A Phase II Study of Combined CPT-11 and Mitomycin-C in Platinum Refractory Clear Cell and Mucinous Ovarian Carcinoma

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Abstract

This article reviews the preliminary but encouraging clinical data obtained from patients with platinum-refractory clear cell or mucinous carcinoma of the ovary who were treated with a chemotherapy regimen including irinotecan hydrochloride (CPT-11). Twenty-five patients with platinum-refractory macroscopic disease of which histologic type was either clear cell or mucinous carcinoma were treated. CPT-11 was administered at a dose of 120 mg/m2 intravenously (IV) over 4 hours on days 1 and 15, and mitomycin-C (MMC) was given IV as a bolus at a dose of 7 mg/m^2 on days 1 and 15. At least 2 cycles of this regimen, 4 weeks apart, were given to the 25 patients. After a median of 4 cycles (range 2 to 8), we observed objective responses in 13 patients (52%), with 5 complete responses (CRs; 20%) and 8 (32%) partial responses (PRs) (95% confidence interval, 32.4% to 71.6%, 4.3% to 35.7%, 13.7% to 50.3%, respectively). The median overall survival time for all 25 patients was 15.3 months (range 3.5 to 38.0). Median overall survival time of the responders was 33.7 months versus 6.1 months of the non-responders (Log-rank, P = 0.0003). The median progression-free survival times for patients obtaining CR, PR, and CR + PR were 31.8 months (range 12.9 to 34.4), 10.5 months (range 5.6 to 18.2), and 12.9 months (range 5.6 to 34.4), respectively. Toxic effects were acceptable and included manageable haematologic reactions, diarrhoea, nausea/vomiting, and alopecia.

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Introduction

Platinum resistance, either *de novo* or acquired, is a major obstacle in the treatment of advanced ovarian cancer. Platinum-resistance has been classified into the following three categories; (1) primarily (intrinsically) platinum-resistant disease: tumours showing no change (NC) or progressive disease (PD) while on initial platinum-based chemotherapy; (2) secondarily platinum-resistant disease: tumours initially responded to cisplatin or carboplatin therapy with at least a partial response (PR) but disease subsequently relapsed within 6 months after discontinuation of initial platinum-based chemotherapy; (3) potentially platinum-sensitive disease: tumours initially responded to cisplatin or carboplatin therapy with at least a PR but relapsed more than 6 months after discontinuation of initial platinum-based chemotherapy.[1,2] Of these categorised groups, patients with secondary platinum-resistant or potentially platinum-sensitive disease have been reported to benefit from second line regimens including ifosfamide,[1] topotecan,[2] paclitaxel,[3-8] docetaxel,[9,10] etoposide,[11,12] vinorelbine,[13] and organoplatinum[14] given singly or in combination. On the other hand, there have never been any literature reporting regimens effective for consecutive patients with primarily platinum-resistant disease.

Recently, it became obvious that chemo-sensitivity of ovarian carcinoma was closely related with histologic subtype of each tumour. According to the few reports analyzing the response to platinum-based chemotherapy by histologic subtypes, ovarian carcinoma can be classified into the following two distinct groups in terms of sensitivity to platinum-based chemotherapy[15-20]: a chemo-sensitive group that includes serous, endometrioid and transitional cell carcinoma, with a clinical response rate to platinum-based chemotherapy of approximately 70% to 80% and a pathological complete response rate of 20% to 30 % or more,[15-17,19-23] and a platinum-resistant group consisting of mucinous and clear cell carcinoma.[15-20,24-28] Thus, most of secondarily platinum-resistant or potentially platinum-sensitive tumours consist of serous, endometrioid, and transitional cell carcinoma. On the other hand, mucinous and clear cell carcinoma have been considered to be primarily platinum-refractory. Indeed, there have been no documented cases of achievement of a pathologically complete response (pCR) to a platinum-based regimen in histologically-

