

## Phase I Study of Irinotecan Combined with Mitomycin-C and 5-Fluorouracil for Gynecological Malignancies: The JGOG Study

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**Abstract.** *Background:* A phase I study to evaluate combined therapy with irinotecan (CPT-11), mitomycin-C (MMC), and 5-fluorouracil (5-FU) was performed in patients with gynecological malignancy, especially non-squamous cell carcinoma of the uterine cervix. *Materials and Methods:* Eligibility for the study included patients with previously untreated, chemotherapy-naïve cervical and ovarian carcinoma. CPT-11 and MMC were administered on days 1 and 15 by intravenous infusion, while 5-FU was given on days 3 to 7. This regimen was repeated after 5 weeks. Four escalating dose levels were carried out (CPT-11/MMC: 120/5, 120/6, 150/6, and 150/7 mg/m<sup>2</sup>; 5-FU 600 mg/m<sup>2</sup> fixed). *Results:* Fourteen patients were enrolled in the study. Although all the patients had no previous chemotherapy, three patients had undergone a simple hysterectomy and nine had a radical hysterectomy performed before this chemotherapy. The maximum tolerated dose was not reached by using CPT-11 150 mg/m<sup>2</sup>, MMC 7 mg/m<sup>2</sup>, and 5-FU 600 mg/m<sup>2</sup> because none of the patients experienced any hematological or non-hematological toxicities of grade 4 during the first cycle. *Conclusion:* The recommended doses of this new regimen are CPT-11 150 mg/m<sup>2</sup>, MMC 7 mg/m<sup>2</sup>, and 5-FU 600 mg/m<sup>2</sup> which can be well tolerated for gynecological malignancies.

The major treatments for gynecological malignancies consist of surgery, radiotherapy, and chemotherapy. In patients with epithelial ovarian carcinomas, the histological subtype is one

of the most important prognostic factors. It is widely acknowledged that the prognosis of clear cell carcinoma and mucinous adenocarcinoma of the ovary is poorer than that of serous and endometrioid adenocarcinoma (1, 2). The platinum-based regimens such as paclitaxel (PTX) plus carboplatin (CBDCA) therapy (TC), which has been introduced broadly as a standard regimen for ovarian cancer (3, 4), may not be the optimal chemotherapy in patients with mucinous and clear cell carcinoma (1, 2). Thus new combined chemotherapies including irinotecan hydrochloride (CPT-11) have been examined (5) and a randomized phase III trial of TC compared with CPT-11 plus cisplatin (CDDP) for clear cell carcinoma is an ongoing study (international collaborative study: GCIG/JGOG3017).

Although the number of patients with cervical cancer has decreased recently, the incidence of adenocarcinoma of the cervix has increased. A recent report of SEER data demonstrated that the rate of non-squamous cell carcinoma has increased by 29.1% over the last 20 years (6). Most patients with locally advanced squamous cell carcinoma of the uterine cervix are commonly treated with radiotherapy or chemoradiotherapy (7-9), but other types of cervical carcinomas are less sensitive to radiotherapy (10, 11) and have a poorer prognosis (12-15). However, there have been few studies of the efficacy of adjuvant chemotherapy for cervical adenocarcinoma (16, 17). CDDP has commonly been used in patients with gynecological malignancies and the response rate of CDDP alone was 20% and for combined chemotherapy with CDDP plus PTX was 60% in non-squamous carcinoma of the cervix (18, 19). However, patients with advanced and recurrent cervical carcinoma often have complications such as ureteral stenosis and renal dysfunction and since it is known that CDDP can cause renal disorders, a new combined regimen to achieve clinical benefits needs to be developed.

CPT-11 is a semisynthetic derivative of camptothecin, a plant alkaloid obtained from *Camptotheca acuminata* (20).

