Salvage chemotherapy with a combination of irinotecan hydrochloride and mitomycin C in platinum- and paclitaxel-resistant epithelial ovarian cancer: case reports

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Summary

Introduction: The efficacy and toxicity of salvage chemotherapy with a combination of irinotecan hydrochloride (CPT-11) and mitomycin C (MMC) for platinum-and paclitaxel-resistant epithelial ovarian cancer are reported.

Case Report: Three consecutive patients with platinum- and paclitaxel- resistant epithelial ovarian cancer were treated with 120 mg/m^2 of CPT-11 (days 1 and 15) and 7 mg/m^2 of MMC (days 1 and 15) every four weeks. In all three cases partial responses were achieved and overall survivals were 17 months or longer. Most of the adverse side-effects were manageable.

Conclusions: This regimen could be administered even in heavily pretreated patients with platinum- and paclitaxel- resistance. Phase I and II studies are needed to confirm the feasibility of this treatment. The efficacy of most salvage treatments for platinum- and paclitaxel-resistant epithelial ovarian cancer is disappointing, and our cases might be of interest from the perspective of treating platinum- and paclitaxel-resistant ovarian cancer.

Key words: Irinotecan; Mitomycin C; Platinum resistant; Ovarian carcinoma.

Introduction

Unfortunately, most patients with epithelial ovarian cancers who receive first-line chemotherapy will have recurrence, and an important prognostic predictor is whether the recurrence is < 6 months (platinum-resistant) or > 6 months (platinum-sensitive) after completion of chemotherapy. Patients with platinum-resistant tumors have a response rate of < 10% when retreated with platinum compounds [1]. The current alternatives include paclitaxel, topotecan, gemcitabine, liposomal doxorubicin, and oral etoposide; however, the overall response rates remain low, 18%-30% [2-9].

Three consecutive cases of platinum- and paclitaxel-resistant ovarian cancer that were treated with irinotecan hydrochloride (CPT-11) and mitomycin C (MMC) chemotherapy as a salvage therapy are reported. The effects and toxicities of this regimen are described.

Patients and Methods

All patients were treated at Mie Prefectural Shima Hospital and had a clinical diagnosis of platinum- and paclitaxel- resistant ovarian cancer. At least one regimen of platinum- and paclitaxel- based salvage therapy had been attempted and failed in each of the three patients before they entered the current study. Both platinum- and paclitaxel-resistant diseases were defined by progression of disease during treatment with these drugs, or relapse within six months of treatment. Each patient had documented recurrent or progressive disease evaluable by computed tomography (CT) scan and tumor markers (except Case 2). Complete response was defined as total disappearance of all clinically or radiologically measurable tumor with normalization of carbohydrate antigen (CA) 125 (normal range < 35U/ml) for at least one month. Partial response (PR) was defined as a 50% reduction in the sum of the two perpendicular diameters of all measurable tumors for at least one month. Progression of the disease was defined as appearance of new lesions or an increase of > 50% in the sum of two perpendicular diameters of any existing lesion.

All three cases had 1) a performance status 0-2; 2) adequate hematologic status (WBC count > 3000 µl, hemoglobin > 9.0 g/dl, and platelet count > 100,000 µl), adequate hepatic function [total bilirubin < 2.0 mg/dl; SGOT < 2 times the upper limit of normal (ULN); or alkaline phosphatase < 2 times of ULN, and adequate renal function (serum creatinine < 1.0 mg/dl and creatinine clearance > 50 ml/min); 3) there was no concurrent malignancy or serious systemic disease.