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confirmed bulky mucinous or clear cell carcinoma of the ovary. According to the Gynecologic Oncology Group (GOG) report on long-term follow-up and prognostic factors in patients with stage IV and suboptimally debulked stage III ovarian carcinoma, both clear cell and mucinous histologies were significant factors indicating a poor prognosis.[17] In their study, none of the 32 patients with mucinous (14 cases) or clear cell carcinoma (18 cases) had a negative second look following intensive platinum-based chemotherapy subsequent to maximal surgical efforts. This refractoriness has not been regarded as a serious issue since approximately 60% of mucinous or clear cell carcinoma are diagnosed at FIGO stage I or II,[24,26-33] which means that only a small percentage of patients with such tumours require chemotherapy for residual disease. Another reason is the relatively low frequency of both histologies, with a reported prevalence of 10% or less of all ovarian epithelial carcinomas in Europe and North America.[24,26,30-32] However, ovarian clear cell adenocarcinoma (OCCA) has recently been increasing in prevalence and now accounts for approximately 20% of all ovarian epithelial carcinomas in our institute, although the frequency of mucinous carcinoma has been unchanged these two decades.[33] Thus, there is an urgent need to establish effective chemotherapeutic regimens for both clear cell and mucinous carcinoma. Based on the results of chemosensitivity tests previously performed both *in vitro* and *in vivo*,[34,35] we designed a combination of irinotecan hydrochloride (CPT-11) and mitomycin-C (MMC). We report below the efficacy of this regimen in consecutive patients with platinum-refractory clear cell and mucinous carcinoma of the ovary.

Materials and Methods

Eligibility Criteria

Patients with histologically confirmed mucinous or clear cell carcinoma of the ovary without other histological elements, persistent or recurrent disease, measured more than 1.0 cm in diameter, and who had shown no response to platinum-based chemotherapy were eligible for this study. Patients with platinum-based therapy failure were categorized into the following two strata: (1) patients with macroscopic disease showing NC or PD while on initial cisplatin-based chemotherapy; (2) patients who experienced recurrence during cisplatin-based chemotherapy or recurrent disease within 4 months of completing a planned 6 cycles of cisplatin-based chemotherapy subsequent to complete surgery with no residal disease. The number of previous chemotherapy regimens was not used as an exclusion criterion. Prior chemotherapy must have been completed at least 4 weeks before entering this study. The other eligibility criteria were as follows: age between 18 and 75 years; World Health Organization (WHO) performance status (PS) of 0 to 3; adequate bone narrow reserve (WBC count ≥3500 /μL, neutrophil count ≥1500/μL, platelet count ≥100,000 /μL, and haemoglobin level ≥9 g/dL); total bilirubin level ≤1.5 mg/dL; serum creatinine level ≤1.2 mg/dL; creatinine clearance ≥70 mL/min, other routine parameters not exceeding twice the normal values, and no other previous neoplastic disease.

Written informed consent was obtained from all patients before enrolment in the study, and the study protocol was approved by the Institutional Review Board of the Clinical Oncology Program of this hospital.

Treatment Plan

Each chemotherapy cycle consisted of 120 mg/m^2 of CPT-11 IV-infused over 4 hours on days 1 and 15, and 7 mg/m^2 of MMC IV-injected as a bolus on days 1 and 15. At least 2 cycles of this regimen, 4 weeks apart, were given to the eligible patients. The next treatment cycle was administered if the neutrophil count was ≥1000 /μL and platelet count ≥100,000 /μL. No prophylactic antidiarrhoeal agents were given before this regimen was administered. Dose modification was based on neutrophil and platelet counts, as well as on the grade of diarrhoea. If the diarrhoea was ≥ grade 2 on the treatment day, the scheduled dosing was postponed until the diarrhoea completely resolved. The dose of CPT-11 in the cycle was reduced by 20 mg/m^2 if grade 2 or 3 diarrhoea was present. If a patient experienced grade 4 diarrhoea, the chemotherapy regimen was discontinued. In addition, CPT-11 and MMC were reduced by 20 mg/m^2 and 2 mg/m^2 respectively, if grade 3 or 4 thrombocytopenia lasted ≥10 days, or if grade 3 or 4 neutropenia lasted ≥10 days during the treatment cycle despite the use of granulocyte-colony stimulating factor (G-CSF). Conversely, the infusion dose was increased by 10 mg/m^2 for CPT-11 and by 2 mg/m^2 for MMC if there was no toxic reaction greater than grade 0 during the previous cycle. Such dose escalations were performed only one step. Thus, the maximum allowed infusion dose was 130 mg/m^2 for CPT-11 and 9 mg/m^2 for MMC.

The first evaluation of the clinical response was performed after the second cycle, unless there was clinically evident disease progression before then. Patients having a PD or a response less than a minor response (MR: defined as a ≥25% but <50% decrease in the sum of the products of the diameters of measurable lesions) after a second cycle of this regimen did not receive further cycles of the present protocol, and were instead managed with other individualized treatment programs. In patients with MR, PR, or complete response (CR) after the second cycle, chemotherapy was continued as long as possible, depending on the treatment response and patients' tolerance, but was discontinued if there was any evidence of disease progression. Development of

unacceptable toxic signs and patients' refusal to continue treatment were also criteria for discontinuation of treatment.