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The antitumor effects of CPT-11 are related to the inhibition of DNA topoisomerase I (21). CPT-11 has shown strong activity against various experimental tumors with little renal toxicity because CPT-11 is excreted into the gastrointestinal tract (22). In patients with gynecological malignancies, monotherapy and combined chemotherapy using CPT-11 have been performed (23-28). 5-Fluorouracil (5-FU) is a key drug for colorectal adenocarcinoma, which is histologically like cervical adenocarcinoma and mucinous ovarian carcinoma. Combined therapy with CPT-11 plus 5-FU/leucovorin (LV) is one of the most standard regimens for primary and metastatic colon cancer (29-31). 5-FU had an effect on cervical adenocarcinoma, with a response rate of 14% (32). In our preliminary study (JGOG 1057, unpublished data), the response rate was 2 out of 17 (11.8%) patients with CPT-11 (150 mg/m<sup>2</sup>, days 1 and 15) plus 5-FU (600 mg/m<sup>2</sup>, days 3 to 7). Grade 4 leukopenia, thrombocytopenia, and diarrhea using this combined chemotherapy was present in 21.2%, 5.3%, and 5.3% patients, respectively. This combination chemotherapy was well tolerated and there appears to be the possibility of adding another antitumor agent. In *in vitro* experiments using cervical adenocarcinoma cell lines, mitomycin-C (MMC) is one of the most effective antitumor agents (33). It has been reported that MMC is a modulator of CPT-11 activity because it increases topoisomerase I expression (34).

Non-squamous cell carcinoma of the uterine cervix and mucinous or clear cell adenocarcinoma of the ovary are diseases with poor prognosis, and are not effectively treated with the present chemotherapy. Therefore, the cervical cancer committee members of the Japanese Gynecologic Oncology Group (JGOG) performed a phase I trial of CPT-11, MMC and 5-FU for gynecological malignancies, especially non-squamous cell carcinoma of the cervix, in order to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT).

## Patients and Methods

**Patient selection.** Patients enrolled in this study were required to fulfil the following eligibility criteria: histologically proven non-squamous cell carcinoma of the cervix or clear cell or mucinous adenocarcinoma of the ovary; no prior chemotherapy or radiotherapy; age ≤75 years; performance status (WHO) ≤2 and life expectancy ≥3 months. The patients were also required to meet all of the following laboratory criteria: an adequate bone marrow reserve (leukocyte count of 4.0-12.0×10<sup>3</sup>/μl, platelet count ≥100×10<sup>3</sup>/μl, and hemoglobin ≥9.5 g/dl), and adequate renal and hepatic function (24-hour creatinine clearance ≥60 ml/min, serum creatinine ≤1.5× the upper limit of normal, serum total bilirubin ≤1.5 mg/dl, and AST/ALT ≤2× the upper limit of normal). All the participants gave written informed consent for the study. Patients were excluded for any of the following reasons: metachronous or synchronous other carcinomas, concurrent infection, pre-existing diarrhea, ileus, or bowel obstruction, interstitial pneumonia or

Table I. Dose escalation scheme.

Dose level	Irinotecan mg/m <sup>2</sup>	Mitomycin-C mg/m <sup>2</sup>	5-Fluorouracil mg/m <sup>2</sup>	No. of patients	No. of cycles
1	120	5	600	4	7
2	120	6	600	4	4
3	150	6	600	3	5
4	150	7	600	3	3

pulmonary fibrosis, massive ascites, pleural effusion, uncontrolled diabetes, or a history of severe drug hypersensitivity. This trial was approved by the Review Board of the Japanese Gynecologic Oncology Group and by the Institutional Review Board of each participating hospital.

**Regimen.** On day 1, MMC dissolved in 20 ml physiological saline was administered as a bolus infusion, after which CPT-11 (in 500 ml of normal saline or 5% glucose solution) was also administered intravenously over 90 min. On days 3 to 7, 5-FU (600 mg/m<sup>2</sup>) was given intravenously over 12 hours. On day 15, MMC dissolved in 20 ml physiological saline was administered as a bolus infusion, after which CPT-11 (in 500 ml of normal saline or 5% glucose solution) was also administered intravenously over 90 min. Granulocyte colony-stimulating factor (G-CSF) was administered if grade 3 neutropenia occurred with a fever ≥38.5°C or if grade 4 neutropenia developed with or without fever. This treatment schedule was repeated every 5 weeks.

The doses and the treatment schedule were modified to avoid severe side-effects. CPT-11 and MMC were not given on day 15 if the leukocyte count was <3.0×10<sup>3</sup>/μl or the platelet count was <100×10<sup>3</sup>/μl. The treatment was also withheld if the patient developed diarrhea ≥grade 2 according to the Eastern Cooperative Oncology Group scale (35). Before the next course was started, the patient condition was evaluated and the starting criteria included a leukocyte count of ≥4.0×10<sup>3</sup>/μl and a platelet count ≥100×10<sup>3</sup>/μl. In addition, there had to be no diarrhea and the renal function of eligibility criteria had to be within acceptable limits. Dose modification was not carried out for low blood cell counts or diarrhea during the same course.

