

## Adjuvant chemotherapy with irinotecan hydrochloride and cisplatin for clear cell carcinoma of the ovary

MASASHI TAKANO<sup>1,13</sup>, YOSHIHIRO KIKUCHI<sup>1</sup>, NOBUO YAEGASHI<sup>2</sup>, MITSUAKI SUZUKI<sup>3</sup>, HIROSHI TSUDA<sup>4</sup>, SATORU SAGAE<sup>5</sup>, YASUHIRO UDAGAWA<sup>6</sup>, KAZUO KUZUYA<sup>7</sup>, JUNZO KIGAWA<sup>8</sup>, SATOSHI TAKEUCHI<sup>9</sup>, HITOSHI TSUDA<sup>10</sup>, TAKUYA MORIYA<sup>11</sup> and TORU SUGIYAMA<sup>12</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Saitama 359-8513;

<sup>2</sup>Department of Obstetrics and Gynecology, Tohoku University, Sendai, Miyagi 980-8574; <sup>3</sup>Department of Obstetrics and Gynecology, Jichi Medical College, Kawachi-gun, Tochigi 329-0498; <sup>4</sup>Department of Obstetrics and Gynecology, Osaka City General Hospital, Osaka, Osaka 534-0021; <sup>5</sup>Department of Obstetrics and Gynecology, Sapporo Medical University, Sapporo, Hokkaido 060-8556; <sup>6</sup>Department of Obstetrics and Gynecology, Fujita Health University, Toyoake, Aichi 470-1192; <sup>7</sup>Department of Gynecology, Aichi Cancer Center Hospital, Nagoya, Aichi 464-8681; <sup>8</sup>Department of Obstetrics and Gynecology, Tottori University, Yonago, Tottori 683-8504; <sup>9</sup>Department of Obstetrics and Gynecology, Kobe National Hospital, Kobe, Hyogo 554-0155; <sup>10</sup>Department of Pathology II, National Defense Medical College, Tokorozawa, Saitama 359-8513; <sup>11</sup>Pathology Laboratory of Central Clinical Facilities, Tohoku University, Sendai, Miyagi 980-8574; <sup>12</sup>Department of Obstetrics and Gynecology, Iwate Medical University, Morioka, Iwate 020-8505, Japan

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**Abstract.** Clear cell carcinoma (CCC) of the ovary has distinct characteristics showing resistance to conventional platinum-based regimen. Our aim was to evaluate the effects of combination therapy with irinotecan hydrochloride and cisplatin (CPT-P), comparing to regimen with paclitaxel and platinum (TP). We retrospectively reviewed 172 patients with complete surgical staging procedures including lymphadenectomy. Forty-six patients received CPT-P and 126 patients were treated with TP. Survival of the two groups was compared. Between CPT-P group and TP group, there was no significant difference in median age, performance status, FIGO stage, rate of optimal cytoreduction, and follow-up period. There was no significant difference in progression-free survival of patients with stage I tumors ( $p=0.95$ ) and suboptimally debulked stage II-IV tumors ( $p=0.92$ ). Although there was no significant difference of overall survival, progression-free survival of CPT-P group was significantly better than that of TP group in optimally debulked stage II-IV ( $p=0.03$ ). Multiple regression survival analysis revealed

CPT-P regimen ( $p=0.02$ ) and residual tumor diameter ( $p<0.01$ ) were both independent prognostic factors in stage II-IV tumors. The combination of CPT-P was shown to have a potential therapeutic benefit for advanced CCC of the ovary, especially for cases with optimal debulking surgery. However, this is a limited retrospective study, therefore we recommend that the CPT-P regimen be evaluated in a larger prospective study.