Determination of Response and Toxicity

Tumour response and treatment toxicity were evaluated according to WHO criteria.[36] CR was defined as complete disappearance of all clinically detectable malignant disease for at least 4 weeks. PR was defined as a ≥50% reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions for at least 4 weeks, during which time no new lesions appeared and there was no growth of existing lesions. NC was defined as less than a 50% decrease or less than a 25% increase in the sum of the product of the two longest perpendicular diameters of all measurable lesions with no new lesions appearing. PD was defined as a ≥25% increase in the sum of the product of the two longest perpendicular diameters of one measurable lesion (even with regression of other lesions) or the appearance of an unequivocal new lesion. The duration of CR, PR and NC was defined as the interval between the initial documented response and the first sign of progression.

Evaluations and follow-up study scheme: Before the first treatment, all patients underwent a complete physical and gynaecologic examination, cystoscopy, rectosigmoidoscopy, determination of WHO PS, complete blood cell (CBC) counts including reticulocyte counts, blood chemistry studies including renal and liver function tests, assays of tumour markers including CA 125, CA72-4, ECG, respiratory function, chest X-ray, urinalysis, physical tumour size measurement, ultrasonography (vaginal and / or abdominal), computed tomography (CT) scans, and magnetic resonance imaging (MRI). During treatment, CBC and blood chemistry studies were repeated at least once a week. In addition, physical and gynaecologic examinations, ultrasonography, urinalysis, creatinine clearance, X-ray, WHO PS and toxicity evaluations were conducted after each cycle, and complete evaluations of tumour response by CT scan, MRI, and ultrasonography were performed after the second, third, fourth, and sixth cycles, and at the end of the study.

Statistics: Statistical analyses were performed using the SAS software program.[37] The 95% confidence intervals (CI) were computed for the response rates observed in all patients. Response distributions according to variables, including tumour size, site of disease, and previous chemotherapy, were analyzed by using the Kruskal-Wallis rank test[38] and the Chi-square test.[39] Overall survival was measured from the start of the chemotherapy regimen. Survival time was measured to the date of death or date of last contact. The duration of progression-free survival was calculated from the day chemotherapy was begun to the time of disease progression, death, or last contact. All causes of death were used to calculate survival. The estimates of the cumulative proportion surviving were based on Kaplan-Meier procedures[40] and compared with the log-rank test.[41]

Results

Patients Profile

Patient characteristics of the study population are outlined in Table I. Between January 1994 and September 1997, 20 patients with clear cell carcinoma and 5 with mucinous carcinoma, all of whom had failed to respond to platinum-based chemotherapy, were enrolled in this trial. All 25 patients were considered eligible for evaluation of response, toxicity, and survival. The median follow-up time of the 25 patients was 15.6 months (range 3.6 to 46.4 months; mean 19 months). None of the patients were lost to follow-up. The patients ranged in age from 28 to 69 years, with a median age of 53 years. The median PS was WHO 1. Of the 25 patients studied, 13 developed recurrent tumours within 4 months after completion of 6 cycles of platinum-based chemotherapy. The remaining 12 patients

TABLE I: PROFILES OF PATIENTS

Variables	No. of patients
Elligible patients	25
Median age [range] (in years):53 [28 to 69]	
28 to 52	12
53 to 69	13
WHO performance status	
0 to 1	16
2 to 3	12
Initial FIGO stage	
IC	3
IIIC	20
IV	2
Histologic subtype	
Clear cell	20
Mucinous	5
Disease status	
Recurrence	13
Persistence	12
Prior surgery	
Exploratory	4
TAH+BSO+OM+PLA+PALA	15
More extensive	6
Size of tumour at the time of entry	
<2 cm	6
2 to 4 cm	9
>4 cm	10

TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; OM: omentectomy; PLA: pelvic lymphadenectomy; PALA: para-aortic lymphadenectomy; More extensive: including colectomy, splenectomy, diaphragmal resection, and Douglas peritonectomy

TABLE II: TOXICITIES BY NUMBER OF COURSES†

Toxic signs	No. of courses affected (WHO grade)				
Grade	0	1	2	3	4
Leukopenia	10	30	30	16	2
Anaemia	38	30	16	4	0
Thrombocytopenia	37	30	16	5	0
Diarrhoea	46	22	20	0	0
Anorexia	31	32	20	5	0
Nausea/vomiting	39	29	18	2	0
Alopecia	8	33	30	17	0
Renal	81	7	0	0	0