**Dose escalation plan and toxicity evaluation.** The starting dose of CPT-11 was 120 mg/m<sup>2</sup> and MMC was 5 mg/m<sup>2</sup> and the dose of 5-FU was fixed at 600 mg/m<sup>2</sup>. Four escalating dose levels of CPT-11/MMC (120/5, 120/6, 150/6, and 150/7 mg/m<sup>2</sup>) were studied (Table I). Intra-patient dose modification was not permitted. Toxicity was evaluated by the Japan Clinical Oncology Group (JCOG) Criteria (36), except for diarrhea which was assessed by the Eastern Cooperative Oncology Group scale (35). The DLT was defined as any grade 3 or higher nonhematological toxicity (except alopecia, nausea or vomiting, appetite loss and general fatigue) and hematological toxicity of leukopenia grade 4 (>5 days), leukopenia grade 3 with a fever ≥38.5°C, thrombocytopenia grade 4 or thrombocytopenia grade 3 with severe bleeding. Three patients were initially enrolled at each dose level, however, the number of patients at levels 1 and 2 was 4 because the last 2 patients were registered on the same day. If none of the patients experienced DLT during the first treatment cycle, the next cohort of three patients was tested at the next higher dose level. If any DLT was observed in one of the

patients, an additional three patients were enrolled at the same dose level. If two patients in the first cohort or three or more of all the patients at each dose level experienced any DLT, the MTD had been reached and the dose level below the MTD was considered to be the recommended dose for further study. The determination of MTD was based on the toxicity observed in the first cycle of each patient. Toxicity in the patients was evaluated if the patients received at least one full course of the protocol therapy, except for an omission of therapy on day 15.

## Results

**Patient demographics.** Between 2001 and 2006, 14 patients with carcinomas of the cervix or ovary who had no prior chemotherapy entered this trial in four cooperative institutions in Japan. The characteristics of the patients are listed in Table II. Among the 14 eligible patients, 8 were diagnosed with adenocarcinoma of the cervix, 3 with adenosquamous carcinoma of the cervix, 2 with clear cell carcinoma of the ovary, and 1 with mucinous adenocarcinoma of the ovary. The median age was 57 (39-70) years and all the patients had a performance status of 0 to 1. In the patients with cervical carcinoma, the following clinical stages based on the International Federation of Gynecology and Obstetrics (FIGO) were found; five patients had stage Ib, two patients had stage IIa, and four patients had stage IIb. The patient with mucinous ovarian carcinoma was diagnosed as stage Ic and the two patients with clear cell carcinoma had stage IIIb and IIIc disease. All three patients with ovarian carcinoma received simple hysterectomy and bilateral adnexectomy before this protocol chemotherapy. Nine out of the 11 patients with cervical carcinoma had radical hysterectomy performed before this chemotherapy. Only two patients received this chemotherapy in a neoadjuvant setting. Thus, 12 out of the 14 patients did not have any measurable disease.

**Treatment under study.** Out of a total of 19 cycles of this protocol therapy, 4 dose levels were administered in 14 patients (Table I). Ten patients (71%) received one cycle of protocol therapy and the other patients received 2 or 3 cycles (Table II). All the patients were assessable for toxicity. Ten out of the 14 patients received at least one complete cycle of protocol therapy, whereas four patients (dose level 1, one patient; dose level 2, one patient; dose level 4, two patients) were not administered CPT-11 and MMC on day 15. Only the two patients with cervical adenocarcinoma who received this chemotherapy in a neoadjuvant setting had a tumor >4 cm in diameter in the uterine cervix at the time of treatment. After cycle 1, one patient showed no change (NC) and the other was a partial response (PR) and these patients underwent radical hysterectomy after this protocol therapy. There were no treatment-related deaths. The median overall survival (OS) period was 47.5 months (range: 6-65). The reasons for protocol termination were as follows: eight patients were due to finish adjuvant therapy; two patients

Table II. *Characteristics of the eligible patients.*

	No. of patients	(%)
Overall	14	100
Age (years)		
Median (range)	57 (39-70)	
WHO performance status score		
0	5	36
1	9	64
Histology		
Adenocarcinoma of the uterine cervix	8	57
Adenosquamous carcinoma of the uterine cervix	3	21
Clear cell adenocarcinoma of the ovary	2	14
Mucinous adenocarcinoma of the ovary	1	7
Prior therapy		
None	2	14
Simple hysterectomy	3	21
Radical hysterectomy	9	64
No. of cycles		
1	10	71
2	3	21
3	1	7

were due to undergo surgical procedures; three patients requested to discontinue the study therapy and one patient with clear cell carcinoma of the ovary had increased ascites during the treatment period. Among the 14 patients, only two patients who had been diagnosed with adenocarcinoma of the cervix with stage Ib and IIb disease died of the disease at 21 months and 30 months after this protocol therapy, respectively.