### Introduction

Clear cell carcinoma (CCC) was initially termed as mesonephroid by Schiller in 1939 (1), and since 1973 it was strictly defined by World Health Organization as lesions characterized by clear cells growing in solid/tubular or glandular patterns as well as hobnail cells (2). Since then, many studies have identified the distinctive behavior of the tumors. The most distinctive difference is that patients with CCC of the ovary have poorer prognosis compared with those with other pathological types of epithelial ovarian carcinomas (3,4). Additionally, CCC of the ovary was implied to show resistance to conventional platinum-based chemotherapy (5,6). Recent studies confirmed the evidence in the analysis of measurable CCC patients: response was observed in 11-45% with conventional platinum-based regimen, whereas patients with serous subtype showed a significantly higher response rate of 73-81% (7,8).

Combination with paclitaxel and platinum (TP), recognized as 'Gold standard' regimen for ovarian cancer, is now used to treat patients with all subtypes of ovarian neoplasms, but in measurable CCC cases treated with TP regimen, response was relatively low, ranging from 22 to 56% (9,10; Enomoto T, *et al*, Proc Am Soc Clin Oncol 22: 447, abs. 1797, 2003). One

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*Correspondence to:* Dr Masashi Takano, <sup>13</sup>Present address: Institute of Reproductive and Developmental Biology (IRDB), Imperial College of London, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK  
E-mail: m.takano@imperial.ac.uk

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report showed survival benefit of conventional chemotherapy with paclitaxel and platinum after complete surgery in CCC patients (11). However, the result from large series of CCC patients treated with paclitaxel and platinum showed no survival benefit compared with conventional platinum-based chemotherapy in both early and advanced cases (12).

Irinotecan hydrochloride, a semi-synthetic derivative of camptothecin, has additive and synergic effects in combination with cisplatin *in vitro* (13-15). The combination therapy with irinotecan hydrochloride and cisplatin (CPT-P) was reported to be effective for patients with various solid tumors. Especially, a large clinical trial revealed that CPT-P had significant activity for extensive small-cell lung cancer (16). Additionally, CPT-P has been reported to be effective in first-line and second-line chemotherapy for the treatment of CCC of ovary (17,18). The aim of the present study was to evaluate the therapeutic activity of CPT-P and TP in a retrospective analysis.

### Patients and methods

A retrospective review of the patients seen at ten Japanese hospitals from 1 January 1992 to 31 December 2003 was done. Of all the patients treated in those hospitals, the following patients were selected: a) patients who underwent complete surgical staging procedures including hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, pelvic lymphadenectomy and paraaortic lymphadenectomy; b) patients whose tumor specimens were confirmed as CCC of the ovary by two pathologists in central pathologic review; c) patients treated with six courses of combination chemotherapy using irinotecan hydrochloride and cisplatin (CPT-P) or six courses of paclitaxel and platinum combination (TP); d) age  $\leq 75$  years; e) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of  $\leq 2$ ; f) pretreatment leukocyte count  $\geq 4000/\text{mm}^3$ , platelet count  $\geq 100000/\text{mm}^3$ , hemoglobin  $\geq 9.0$  g/dl, serum creatinine  $< 1.5$  mg/dl, creatinine clearance  $\geq 60$  ml/min, and GOT and GPT less than twice upper limit of normal at the hospitals; g) the study approved by the Committee on Ethics of each hospital.

One cycle of CPT-P regimen consisted of a drip infusion of 50-60 mg/m<sup>2</sup> of cisplatin on day 1 and 50-60 mg/m<sup>2</sup> of CPT-11 on days 1, 8 and 15, and one week off and it was repeated every 4 weeks. TP regimen consisted of a drip infusion of 175-180 mg/m<sup>2</sup> of paclitaxel and 50-75 mg/m<sup>2</sup> of cisplatin or carboplatin (AUC = 5-6).

Response was evaluated with CT or MR images at least every 2 cycles of chemotherapy in the patients with measurable disease. A complete response (CR) was defined as the complete disappearance of all detectable disease for at least 4 weeks. A partial response (PR) was defined as a  $>50\%$  decrease in tumor size for at least 4 weeks. Stable disease (SD) was defined as the absence of any significant change in measurable lesions for at least 4 weeks. Progressive disease (PD) was defined as the appearance of a new lesion or a  $>25\%$  increase in tumor size. Serum levels of tumor markers including CA125 were not used for response evaluation of chemotherapy in the present study.

