

## Salvage Chemotherapy for Ovarian Carcinoma Recurring During or After Consolidation Chemotherapy with Paclitaxel

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**Abstract.** *Background: The aim of the study was to analyze the effectiveness of salvage chemotherapy for recurring ovarian carcinoma during or after consolidation chemotherapy. Patients and Methods: During the study period, 12 patients received salvage chemotherapy for recurrence during or after consolidation chemotherapy. These cases were retrospectively reviewed. Results: The response rate for salvage chemotherapy was 67% and was significantly associated with treatment-free interval (TFI) after consolidation ( $p=0.038$ ). Progression-free survival was also significantly related to TFI ( $p=0.032$ ). Combination chemotherapy of cisplatin plus irinotecan was effective in all five cases with  $TFI \geq 6$  months and in three out of seven cases with  $TFI < 6$  months. Conclusion: Our study provides, for the first time, evidence that effectiveness of salvage chemotherapy for recurrent ovarian carcinoma occurring during or after consolidation chemotherapy can be predicted by TFI, and that combination chemotherapy of cisplatin plus irinotecan is potentially useful for these cases.*

Ovarian cancer is the ninth most common cancer in women in the U.S. and ranks fifth as the cause of cancer death in women (1). The American Cancer Society estimated for 2010 that there were 21,880 new cases of ovarian cancer in the United States and 13,850 deaths resulting from it. They also estimate a woman's lifetime risk of invasive ovarian cancer is about 1 in 71, and their chance of dying from it is about 1 in 95 (<http://www.cancer.org/Cancer/OvarianCancer/OverviewGuide/>).

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At first diagnosis, three-fourths of ovarian carcinomas are at an advanced stage, thus the prognosis for these women is generally very poor, with a 5-year survival rate of 23-41% for stage III cases, and only 11% for stage IV (1). The gold standard of therapy established for advanced ovarian carcinoma, consists of cytoreductive surgery followed by a combination chemotherapy using paclitaxel and carboplatin (TC therapy). However, even with this treatment, approximately 90% of patients after suboptimal resection, and 70% of patients after optimal cytoreduction, will go on to experience relapse within 18-24 months (2).

Consolidation (maintenance) chemotherapy, which was first introduced for acute leukemia, has now been applied for advanced ovarian carcinoma. It is widely used as a recurrence prophylaxis in patients who undergo cytoreductive surgery followed by post-operative chemotherapy and who are exhibiting complete remission. The Southwest Oncology Group and Gynecologic Oncology Group (GOG) (GOG178 study) conducted a randomized study of stages III and IV ovarian carcinoma cases who underwent cytoreductive surgery followed by a complete response (CR) to paclitaxel and platinum. The patients then randomly underwent either 3 or 12 cycles of consolidation therapy with paclitaxel every 4 weeks. This study showed that progression-free survival (PFS) was significantly higher in the 12-cycle arm than in the 3-cycle arm; however, the all-important overall survival (OS) was not different between the two groups (3-5).

Even though the clinical outcome significance of the currently used 12 monthly cycles of paclitaxel consolidation chemotherapy may be of limited value, many patients with advanced ovarian carcinoma are still being treated by this regimen. As predicted by the GOG study, recurrence of the disease is detected in a significant fraction of these patients during or after their consolidation chemotherapy, ultimately leading to last ditch attempts with salvage therapy.

In our current study, we investigated the effectiveness of salvage chemotherapy for recurrent disease which occurred during or after consolidation chemotherapy with paclitaxel

against advanced ovarian carcinoma in which CR was initially achieved by primary cytoreductive surgery followed by TC chemotherapy, and we also analyzed its relationship to the treatment-free interval (TFI), neither of which has been previously adequately evaluated.

## Patients and Methods

**Patients' characteristics.** During the 7-year study period of 2004 to 2010, 20 patients received consolidation chemotherapy with paclitaxel (135 mg/m<sup>2</sup> every 4 weeks after CR by cytoreductive surgery) followed by 6 courses of TC therapy (paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC=5) for advanced stage III and IV ovarian carcinomas, including one carcinosarcoma case, at the Department of Obstetrics and Gynecology of the Osaka University Hospital, Osaka, Japan. Consolidation chemotherapy was performed, based on informed choice of the patients, for 12 monthly courses, or until recurrent disease was detected. During and after consolidation therapy the status of the disease was evaluated by pelvic and physical examinations and a tumor marker, CA125, every month, and by computed tomography (CT) every 3 months. Recurrence was diagnosed by a CT scan, magnetic resonance imaging (MRI), or histological sections, but not by an elevation of the tumor marker. Informed written consent was obtained from all patients before treatments commenced. This study was approved by both the Institutional Review Board and the Ethics Committee.