CPT-11 (120mg/m^2) was administered intravenously for four hours with 500 ml of normal saline solution followed by 7 mg/m^2 of MMC with 100 ml of normal saline for 60 min on day 1, 15 every four weeks [10]. To reduce the gastrointestinal toxicity, an anti-emetic agent (5-HT$_3$ antagonist) was administered prophylactically from day 1 to 2, and from day 15 to 16. To reduce the severity of diarrhea, 7.5 mg/day of herbal medicine, Hange-shashin-toh (Tsumura Pharmaceutical Tokyo), was administered every day during treatment [11]. Granulocyte colony stimulating factor was administered subcutaneously (2 µg/kg) when the WBC count was < 1000 µl or the neutrophil count was < 500 µl. Treatment was repeated more than twice when there was no evidence of tumor progression and the following criteria were met: 1) WBC > 3000/µl, 2) platelets > 100,000/µl, 3) hemoglobin > 8.0 g/dl. Informed consent was obtained after satisfactory understanding of the potential risk and benefits.

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Duration of response was measured from the time of maximal response until disease progression. Progression-free interval was measured from initiation of CPT-11 and MMC treatment until disease progression. Overall survival was measured from the time treatment was initiated until death.

Case Reports

Previous treatments and profiles are described in Table 1.

Case 1

A 65-year-old woman presented in October 1997 because of a massive accumulation of ascitic fluid. She was diagnosed as having Stage IIIC ovarian cancer and then underwent surgery (probe laparotomy). The pathological diagnosis was endometrioid adenocarcinoma (G3) of the ovary.

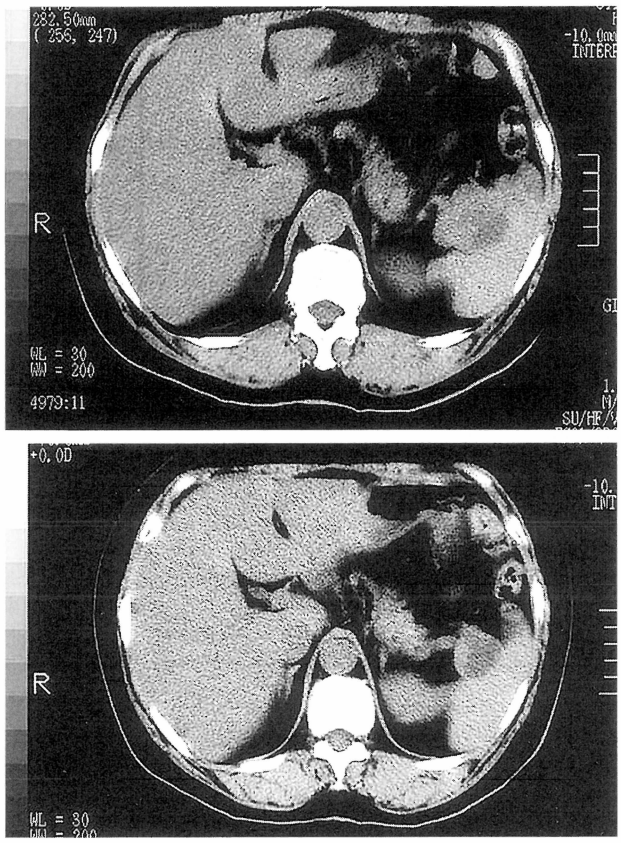
Despite three cycles of paclitaxel and carboplatin (TJ) chemotherapy started in December 1998, a recurrent tumor of the splenic hilus progressed, as shown by CT scanning (Figure 1/a) and CA125 value was 172.0 U/ml.

