6 (21)
Number of prior chemotherapy regimens	
1	22 (78)
2	3 (11)
3	3 (11)
CPT-Pt regimens	
5-day CPT-P	13 (46)
wCPT-P	9 (32)
wCPT-N	5 (18)
wCPT-C	1 (4)
UGT1A1	
Wild-type	9 (32)
Hetero-type (*6)	3 (11)
Hetero-type (*28)	2 (7)
Not available	14 (50)

PS, performance status; FIGO, International Federation of Gynecology and Obstetrics; AC, adenocarcinoma; NOS, not otherwise specified; CPT-Pt, irinotecan and platinum; CPT-P, irinotecan and cisplatin; wCPT-P, weekly irinotecan and cisplatin; wCPT-N, weekly irinotecan and nedaplatin; wCPT-C, weekly irinotecan and carboplatin; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Table II. Adverse events of CPT-Pt regimens according to CTCAE version 4.0.

	CTCAE grade of adverse event (n)			
Adverse event	2	3	4	3/4 (%)
Hematologic toxicities				
Anemia	16	6	0	6 (21)
Neutropenia	5	11	8	19 (68)
Thrombocytopenia	3	3	3	6 (21)
Febrile neutropenia	0	3	0	3 (11)
Non-hematologic toxicities				
Diarrhea	7	3	0	3 (11)
Nausea/vomiting	2	1	0	1 (4)
Anorexia	2	1	0	1 (4)
Allergic reaction	2	1	0	1 (4)

CPT-Pt, irinotecan and platinum; CTCAE, Common Terminology Criteria for Adverse Events.

2012 were identified from a retrospective review of medical charts. All patients received combination therapy with TC as the first-line chemotherapy, and received CPT-Pt for the treatment of recurrent tumors with Pt-R. Platinum-resistance was sub-classified as follows (14,20): i) Platinum-refractory, patients who relapsed during TC therapy; ii) primary platinum-resistance, patients who relapsed within 6 months after the primary TC therapy; and iii) secondary platinum-resistance, patients who relapsed within 6 months after the second-line therapy with platinum-based regimen for the first relapse following primary TC therapy.

Treatment. Four CPT-Pt regimens were used for the patients with Pt-R ROC: i) Five-day CPT-P, irinotecan 22.5 mg/m^2 and cisplatin 10 mg/m^2 on days 1-5, once every 4 weeks; ii) weekly (w)CPT-P, irinotecan 40-60 mg/m^2 on days 1, 8, and 15 and cisplatin 50-60 mg/m^2 on day 1, once every 4 weeks; iii) weekly CPT-nedaplatin (wCPT-N), irinotecan 40-60 mg/m^2 on days 1, 8 and 15 and nedaplatin 60 mg/m^2 on day 1, once every 4 weeks; and iv) weekly CPT-carboplatin (wCPT-C), irinotecan 40-60 mg/m^2 on days 1, 8, 15 and carboplatin target area under the concentration vs. time curve = 5 on day 1, once every 4 weeks. Five-day CPT-P was used between 2002 and 2007. From 2007, other regimens aside from five-day CPT-P were selected by clinicians according to kidney function and history of allergic reactions. CPT-Pt regimens were administrated until progression of the disease or development of unacceptable AE. Approximately 80% of the initial dose of CPT-Pt was delivered in subsequent cycles when the patients developed severe AE (grade ≥3) in prior cycles. Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotyping was available in approximately half of the cases, and the incidences of severe AE grade >2 were analyzed according to UGT1A1 genotype.

Assessments. Performance status (PS) was evaluated according to the Eastern Cooperative Oncology Group criteria (21). Response to treatment was assessed by computed tomography (CT) imaging using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (22), or cancer antigen (CA)-125 criteria defined by Rustin *et al* (23). CA-125 levels were checked before every cycle. CT was performed every 2-3 cycles, or when disease progression was clinically suspected. Clinical benefit rate (CBR) was defined

Table III. Grade 3/4 adverse events of CPT-Pt regimens according to UGT1A1 genotype.