† Worst toxicity recorded
Total number of courses = 88

TABLE III: RESPONSE BY TUMOUR SIZE

Tumour size	No. of patients	Response to CPT-11/MMC				
		CR	PR	NC	PD	CR + PR/Evaluable
<2 cm	6	3	2	1	0	5/6
2 to 4 cm	9	2	4	3	0	6/9
>4 cm	10	0	2	5	3	2/10
Total	25	5	8	9	3	13/25

Chi-square test among 3 group: $P = 0.07964$, $\chi^2 = 11.29629$, $P = 0.07964$
Comparison of response for [<2 cm] vs [2 to 4 cm] + [>4 cm];
Chi-square test: $P = 0.02343$, $\chi^2 = 9.49074$
Wilooxon's rank-sum test: $P = 0.00336$, z = 2.93278

TABLE IV: RESPONSE BY HISTOLOGIC SUBTYPE

Histology	No. of patients	Response to CPT-11/MMC				
		CR	PR	NC	PD	CR + PR/Evaluable
Clear cell	20	4	5	8	3	9/20
Mucinous	5	1	3	1	0	4/5
Total	25	5	8	9	3	13/25

with persistent disease following an initial maximal debulking had a progressive disease while on initial platinum-based chemotherapy given at least 2 cycles. Thus, all patients were considered to be primarily platinum-refractory.

A total of 88 cycles of the CPT-11 plus MMC combination were given during the trial (median number of cycles per patient 4; range 2 to 8).

Toxicity

Detailed toxicity data according to the WHO scale were available for 88 cycles (Table II). Of 88 cycles of this regimen, 77 (88%) were administered at equal to or more than full dose. The dose-limiting toxic effect was myelosuppression. Leukopenia was the most common grade 2 or more toxic effect, and its severity was grade 3 or 4 in 20.5% of the 88 cycles, all of which could be safely managed with G-CSF. Grade 3 anaemia and thrombocytopenia occurred in 4.5% and 5.7% of the cycles, respectively. Alopecia was the most common grade 2 or more toxic non-haematologic sign with 19.3% of patients developing grade 3 alopecia during therapy. Other toxic non-haematologic signs consisted primarily of grade 2 or 3 nausea / vomiting (22.7%) and grade 2 diarrhoea (22.7%), all of which were manageable and did not necessitate discontinuation of the treatment. No more than grade 2 toxic signs were observed with regard to diarrhoea, which was considered to be one of the dose-limiting toxic effects of CPT-11, by the present 4-hour infusion method. No significant renal toxic effects were observed. In conclusion, the treatment was well tolerated.

Response

We observed objective clinical responses in 13 patients (52.0%), with 5 CRs, and 8 PRs (32.0%) (95% CI, 32.4% to 71.6%, 4.3% to 35.7%, 13.7% to 50.3%, respectively). The median response duration for CR and PR were 28.9 months (range 10.0 to 31.5 months) and 7.6 months (range 2.9 to 15.3 months). Table III lists the response data by tumour size. Comparison of responses between tumours <2 cm versus those ≥2 cm by both Wilcoxon's rank-sum test ($P = 0.00336$) and chi-square test ($P = 0.02343$) revealed that significantly better responses were observed in the former group. Indeed, CR was achieved only for tumours ≤3 cm in diameter. Of 10 patients with tumours >4 cm, only 2 achieved PR. As shown in Table IV, no significant difference in response rate was observed between clear cell and mucinous carcinoma.

The regimen was found to be effective for para-aortic lymph node disease as well as intraperitoneal disease. One of the 8 patients with para-aortic lymph node disease achieved a pathological CR which was confirmed by the second operation, which included para-aortic lymphadenectomy extending to the upper margin of renal vein. It should be noted that this regimen was effective (1 CR and 2 PRs) even after failure of second line CPT-11 alone, suggesting the need for MMC to induce an appreciable response in primary platinum-refractory mucinous or clear cell carcinoma.

Survival

The overall survival time curve is shown in Figure 1. The median overall survival time for all 25 patients was 15.3 months (range 3.5 to 38.0). The median survival times of patients with CR and PR were "not reached (NR)" (range 21 to 42 months) and 15.5 months (range 8.8 to 19.8), whereas those with NC and PD were 7.1 months (range 4.6 to 15.3) and 5.9 months (range 3.5 to 7.7), respectively. Thus, patients achieving objective