Four cycles of CPT-11 and MMC chemotherapy were administered, and PR was achieved (Figure 1/b) on August 17, 1999. CA125 was reduced to within the normal limit (Table 2). Laparotomy was performed with splenectomy to completely resect the residual tumor, followed by three cycles of CPT-11 and MMC chemotherapy. Grade 3 thrombocytopenia occurred after the last cycle of the chemotherapy but regressed six weeks after the last cycle. The patient also experienced hemolytic anemia (hemoglobin: 6.5 g/dl, hematocrit: 20.0%, markedly reduced value of haptoglobin: < 10 mg/dl), thrombocytopenia (4.5 x 10^4/mm^3), and renal dysfunction (serum creatinine 1.6 mg/dl) six weeks after recovery from thrombocytopenia (3 months after the end of the treatment). The bone marrow aspiration specimen did not demonstrate any evidence of ovarian cancer relapse or secondary leukemia, but the existence of hemolysis was suspected. A cancer-related hemolytic uremic syndrome (C-HUS), probably due to MMC was diagnosed. Because her C-HUS was thought to be manageable, she was not treated with staphylococcal protein A (SPA) immunopheresis or blood transfusion. The patient died of progression of ovarian cancer 23 months after the start of CPT-11 and MMC chemotherapy (Table 2).

Table 1. — *Previous treatments and profiles.*

No.	Age (years)	Histology	Previous treatment
1	65	Endometriol	1997 - 11 mCAP (4 cycles) 1998 - 4 TAH+BSO+PLN+PAN+OM followed by TJ (6 cycles) 1998 - 12 TJ (3 cycles)
2	48	Serous	1995 - 7 TAH+BSO+PLN+OM followed by CAP (6 cycles) 1998 - 7 TJ (4 cycles) 1998 - 10 Mass debulking surgery + PAN followed by TJ 5 cycles 1999 - 12 TJ (4 cycles)
3	61	Serous	1994 - 4 TAH+BSO followed by CAP (3 cycles) 1997 - 4 EP (4 cycles) 1997 - 8 Mass debulking surgery + PAN+OM followed by EP (3 cycles) 1999 - 3 TJ (6 cycles) 2000 - 6 TJ (6 cycles)

mCAP: combination chemotherapy composed of carboplatin (AUC=5), epirubicin hydrochloride and cyclophosphamide, TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, PLN: pelvic lymph-node dissection, PAN: paraaortic lymph-node dissection, OM: omentectomy, TJ: carboplatin (AUC=5) and paclitaxel chemotherapy, CAP: cisplatin (75 mg/m^2), adriamycin and cyclophosphamide, EP: cisplatin (70 mg/m^2) and etoposide chemotherapy.
All cycles were performed every 4 weeks.



1/a

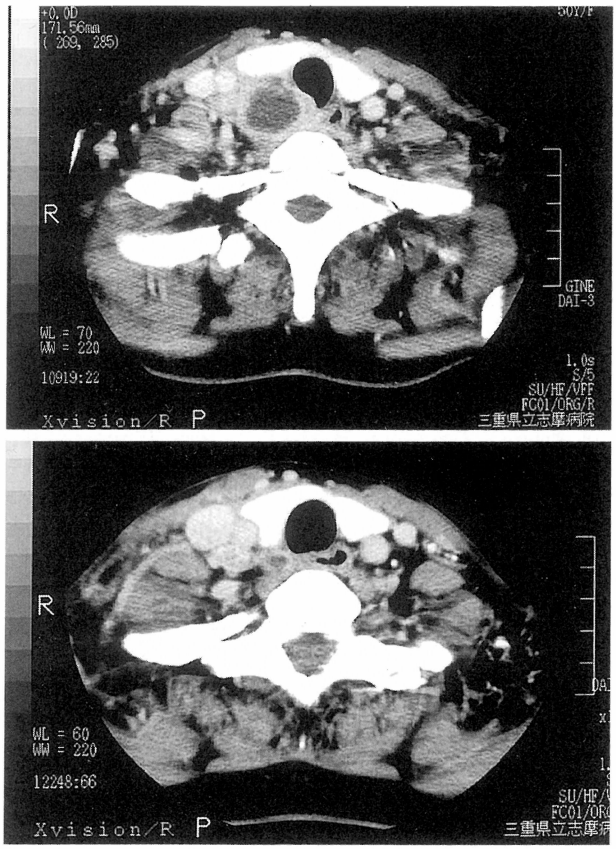
1/b

Figure 1. — CT scan revealed a recurrent tumor of the splenic hilus before (1/a) and after (1/b) chemotherapy.