**Toxicity observed in cycle 1.** Tables III and IV list the major toxicities encountered during the first cycle. At dose level 1, three patients developed grade 3 leukopenia and two of them received G-CSF. Two patients experienced grade 2 diarrhea and one of them received loperamide and hangeshashinto. Only one patient was not administered CPT-11 and MMC on day 15, because grade 2 leukopenia was still present. At dose level 2, one patient developed grade 3 leukopenia and administration of CPT-11 and MMC was not carried out on day 15. At dose level 3, one patient developed grade 3 neutropenia and grade 2 diarrhea and the patient received G-CSF and hangeshashinto. Another patient showed grade 3 leukopenia and grade 4 neutropenia and was administered G-CSF. At dose level 4, two out of the three patients developed grade 3 leukopenia and the administration of CPT-11 and MMC was cancelled on day 15. As mentioned above, leukopenia was the major toxicity, but no DLTs were observed at any of the dose levels. Therefore, the MTD had not been reached and the maximum dose level (CPT-11/MMC, 150/7 mg/m<sup>2</sup>) was considered to be the recommended dose for further study.

Table III. Hematological toxicity: Cycle 1.

Dose level	No. of patients	Leukopenia					Anemia					Thrombocytopenia				
		G1	G2	G3	G4	G 3/4 (%)	G1	G2	G3	G4	G 3/4 (%)	G1	G2	G3	G4	G 3/4 (%)
1	4	0	1	3	0	75	2	2	0	0	0	1	0	0	0	0
2	4	0	3	1	0	25	2	1	0	0	0	0	0	0	0	0
3	3	0	1	1	0	33	0	2	0	0	0	0	1	0	0	0
4	3	0	1	2	0	67	1	0	0	0	0	0	1	0	0	0

Table IV. Nonhematological toxicity: Cycle 1.

Dose level	No. of patients	Diarrhea				Nausea/vomiting				Hepatotoxicity				Alopecia			
		G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
1	4	0	2	0	0	2	1	0	0	0	0	0	0	3	1	0	0
2	4	0	1	0	0	1	0	0	0	2	0	0	0	3	1	0	0
3	3	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
4	3	1	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0

Table V. Hematological toxicity: Overall.

Dose level	No. of cycles	Leukopenia					Anemia					Thrombocytopenia				
		G1	G2	G3	G4	G 3/4 (%)	G1	G2	G3	G4	G 3/4 (%)	G1	G2	G3	G4	G 3/4 (%)
1	7	1	3	3	0	47	3	3	0	0	0	3	0	0	0	0
2	4	0	3	1	0	25	2	1	0	0	0	0	0	0	0	0
3	5	0	1	3	0	60	0	3	1	0	20	0	1	1	0	20
4	3	0	1	2	0	67	1	0	0	0	0	0	1	0	0	0

Table VI. Nonhematological toxicity: Overall.

Dose level	No. of cycles	Diarrhea				Nausea/vomiting				Hepatotoxicity				Alopecia			
		G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
1	7	3	2	0	0	4	1	0	0	0	0	0	0	4	3	0	0
2	4	0	1	0	0	1	0	0	0	2	0	0	0	3	1	0	0
3	5	1	1	0	0	0	2	0	0	0	0	0	0	1	0	0	0
4	3	1	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0

*Toxicity observed in overall treatment cycles.* In our series, grade 3 leukopenia was noted in 9 cycles (47%), but no grade 4 leukopenia occurred (Table V). Grades 3 and 4 neutropenia were observed in 7 out of 11 (63%) estimated cycles and 4 cycles (36%), respectively. G-CSF was administered in 6 out of 19 (32%) cycles. Only one patient in the second cycle treated with dose level 3 demonstrated grade 3 anemia and thrombocytopenia and none of the patients had any other hematological grade 4

toxicities. Grade 1 diarrhea was observed in 5 out of the 19 cycles and grade 2 diarrhea was observed in 4 out of the 19 cycles (Table VI). Three patients were treated with loperamide and/or hangeshashinto. No grade 3 or 4 non-hematological toxicities occurred in any of the cycles. Fifteen out of the 19 cycles (79%) completed the full scheduled dosage, while CPT-11 and MMC were omitted in 4 cycles (21%) on day 15 because of the delay in the recovery of toxicities.