Adverse event	UGT1A1 wild-type, n (%) (n=9)	UGT1A1 hetero-type, n (%) (n=5)	UGT1A1 unknown, n (%) (n=14)	P-value
Hematologic toxicities				
Anemia	1 (3)	1 (20)	4 (29)	0.61
Neutropenia	6 (67)	2 (40)	10 (71)	0.45
Thrombocytopenia	1 (3)	1 (20)	4 (29)	0.61
Febrile neutropenia	0 (0)	0 (0)	3 (21)	0.06
Non-hematologic toxicities				
Diarrhea	1 (3)	1 (20)	1 (7)	0.73
Nausea/vomiting	1 (3)	0 (0)	0 (0)	0.33
Anorexia	0 (0)	0 (0)	1 (7)	0.60
Allergic reaction	0 (0)	1 (20)	0 (0)	0.09

CPT-Pt, irinotecan and platinum; UGTA1, uridine diphosphate glucuronosyltransferase 1A1.

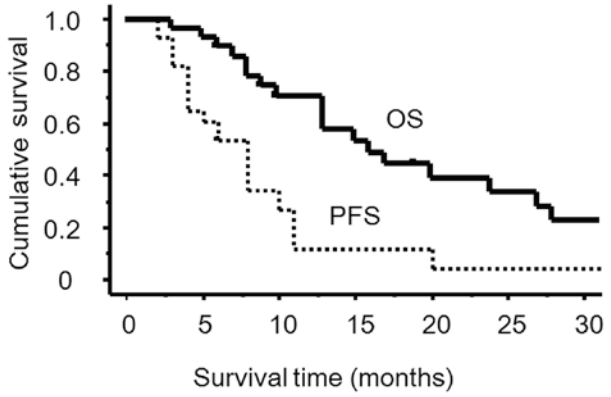

Figure 1. PFS and OS curves. The median PFS was 8 months (95% CI, 4-10 months), and median OS was 15 months (95% CI, 10-27 months). PFS, progression-free survival; OS, overall survival; CI, confidence intervals.

as the percentage of the patients who achieved complete response (CR), partial response (PR) and stable disease (SD) to all enrolled patients (24). AE were assessed using Common Terminology Criteria for AE version 4.0 (25). PFS was defined as the period of time between the date of the first cycle of CPT-Pt and the date of progression or mortality. OS was defined as the period of time between the date of the first cycle of CPT-Pt and mortality.

Statistical analysis. The χ^2 test was used to evaluate difference in patient's characteristics and the incidence of AE. Survival curves were generated using the Kaplan-Meier method, and a 95% two-sided confidence interval (CI) was also estimated. Survival variation among the regimens was analyzed using log-rank test. The data was analyzed using StatView software version 5.0 (SAS Institute Inc., Cary, NC, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

The patient characteristics are presented in Table I. The median age of the patients was 59 years (range, 16-78) and their PS was 0. The median number of administrated cycles was 5.5 (range, 2-16). Thirteen patients received the 5-day CPT-P regimen, 9 patients received wCPT-P, 5 patients received wCPT-N and 1 patient received wCPT-C. Twelve patients (43%) were platinum refractory, 10 patients (36%) had primary resistance and 6 patients (21%) had secondary resistance. In total, 25 patients were assessed for progression and response using CT imaging using RECIST guidelines (version 1.1), and other 3 patients were assessed using CA-125 criteria due to lack of measurable disease. The overall response rate was 14%: 2 patients with a CR and 2 patients with a PR. Additionally, 15 patients (54%) achieved SD, resulting in a CBR of 68%. There were no differences in CBR among platinum refractory disease, primary resistance cases and secondary resistance cases (67 vs. 70 vs. 67%, respectively; P=0.93). In addition, there was no difference in CBR between 5-day CPT-P and other regimens (69 vs. 67%, P=0.99). The median PFS of 5-day CPT-P and other regimens were 8 and 6 months, respectively (P=0.27). A total of 21 patients (75%) succumbed to disease, and the median follow-up time of these patients was 10 months (range, 6-94 months). The median PFS was 8 months (95% CI = 4-10 months), and the median OS was 15 months (95% CI = 10-27 months) (Fig. 1).