**Methods.** The clinicopathological features of these cases, including the age of the patient, the histology, the initial stage of the disease, and the regimen of salvage chemotherapy, were retrospectively reviewed utilizing their clinical records, including physical examination notes, radiological reports, operative records, and histopathology reports. The histological diagnoses were performed by authorized pathologists from the Department of Pathology of the Osaka University Hospital.

In order to evaluate the therapeutic effect of the salvage chemotherapy, previously described standard criteria from the World Health Organization (WHO) (6) was used. The tumors were assessed with a CT scan and/or MRI at baseline and every three treatment courses thereafter. A CR was defined as the disappearance of all known disease, as determined by two observations not less than 4 weeks apart. Partial response (PR) was defined as a 50% or more reduction in the summed products of the two largest perpendicular dimensions of bi-dimensionally measurable lesions, for at least 4 weeks. Stable disease (SD) was defined as a less than 50% decrease, or a less than 25% increase, of tumor size, with no new detectable lesions. Progressive disease (PD) was defined as a greater than 25% increase in tumor size or as the appearance of new lesions.

TFI was defined as the period between the last administration of consolidation chemotherapy and the initiation of the salvage chemotherapy, as previously described (7). PFS was measured from the date of the first administration of salvage chemotherapy to the date of the radiologic or pathologic relapse, or to the date of the last follow-up. OS was defined as the period from the start of salvage chemotherapy to the patient's disease-specific death or to the date of the last follow-up.

**Statistical analysis.** The association between sensitivity to salvage chemotherapy and TFI was analyzed by Fisher's exact test. PFS and

Table I. *Clinical characteristics of the study cases. A total of 12/13 patients received salvage chemotherapy for recurrence during or after consolidation chemotherapy with paclitaxel.*

Characteristic	
Number (cases)	12
Median age (years)	57 (38-76)
Initial stage (cases)	
III	12
IV	0
Histology (cases)	
Serous	9
Endometrioid	1
Clear cell	1
Carcinosarcoma	1

OS curves were constructed using the Kaplan-Meier method. PFS curves determined by a TFI were evaluated for statistical significance by the log-rank test. Results were considered to be significant when the *p*-value was less than 0.05.

## Results

**Clinical characteristics of the study cases.** During the 7-year study period, 20 patients received consolidation chemotherapy using paclitaxel. The initial disease was stage III in 19 of the cases and stage IV in the remaining case. Optimal cytoreduction had been performed in 19 of these cases. Recurrence of the disease was diagnosed in 13 cases. Recurrence was detected during consolidation chemotherapy in five cases and after consolidation in eight. Among the 20 recurrent cases, salvage chemotherapy was performed in 12 cases. Clinical characteristics of the cases are demonstrated in Table I.

**Efficacy of salvage chemotherapy.** A combination chemotherapy with cisplatin plus irinotecan was performed in six cases, liposomal doxorubicin (PLD) and carboplatin in three cases, TC in two cases and the single agent gemcitabine was used in another case (Table II). The overall response rate for salvage chemotherapy was 67% (8 out of 12 cases). The PFS and OS curves of the patients are shown in Figure 1.

**Effect of TFI on the response of salvage chemotherapy and the survival.** All five cases with a TFI of 6 months or longer from the last administration of consolidation chemotherapy using paclitaxel, exhibited CR or PR to salvage chemotherapy. On the other hand, 4 out of the 7 cases with a TFI shorter than 6 months did not respond to salvage chemotherapy (Table III). This difference was statistically significant (*p*=0.038 by Fisher's exact test). The PFS of the