The time to progression was defined as the interval from the date of primary surgery until the date of recurrence or tumor progression. Survival duration was determined as the

time from the date of primary surgery until death or the date of last follow-up contact. Kaplan-Meier method was used for calculation of patient survival distribution. The significance of the survival distribution in each group was tested by a generalized Wilcoxon test and the log-rank test. The  $\chi^2$  test and Student's t-test for unpaired data were used for statistical analysis. A p-value of  $< 0.05$  was considered statistically significant. The Stat View software ver. 5.0 (SAS Institution Inc., Cary, NC, USA) was used to analyze the data.

### Results

In total, 46 cases with CPT-P regimen and 126 cases with TP regimen were enrolled in the present retrospective study. TP group included 118 cases treated with paclitaxel and carboplatin and 8 cases treated with paclitaxel and cisplatin. The characteristics of the patients are outlined in Table I. There was no significant difference in median age, performance status, FIGO stage, rate of optimal cytoreduction, and follow-up period between CPT-P group and TP group. Median age of all cases was 53 years (range, 27-75 years). CPT-P group included 24 patients (52%) of stage I, 6 (2%) in stage II, 13 (28%) in stage III and 3 (6%) in stage IV. In TP group, 72 cases (56%) were in stage I, 15 (12%) in stage II, 34 (27%) in stage III and 5 (4%) in stage IV. Optimal cytoreduction (residual tumor diameter  $< 1$  cm) with their initial surgery was achieved in 83% (39/46) in CPT-P group and 83% (104/126) in TP group, respectively. The patients with optimal cytoreductive surgery included 6 stage II, 7 stage III and 2 stage IV tumors in CPT-P group and 14 stage II, 16 stage III and 2 stage IV tumors in TP group. Median follow-up period was 28 months in CPT-P group and 27 months in TP group.

All patients who received CPT-P regimen were evaluable for toxicity. In 46 cases who received CPT-P regimen, 35 cases were treated with 50 mg/m<sup>2</sup> of cisplatin and 60 mg/m<sup>2</sup> of CPT-11, 7 cases with 60 mg/m<sup>2</sup> of cisplatin and 60 mg/m<sup>2</sup> of CPT-11, and 4 cases with 50 mg/m<sup>2</sup> of cisplatin and 50 mg/m<sup>2</sup> of CPT-11, respectively. Hematological and non-hematological toxicities in all cases with CPT-P regimen are shown in Table II. The major toxicities were neutropenia and diarrhea. The incidences of grade 3 and 4 neutropenia were 22 and 7%, respectively. Grade 3 nausea and grade 3 diarrhea was observed in 4 and 9% of all cases, respectively. CPT-11 was omitted in 12 (26%) patients on days 8 or 15 because of toxicities, and 20% dose reduction of CPT-11 was documented in 10 (22%) patients.

Response evaluation was assessed in the patients with suboptimal reduction; 22 cases of TP regimen and 7 cases of CPT-P regimen. The patients treated with TP included 1 (5%) CR, 6 (27%) PR, 3 (14%) SD and 12 (55%) PD. CPT-P group consisted of 3 (43%) PR, 2 (29%) SD and 2 (29%) PD, respectively. Response was observed in 7 (32%) of 22 cases in TP group and 3 (43%) of 7 cases in CPT-P group. The rates of non-PD patients were 71% (5 of 7 cases) in CPT-P group and 45% (10 of 22 cases) in TP group, respectively (p=0.047).

Two-year and progression-free and overall survival in stage I tumors was 77 and 92% in CPT-P group and 78 and 94% in TP group, respectively. There were no significant survival differences in progression-free survival (Fig. 1A, p=0.95) and overall survival (p=0.40) in stage I tumors.