There were no cases that developed treatment-related mortality, or that discontinued CPT-Pt therapy due to unmanageable AEs. AE are summarized in Table II. Neutropenia was the most common AE, and neutropenia of grade >2 was observed in 68% of the patients. Neutropenia was resolved by treatment delay, dose reduction of CPT-Pt, or administration of granulocyte-colony stimulating factor. Diarrhea and nausea/vomiting were also frequently observed. These non-hematological AEs were resolved by conservative management or dose reduction. Among all 28 patients, 15 patients required dose reduction of CPT-Pt in the subsequent cycle dose due to AE. Grade 1-3 diarrhea was observed more frequently in 5-day CPT-P compared with other regimens (85 vs. 20%; P<0.01). The incidence of severe AE of grade >2 according to UGT1A1 genotyping are presented in Table III. UGT1A1 genotypes were available in 14 cases: 9 cases with UGT1A1 wild-type and 5 cases with

UGT1A1 hetero-type. There were no significant differences in the incidence of grade 3/4 AE between these groups.

Discussion

Our preliminary data revealed that CPT-Pt for patients with Pt-R ROC achieved a CBR of 68%, median PFS of 8 months and a median OS of 15 months. Although direct comparison was challenging due to patients' heterogeneity and the four treatment regimens, CPT-Pt had the potential to produce longer PFS compared with other non-platinum single agents such as gemcitabine and pegylated liposomal doxorubicin, which achieved a median PFS of 3-4 months (5-10). On the other hand, combination therapy with conventional chemotherapy with bevacizumab produced a PFS of 6.7 months (26). CPT-Pt regimens had a similar PFS compared with cisplatin/etoposide and paclitaxel/carboplatin (median PFS, ~8 months) (12,13).

A previous study suggested that CPT combined with cisplatin had a CBR of 72% and the median PFS of 6 months in a case series of 25 patients including 21 patients with Pt-R ROC (7). By contrast, CPT combined with carboplatin had a CBR of 53% and the median PFS of 3.7 months in 17 patients with Pt-R ROC (27). In the present study, 22 patients (79%) received cisplatin in combination and only one patient received carboplatin in combination. At present, almost all patients with ovarian cancer receive the TC regimen as the first-line chemotherapy in general clinical practice. Although carboplatin was reported to show cross-resistance with cisplatin *in vitro* (26), the data from the present study suggested that patients with Pt-R ROC benefited from the combination of CPT with cisplatin, and not from CPT with carboplatin.

CPT-Pt for patients with Pt-R disease develop higher frequencies of grade 3/4 hematological AE, compared with single non-platinum single agents (5). In cancer patients treated with CPT, genotyping of UGT1A1 may be a useful predictive marker for severe AEs such as neutropenia (28,29). UGT1A1 genotyping may allow the avoidance of severe AEs occurring as a result of the use of CPT-Pt for the treatment of Pt-R ROC, although there were no significant differences in the incidence of severe AE according to UGT1A1 genotype in the present case series. For the schedule of administration, grade 1-3 diarrhea was observed more frequently in the 5-day CPT-P group compared with other regimens in the present study. A weekly schedule of irinotecan, such as wCPT-P and wCPT-N regimens, may be safer for patients with Pt-R ROC.

Bevacizumab has been widely used for the treatment of ovarian cancer. However, it is inevitable that severe AEs, such as gastrointestinal perforation, may be observed in patients with ROC, particularly in the patients that had peritoneal dissemination (24,30). CPT-Pt regimens might be an alternative treatment for patients with Pt-R ROC who may suffer from bevacizumab-associated AEs.

In conclusion, CPT-Pt achieved a longer PFS in patients with Pt-R ROC, although a slight elevation of AE frequency was observed compared with reported incidence by non-platinum single agents. Weekly schedules of irinotecan, such as wCPT-P and wCPT-N, may be safer regimens compared with 5-day CPT-P regimens. CPT-Pt may be a candidate regimen for the treatment of Pt-R ROC; however, further investigation is needed.

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