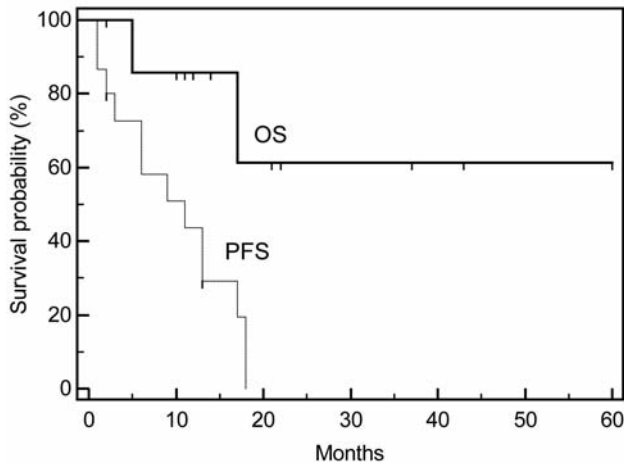


Figure 1. Progression-free survival (PFS) and overall survival (OS) after salvage chemotherapy.

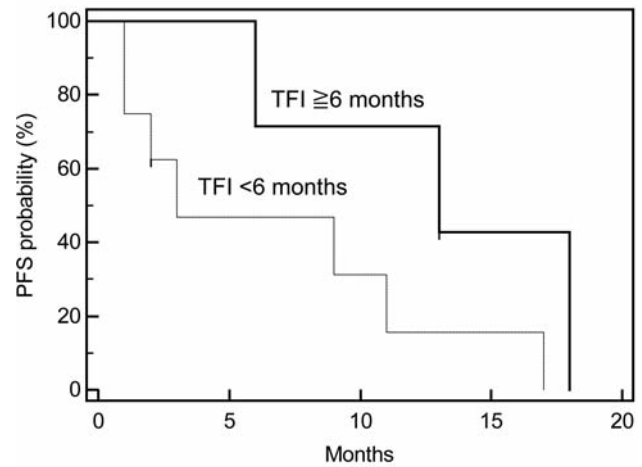


Figure 2. Progression-free survival (PFS) after salvage chemotherapy by treatment-free interval (TFI). PFS probability and overall survival (OS) probability after salvage chemotherapy of the patients whose TFI was of 6 months or more were significantly longer than those whose TFI was less than 6 months ( $p=0.032$  by log-rank test).

patients with a TFI of 6 months or longer was also significantly better than the one of patients with TFI shorter than 6 months ( $p=0.032$  by log-rank test) (Figure 2). Comparison between the survival of the five patients whose recurrences were detected during consolidation chemotherapy and that of the eight cases in which recurrences were detected after consolidation did not exhibit a significant difference. The value of CA125 after consolidation chemotherapy did not grant the prognosis of the patients with recurrence in the present study.

Among the five cases with a TFI shorter than 6 months, which received combination chemotherapy of cisplatin plus irinotecan, three cases demonstrated CR or PR (Table II). However, both cases with a TFI shorter than 6 months (which received salvage chemotherapy of PLD plus carboplatin, or gemcitabine alone) exhibited SD and PD, respectively. All five patients with a TFI of 6 months or longer responded to all regimens of salvage chemotherapy, including a combination of cisplatin plus irinotecan.

**Discussion**

The prognosis for ovarian carcinoma has been somewhat improved by cytoreductive surgery followed by TC clean-up chemotherapy; however, 70-90% of the advanced cases will still relapse within 18-24 months (2). Because of this high rate of recidivism, consolidation chemotherapy is now routinely applied for stage III and IV ovarian carcinoma exhibiting CR to a cytoreductive surgery followed by postoperative chemotherapy. The GOG178 trial demonstrated a somewhat improved PFS in those who were treated by 12 cycles of paclitaxel at 135 mg/m<sup>2</sup> every four weeks as a consolidation therapy (3, 4). The negative OS outcome of consolidation

Table II. Response to salvage chemotherapy.

	TFI	
	<6 Months	≥6 Months
CR	CDDP+CPT-11	PLD+CBDCA
PR	CDDP+CPT-11	CDDP+CPT-11
	CDDP+CPT-11	PLD+CBDCA
SD	TC	
	TC	
PD	PLD+CBDCA	
	CDDP+CPT-11	
	CDDP+CPT-11	
	Gem	

TFI: Treatment-free interval, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, Gem: Gemcitabine, PLD: liposomal doxorubicin, TC: paclitaxel and carboplatin.