## Discussion

Cervical cancer is the second most common cancer among women worldwide. Histological analysis revealed that the incidence of adenocarcinoma has risen in recent years (37, 38). It is commonly accepted that the prognosis for advanced or recurrent cervical adenocarcinoma is poorer than that of squamous cell carcinoma (10, 11, 13). Eifel *et al.* demonstrated that the overall 5-year survival rates for FIGO stage Ib patients with squamous cell carcinoma and adenocarcinoma were 81% and 72%, respectively, and that adenocarcinoma of the cervix had an estimated risk of death 1.9 times that of patients with squamous cell type (11). The efficacy of chemotherapy for advanced or recurrent adenocarcinoma of the cervix has been examined because radiotherapy is less effective. Papadimitriou *et al.* reported that clinical responses of the combination of PTX and CDDP occurred in 6 out of 10 (60%) patients with metastatic and recurrent non-squamous carcinoma (19). However, advanced and recurrent cervical carcinoma is often complicated by ureteral stenosis or obstruction and it seems to be difficult to use CDDP. In our preliminary study (unpublished data), the response rate was 2 out of 17 (11.8%) patients for adenocarcinoma of the cervix treated with CPT-11 and 5-FU. These previous reports of chemotherapy for cervical adenocarcinoma have only been studied in a small population and the efficacy of chemotherapy is controversial. Therefore, a new effective regimen without CDDP would be desirable in patients with non-squamous cell carcinoma of the cervix.

The incidence of clear cell carcinoma is higher in Japan (15-20%) than that in Europe and the United States (5-10%). Sugiyama *et al.* reported that CDDP-based chemotherapy was effective in only 3 out of 27 (11%) cases of clear cell carcinoma, but was effective in 79 out of 109 (73%) cases of serous adenocarcinoma (1). Enomoto *et al.* showed that the response rate with TC was significantly lower in clear cell (18%, 2/11) and mucinous (13%, 1/8) carcinomas than in serous (81%, 61/75) and endometrioid (89%, 16/18) carcinomas (2). Thus, there is a need to evaluate potentially more effective regimens for mucinous and clear cell carcinoma of the ovary.

In the current phase I study against non-squamous cell carcinoma of the cervix and clear cell and mucinous carcinoma of the ovary, DLTs were not observed in any of the three patients studied at dose level 4 (CPT-11, 150 mg/m<sup>2</sup>; MMC, 7 mg/m<sup>2</sup>; 5-FU, 600 mg/m<sup>2</sup>). Therefore, the MTD had not been reached and that dose level was recommended for further study. The incidence of grade 3 leukopenia in the first cycle was 7 out of 14 (50%) cycles. Other grade 3/4 adverse events were not observed. Diarrhea was the most important non-hematological toxic effect of CPT-11. Grade 2 diarrhea occurred in 3 out of 14 (21%) cycles, but no grade 3/4 diarrhea was observed during cycle 1. Only one patient treated with dose level 2 showed grade 1 renal toxicity in the first

cycle. Therefore, this new regimen can be well tolerated for gynecological malignancies. In the present series, one patient with cervical adenocarcinoma was diagnosed as FIGO stage Ib with a tumor 8.5 cm in diameter showed a cervical lesion reduced by 18% after 2 cycles of protocol treatment, and was still alive without disease for 61 months after radical surgery. Another patient who had stage IIB disease showed a partial response (50% reduction) after this therapy, and has survived over 25 months without disease after radical surgery and adjuvant radiotherapy. These data suggested that this protocol regimen may be effective for cervical adenocarcinoma.

The combined chemotherapy with CPT-11 (15 mg/m<sup>2</sup> on days 1 and 15), MMC (7 mg/m<sup>2</sup> on days 1 and 15) and 5-FU (600 mg/m<sup>2</sup> from days 3 to day 7) is well tolerated for non-squamous cell carcinoma of the cervix and mucinous and clear cell carcinoma of the ovary. It is possible that this protocol treatment may be an option for gynecological malignancy with renal disorders and platinum resistance. A phase II study using this protocol regimen will be required to evaluate the response rate and survival benefit for advanced or recurrent gynecological malignancies, especially for non-squamous cell carcinoma of the uterine cervix.

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