	Irinotecan plus cisplatin (%)	Paclitaxel plus platinum (%)	P-value
Patients	46	126	
Median age (years) (range)	52 (32-69)	53 (27-75)	0.85
Performance status			0.17
0	26 (57)	85 (67)	
1, 2	20 (43)	41 (33)	
FIGO stage			0.88
I	24 (52)	72 (57)	
II	6 (13)	15 (12)	
III	13 (28)	34 (27)	
IV	3 (7)	5 (4)	
Primary surgery			0.32
Optimal reduction	39 (85)	104 (83)	
Suboptimal reduction	7 (15)	22 (17)	
Follow-up period (months)			0.43
Median	28	27	
Range	6-83	3-73	

Table II. Hematological and non-hematological toxicity of combination chemotherapy of irinotecan hydrochloride and cisplatin for clear cell carcinoma of ovary.

	Grade of toxicities				
	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
<b>Hematological</b>					
Neutropenia	4 (9)	18 (39)	11 (24)	10 (22)	3 (7)
Anemia	14 (30)	20 (43)	10 (22)	1 (2)	1 (2)
Thrombocytopenia	41 (89)	2 (4)	1 (2)	1 (2)	1 (2)
<b>Non-hematological</b>					
Nausea	1 (2)	23 (50)	20 (43)	2 (4)	-
Fatigue	25 (54)	14 (30)	7 (15)	0 (0)	0 (0)
Diarrhea	12 (26)	21 (46)	9 (20)	4 (9)	0 (0)

Patients with suboptimal cytoreduction surgery included 7 cases of CPT-P group and 22 cases of TP group. In these patients with suboptimal reduction, median survival was 10 months in CPT-P group and 12 months in TP group, and there were no significant differences in progression-free survival (Fig. 1B,  $p=0.92$ ) and overall survival ( $p=0.82$ ).

In stage II-IV tumors, optimal reduction at their initial surgery was achieved in 15 (68%) of 22 patients in CPT-P group and 32 (59%) of 54 patients in TP group. Among optimally debulked patients, CPT-P group included 10 cases (67%) of no residual tumor and 5 (33%) cases of tumor

diameter  $<1$  cm, and TP group consisted of 24 cases (75%) of no residual tumor and 8 cases (25%) of tumor diameter  $<1$  cm. There was no significant distribution difference of residual tumor diameter in optimally debulked patients between CPT-P and TP group ( $p=0.55$ ).

Progression-free survival of CPT-P group was significantly better than that of TP group in the group with stage II-IV optimal cytoreduction (Fig. 2,  $p=0.03$ ). Two-year progression-free survival was 86% in CPT-P group and 44% in TP group, respectively. Median progression-free survival of TP group was 15 months. There was no significant difference in overall