Table III. Association of treatment-free interval (TFI) and the effectiveness of salvage chemotherapy. All 5 patients whose TFI was of 6 months or longer exhibited sensitivity to salvage chemotherapy; however, 4 out of 7 cases whose TFI was shorter than 6 months were resistant to salvage chemotherapy. This association was statistically significant ( $p=0.038$  by Fisher's exact test).

TFI	CR/PR	SD/PD
≥6 Months	5*	0
<6 Months	3	4*

\* $p=0.038$ . TFI: Treatment-free interval, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

chemotherapy in that study may be related to crossover, small sample size or the actual ineffectiveness of the consolidation treatment (5). In the After-6 study, patients with stage IIb to IV disease in CR to six courses of paclitaxel/platinum-based chemotherapy were randomly allocated to either an observation-only group or a group that received six courses of paclitaxel at 175 mg/m<sup>2</sup> every three weeks (8). A consolidation treatment with six cycles of paclitaxel did not prolong PFS or OS. Consolidation chemotherapy using topotecan for four cycles also did not improve PFS or OS in the AGO-OVAR and GINECO trial (9) and the MITO-1 trial (10). These results imply that the clinical significance of the currently used consolidation chemotherapy is of limited value. However, a randomized comparison with three treatment arms (paclitaxel, paclitaxel plus poliglumex, and observation only) is now under trial (GOG212).

Many patients with advanced ovarian carcinoma have been treated, or are currently being treated, by consolidation chemotherapy using paclitaxel, based mostly on the previous result showing a prolonged PFS. Unfortunately, recurrence of the disease is detected in many of these patients. For recurrences during or after paclitaxel consolidation chemotherapy, salvage therapy has not been well analyzed, until now. In our department, consolidation chemotherapy using paclitaxel at 135 mg/m<sup>2</sup> every four weeks was performed for 20 stage III and IV cases after complete response to six cycles of TC therapy following cytoreductive surgery. Among these 20 cases, recurrence was detected in 13 cases. Salvage chemotherapy, including cisplatin plus irinotecan, PLD plus carboplatin, gemcitabine, and TC was performed in 12 of these 13 cases.

Response to second-line chemotherapy after first-line chemotherapy for ovarian carcinoma was previously demonstrated to be associated with TFI (11-14). Recurrent ovarian carcinoma within 6 months from a first-line chemotherapy is significantly more likely to be both resistant to the original drugs and to have a lower response rate to other chemotherapy. On the other hand, tumors which recur after 6 months from the first-line platinum-based chemotherapy have a higher chance of responding well, either to a re-challenge with a platinum-based treatment or to other agents (11).

In the present study, the effectiveness of undertaking salvage chemotherapy was evaluated in association with TFI. The overall response rate for salvage chemotherapy was 67% (8 out of 12 cases). The response to a salvage chemotherapy and the PFS after salvage chemotherapy were demonstrated to be related to TFI ( $p=0.038$  and  $p=0.032$ , respectively, by Fisher's exact test, Table III and Figure 2). All the regimens, including cisplatin plus irinotecan combination chemotherapy, were effective for the patients with TFI $\geq$ 6 months. A regimen of cisplatin plus irinotecan exhibited a good response even in the cases with TFI $<$ 6 months (60%); however no response was observed for the other administered regimens (Table II).

These results were consistent with a clinically useful rule for ovarian and endometrial carcinoma cases, namely that a similar or other regimen is effective for those cases with a TFI $\geq$ 6 months, but a similar regimen cannot be recommended for those with a TFI of less than 6 months (11-16).

Our present study provides good evidence for the effectiveness of a salvage chemotherapy for recurrent ovarian carcinoma during or after consolidation chemotherapy using paclitaxel, the effectiveness of which, for the first time, can be predicted by the TFI, and that a combination chemotherapy of cisplatin plus irinotecan is a potentially useful regimen for these cases. Other platinum-containing regimens also may be useful for these cases. Further investigation is still required to establish a more useful regimen of consolidation therapy and to establish a more efficacious strategy for recurrent disease during or after consolidation chemotherapy.

## Conclusion

The effectiveness of salvage chemotherapy for ovarian carcinoma cases recurring during or after consolidation chemotherapy with paclitaxel can be predicted by TFI. Combination chemotherapy with cisplatin plus irinotecan is a potential regimen for these recurrent cases.

## Disclosure of Interests

None of the Authors have a conflict of interest to declare.

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