Table 2. — *Patient characteristics in this study.*

No.	Response to the previous treatment	The site of measurable lesions	No. of cycles (CPT-11+MMC)	Tumor markers	Response	PFI	OS
1	PD	splenic hilus (Figure 1)	7 (3 after operation)	CA125 (U/ml) 172.0→14.8	PR	10 months	23 months DOD
2	PD	neck lymph node (Figure 2)	2	None	PR	4 months	24 months DOD
3	CR, however relapsed 4 months later	liver mesocolon	4	CA125 (U/ml) 52.6→7.4 amylase (IU/l) 206→60	PR	11 months	17 months AWD

PD: progressive disease, NC: no change, CPT-11: irinotecan hydrochloride, MMC: mitomycin C, PR: partial response, CR: complete response. Normal limits are CA125: < 35 U/ml, amylase: < 137 IU/ml, respectively. DOD: died of the disease, AWD: alive with disease, NED: no evidence of disease, PFI: progression-free interval, OS: overall survival.



1/a

1/b

Figure 2. — CT scan revealed a recurrent tumor of the neck lymph node before (2/a) and after (2/b) chemotherapy.

Case 2

A 48-year-old woman was admitted to her regional hospital in July 1995 because of a 5.5 cm sized ovarian cystic tumor. She was diagnosed as having Stage IIIC ovarian cancer (pelvic lymph node metastasis) and underwent surgery at that time (total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy and pelvic lymph node dissection). The pathological diagnosis was serous papillary adenocarcinoma of the ovary.

She was admitted to our hospital with a complaint of hoarseness due to a recurrent tumor of the right neck lymph node, which was diagnosed by fine needle aspiration cytology. The recurrent tumor progressed despite four cycles of TJ chemotherapy started in December 1999 (Figure 2/a), and was markedly reduced in size by two cycles of CPT-11 and MMC chemotherapy. The hoarseness was improved immediately. A CT scan showed PR (Figure 2/b) on July 7, 2000. There were no manageable side effects of the chemotherapy. On abdominal CT scan about two months after PR was achieved, a paraaortic tumor in the left renal vein was detected. Relapse of the disease was strongly suspected and the combination chemotherapy was discontinued. The patient died of the disease 24 months after the start of the CPT-11 and MMC chemotherapy.

Case 3

A 61-year-old woman presented in March 1994 because of a large abdominal tumor. She had a history of diabetus mellitus and was a hepatitis C virus carrier. She was diagnosed as having Stage IC ovarian cancer and underwent surgery at that time (total abdominal hysterectomy and bilateral salpingo-oophorectomy). The pathological diagnosis was serous papillary adenocarcinoma of the ovary.

Recurrent masses in the liver and the mesocolon, and mild accumulation of ascites appeared four months after six cycles of TJ chemotherapy started in June 2000, and tumor markers were elevated (CA125, 52.6 U/ml; serum amylase, 206 IU/l: normal range < 137 IU/l). A recurrent mass in the liver and ascites were hardly detected after four cycles of CPT-11 and MMC chemotherapy, indicating PR on September 24, 2001. Tumor markers were reduced to within normal limits (Table 2). There were no manageable side-effects of the chemotherapy. A recurrent mass in the mesocolon was only slightly reduced in size, but it was completely removed by laparotomy after the 4th cycle of the CPT-11 and MMC chemotherapy. The patient is alive with disease 17 months after the start of the CPT-11 and MMC chemotherapy.

Discussion

Ovarian cancer patients who respond during induction and subsequently experience disease progression or who are primarily resistant to platinum-containing therapy have a poor prognosis. Salvage chemotherapy remains a major problem for platinum refractory or resistant ovarian cancer patients, with low remission and short survival rates. Thus, new drug combinations should be tested in order to improve the long-term prognosis of this subset of patients with very unfavorable prognostic characteristics [12].