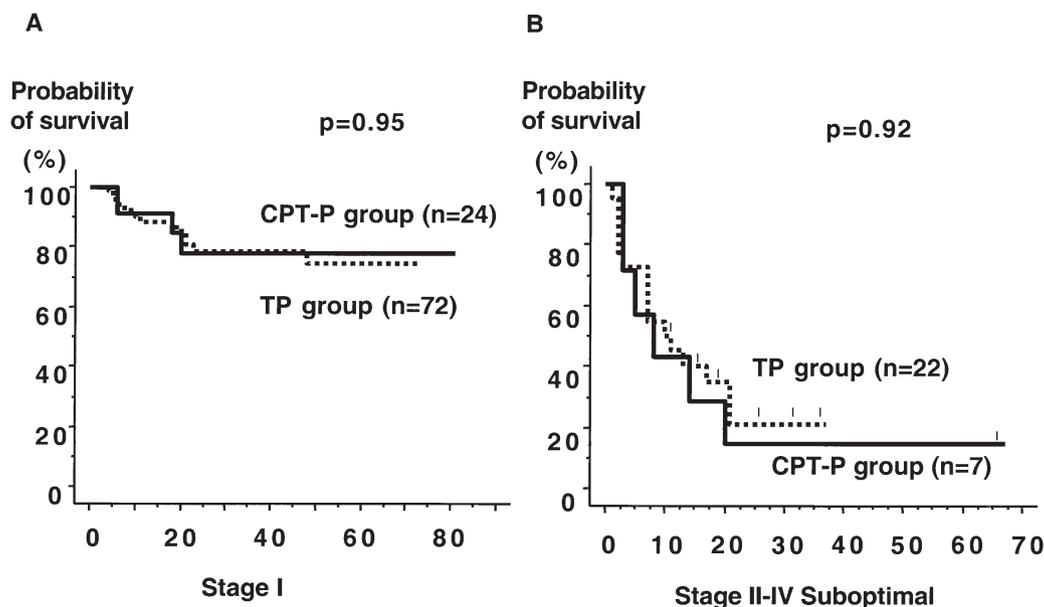


Figure 1. Kaplan-Meier curve comparing the progression-free survival of stage I patients (A) and stage II-IV patients with suboptimal debulking surgery (B) according to adjuvant chemotherapy. No significant difference was observed in patients with stage I ( $p=0.95$ ), and those with stage II-IV suboptimal debulking patients ( $p=0.92$ ).

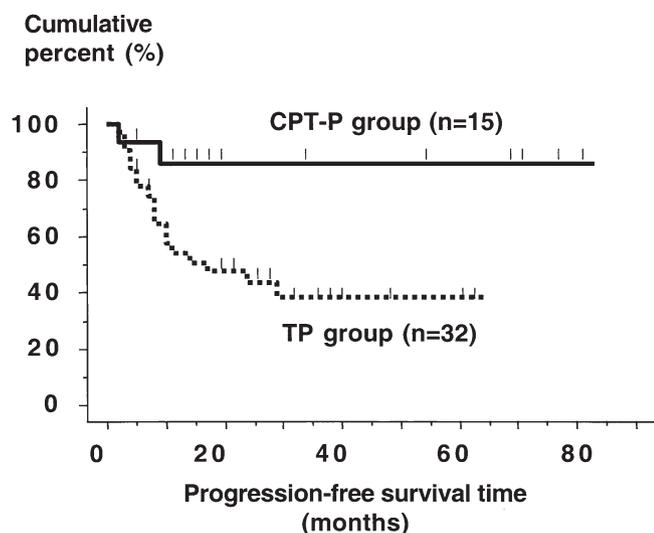


Figure 2. Kaplan-Meier curve comparing the progression-free survival of the stage II-IV patients with optimal debulking surgery according to adjuvant chemotherapy. The survival of the patients with combination with irinotecan hydrochloride and cisplatin (CPT-P) was significantly better than that with paclitaxel and platinum (TP) ( $p=0.03$ ). Two-year progression-free survival was 86% in CPT-P group and 44% in TP group and median progression-free survival time was 13 months in CPT-P group and 11 months in TP group, respectively.

survival of optimally debulked stage II-IV patients according to two regimens ( $p=0.14$ ).

In stage II-IV tumors with optimal reduction, two parameters were independent prognostic factors for progression-free survival as determined by multivariate analysis: residual tumor diameter <1 cm (hazard ratio, 3.77;  $p<0.01$ ); paclitaxel and platinum (hazard ratio, 6.454;  $p=0.02$ ) (Table III). Age, performance status, and FIGO stage were not significant prognostic factors.