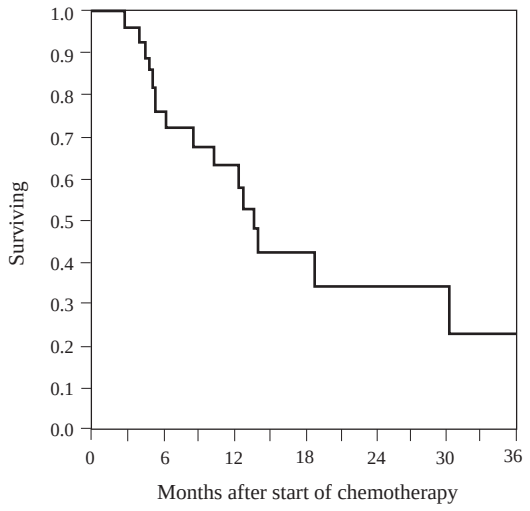

Fig. 1. The overall survival time curve for 25 patients.

responses (median 33.7 months) survived significantly ($P = 0.0003$) longer than those having NC or PD (median 6.1 months). The median progression-free survival times for patients obtaining CR, PR, and CR + PR were 31.8 months (range 12.9 to 34.4), 10.5 months (range 5.6 to 18.2), and 12.9 months (range 5.6 to 34.4), respectively. The progression-free survival times of patients with CR or PR were significantly longer than those of patients having NC or PD ($P < 0.001$).

Discussion

The combination of CPT-11 with MMC allowed achievement of an appreciable response with survival benefit for consecutive patients with clear cell and mucinous carcinoma of the ovary. The regimen was highly effective for tumours <4 cm in diameter, but significantly less effective for tumours >4 cm. As stated in the results, this combination was effective for patients who had failed to respond to CPT-11 alone. This clearly suggests the need for MMC in this regimen to induce an appreciable response in primarily platinum-refractory mucinous or clear cell carcinoma. *In vitro* experiment demonstrated a supra-additive effect (synergism) observed between CPT-11 and MMC, although the precise mechanism of the synergistic interaction between two agents remains unclear.[42]

The optimal dosing mode of CPT-11 given alone or in combination remains to be established. According to phase II studies conducted in gynaecologic[43] and colorectal cancers[44] by the CPT-11 study groups in Japan in which CPT-11 was given at a dose of 100 mg / m^2 on days 1, 8, 15, and 22 of one cycle or 150 mg / m^2 on days 1, 15 and 29 of one cycle, leukopenia was significantly more common with the weekly schedule, though there was no significant response difference for either disease between the weekly and biweekly schedules.[45,46] In addition, toxic signs could be safely monitored with the biweekly schedule in clinical practice. Thus, we chose a biweekly dosing method. The optimal infusion time also remains to be determined. A phase I study revealed that all patients receiving 130 mg / m^2 given over 30 minutes experienced grade 3 diarrhoea and that prolongation of the infusion time from 30 to 90 minutes decreased the severity of diarrhoea.[45] Even a 90-minute infusion of CPT-11 at a dose of 100 to 125 mg / m^2 was associated with grade 4 diarrhoea, nausea / vomiting, and leukopenia in patients with cervical cancer who had received previous platinum-based chemotherapy with or without previous radiation therapy.[46] On the other hand, continuous CPT-11 produced an unexpectedly high incidence of diarrhoea and vomiting.[47] *In vivo* preclinical studies demonstrated that a low-dose protracted dosing schedule was as, or even more, efficacious than a bolus dosing schedule, suggesting that the anti-tumour effect of CPT-11 might be both dose and time-dependent[48,49] while other studies have concluded that this agent was not significantly schedule dependent.[50] We previously demonstrated that a 4-hour IV infusion for 7 consecutive days in one cycle was the optimal dosing mode for cisplatin (consecutive low-dose cisplatin), the anti-tumour activity of which was considered to be dependent on the area under the concentration of the platinum-time curve (AUC) obtained following administration of the agent.[51] A clinical trial using consecutive low-dose cisplatin combined with bleomycin, vincristine, and MMC revealed excellent results in patients with recurrent cervical carcinoma.[52] Thus, we administered CPT-11 by 4-hour infusion in combination with bolus MMC, a practical schedule which was acceptable in an outpatient setting. As shown in Table II, levels of toxicity encountered in this regimen were considered manageable.

In conclusion, the combination of CPT-11 with MMC is the first regimen to demonstrate significant activity, achieving a survival benefit, in consecutive patients with histologically confirmed mucinous and clear cell carcinoma of the ovary which are primarily platinum-refractory. To promote the use of this regimen, further studies designed to establish the optimal dosing mode for both agents are needed. The present encouraging data indicate that this regimen should be given as front-line chemotherapy for mucinous and clear cell carcinoma of the ovary. Moreover, further studies of this regimen may be warranted for secondarily platinum-resistant disease including serous, endometrioid, and transitional cell carcinoma.

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