CPT-11 is a water-soluble camptothecin derivative that reduces the adverse reactions of camptothecin. Resistance to camptothecin derivatives may be mediated via different mechanisms of action than those for paclitaxel and platinum-resistance. Indeed, in experiments with human tumor cell lines, expression of the mdr-1 gene, important in taxene resistance, does not seem to be involved in resistance to the camptothecin analogue CPT-11 [13]. Thus, CPT-11 was expected as an anticancer agent of the treatment for platinum- and paclitaxel-resistance. In clinical research to date, use of camptothecin derivatives as a single-agent salvage therapy for platinum- and paclitaxel-resistance remains low [5]. Therefore, we investigated combination chemotherapy using CPT-11.

Kano *et al.* reported that supra-additive and marginal supra-additive effects (synergism) were observed for CPT-11 in combination with cisplatin, cytosine arabinoside and mitomycin C. Furthermore, the combination of CPT-11 and these agents have been reported to show a high activity against cancer cells [14]. In *in vivo* studies, CPT-11 has been found to have no cross-resistance with cisplatin, cytosine arabinoside or mitomycin C [15]. It was also reported that the simultaneous administration of CPT-11 and cisplatin or mitomycin C was suitable for clinical application in such malignancies and was worthy of clinical trial [14].

Although cisplatin and topotecan were expected to show a synergistic effect, the clinical response rate of salvage therapy with topotecan and cisplatin was only 13.3% in patients with paclitaxel- and platinum- and resistant recurrent ovarian or primary peritoneal cancer and the median survival was short. Thereafter, patients were

retreated by other chemotherapy with platinum compounds. It was concluded that this combination has an antitumor activity similar to that of single-agent topotecan in platinum-and paclitaxel-resistant epithelial ovarian carcinoma at the expense of higher hematologic toxicity [16].

We used combination chemotherapy with CPT-11 and another synergistic agent, mitomycin C as a salvage chemotherapy. To date, combination chemotherapies with MMC, especially combined with 5-fluorouracil have not had a good response [17-19]. However, Shimizu *et al.* [10] designed this regimen for the treatment of mucinous and clear cell adenocarcinoma which were thought to be one of the most platinum-refractory categories, and they showed an excellent efficacy. Tanaka *et al.* [20] also reported a patient with multiple systemic metastases who showed a complete response to combined camptothecin and mitomycin chemotherapy. A phase II study of Shimizu *et al.* [10] was planned as a primary chemotherapy, thus this regimen might not be suitable for patients heavily pretreated by at least one regimen of platinum- and paclitaxel- based chemotherapy. In our cases, most of the side-effects were manageable.

In all three cases, PRs were achieved and overall survivals were 17 months or longer. The effect of most salvage treatments is disappointing, and our cases might be of interest from the perspective of treating platinum- and paclitaxel- resistant ovarian cancer. Phase I and II studies for patients with platinum- and paclitaxel- resistant ovarian cancer, heavily pretreated by at least one regimen of platinum- and paclitaxel- based chemotherapy are needed.

In addition, C-HUS probably caused by MMC occurred in Case 1. Lesesne *et al.* [21] reported an analysis of 85 cases of C-HUS. All but nine received a cumulative dose > 60 mg of MMC, and most HUS induced by MMC occurred when the total dose of MMC had reached 80-100 mg/body during the treatment of gastrointestinal adenocarcinoma. An effective therapy has not yet been established, although treatment with SPA immunopheresis is given to patients with definite syndrome. C-HUS has a high mortality: over 50% of patients died of or with the syndrome, most within eight weeks of syndrome development. Mild renal dysfunction and hemolytic anemia were manageable in our patients. However, we must monitor patients for the occurrence of C-HUS related to MMC and cumulative dose of MMC to avoid C-HUS.

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