## Discussion

In a previous study with CPT-P regimen for ovarian cancer using 70 mg/m<sup>2</sup> of cisplatin on day 1 and 60 mg/m<sup>2</sup> of irinotecan hydrochloride on days 1, 8 and 15, toxicities more than grade 3 was observed in 52-70% for neutropenia and 4-10% for diarrhea (17,19). Japanese large clinical trial using 60 mg/m<sup>2</sup> of cisplatin and 60 mg/m<sup>2</sup> of irinotecan hydrochloride for patients with lung cancer (16) showed high abundance of grade 3-4 toxicities compared with the present study. The lower rates of grade 3-4 toxicities might be explained by a large proportion of patients who received a lower dose (50 mg/m<sup>2</sup>) of irinotecan hydrochloride. A variety of single nucleotide polymorphisms (SNPs) in human UDP-glucuronosyltransferase could cause a different toxicity profile in patients treated with irinotecan hydrochloride (20,21). A variety of SNPs in specific genes might cause the disease-specific toxicity profiles. In the present study, the most common grade 3-4 adverse effect was neutropenia observed in 28% of patients, but it was reversible in all cases. Diarrhea more than grade 3 was observed in 4 (9%) patients and it was reversible with conservative treatment. It was suggested that CPT-P regimen was relatively safe and well-tolerated in first-line chemotherapy in CCC patients.

CCC of the ovary has been suggested to lack sensitivity compared to conventional platinum-based chemotherapy (3,4,7). As combination chemotherapy of TP regimen is now established as 'Gold standard' regimen for epithelial ovarian cancer (22,23), the regimen is widely used for all histological sub-types of ovarian tumors. Some reports indicated survival benefit of TP therapy compared with platinum-based chemotherapy in stage I CCC disease combined with complete surgical staging procedures (11) and stage III, IV tumors (9). However, a recent study including 254 patients with complete surgical staging revealed that there was no significant survival



Variables	Hazard ratio	95% confidence interval	P-value
Age (years)			0.43
<50	1		
>51	1.55	0.53; 4.41	
Performance status			0.88
0	1		
1, 2	1.08	0.40; 2.90	
FIGO stage			0.33
II	1		
III	1.60	0.32; 8.00	
IV	3.04	0.55; 16.67	
Residual tumor			<0.01
None	1		
<1 cm	3.77	1.42; 9.98	
Chemotherapy			0.02
Irinotecan hydrochloride and cisplatin	1		
Paclitaxel and platinum	6.454	1.40; 29.86	

benefit with TP regimen compared with conventional platinum-based chemotherapy in either early or advanced staged patients (12). So far, no anti-cancer agents have been established as a standard regimen for CCC. From view of molecular profiling, CCC is recognized as a completely different category from tumors of other histological subtypes (24,25). These distinct molecular characteristics might support the necessity of another approach for the treatment of CCC of the ovary.

CPT-P regimen, initially introduced as a treatment of platinum-refractory ovarian cancer (19), showed moderate activity for first-line chemotherapy of CCC (17). *In vitro* study suggested that irinotecan hydrochloride as well as paclitaxel was the candidate for anti-neoplastic agents for CCC (26). The present study shows that response rate of CPT-P was almost the same as TP. High abundance of SD patients in CPT-P regimen, acting as 'tumor-dormancy' effects, could possibly lead to better progression-free survival in patients with stage II-IV optimal cytoreductive surgery. The significance of CPT-P regimen was also identified as a favorable prognostic factor with multivariate analysis as well as absence of residual tumor. In addition to the toxicity profile, the efficacy of CPT-P was considered to be satisfactory for the treatment for CCC of the ovary.

Irinotecan hydrochloride was shown to have higher activity than conventional platinum-based regimen for adjuvant setting in combination with mitomycin C (27). Combination chemotherapy including irinotecan hydrochloride was suggested to have a potential anti-tumor effect against CCC of the ovary. CCC of ovary has been reported to have a distinct molecular characteristics as well as a distinctive clinical behavior. Targeting therapy for CCC-specific molecular markers such as hepatocyte nuclear factor-1  $\beta$  (28)

or ABCF2, a member of ATP-binding cassette gene superfamily (29), could possibly be another strategy for the treatment of CCC of the ovary. Although CPT-P could be a candidate regimen showing some efficacy, a large-scale prospective trial is needed to confirm these observations.

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