### How can we predict successful debulking at primary or interval surgery?

In the early studies of NACT, selection of patients was based on the resectability of the tumors or patients characteristics at PDS, such as age, PS and medical conditions. Some investigators proposed criteria to predict successful or unsuccessful debulking. These methods may be also applicable in the setting of NACT to determine an indication or timing of IDS.

Nelson *et al.* defined several CT findings as unresectable disease and the results were compared with surgical outcome in 42 patients [36]. Successful cytoreduction (<2 cm residual disease) was accomplished in 23 out of 24 who fulfilled CT criteria for cytoreduction and six out of 18 with CT criteria predictive of inability to perform cytoreduction. They concluded that CT scan is an accurate method for predicting successful surgical cytoreduction. Dowdy *et al.* selected 17 CT findings and correlated with the possibility of optimal cytoreductive surgery (residual tumor <1 cm) in 87 patients [37]. A combination of diffuse peritoneal thickening and ascites was a most useful predictor of suboptimal cytoreduction and associated with a very low rate of optimal cytoreduction (32%). Qayyum *et al.* defined several imaging criteria for inoperable tumors and compared with operability at surgery in 137 patients [38]. Sensitivity and specificity for the prediction of suboptimal debulking were 76% (16 out of 21 patients) and 99% (115 out of 116 patients), respectively. They also found that CT and MRI were equally effective in the detection of inoperable tumor.

On the other hand, Vergote *et al.* utilized laparoscopic diagnosis to evaluate an operability in 77 patients [39]. In total, 79% of 28 patients, those supposed to be operable, were cytoreduced to <0.5 cm residual tumor. Deffieux *et al.* evaluated the role of laparoscopy in selecting candidates for complete cytoreduction surgery in 15 patients [40]. Among the 11 patients considered to have resectable tumors by laparoscopy, ten women had no macroscopic residual tumor after surgery. Fagotti *et al.* developed a scoring system based on laparoscopic evaluation of metastases in seven regions [41]. They demonstrated that this scoring system predicts suboptimal surgery with 100% sensitivity, 100% positive-predictive value and 74% accuracy.

Although these methods may be useful during the evaluation of resectability from the viewpoints of tumor spread, Aletti *et al.* pointed out the importance of patients' conditions and surgeons' expertise to achieve successful cytoreduction [42]. They found that patients' performance and surgeons' aggressive tendency are independently associated with optimal surgery in multivariate analysis. In another study, they identified a group of high-risk patients characterized by high tumor dissemination or stage IV, poor performance or nutritional status and age ≥75 years [43]. Aggressive debulking surgery was associated with morbidity of 63.6% and limited survival benefit in these patients.

Indication or timing of IDS should be evaluated, taking into account the patient's condition and the surgeon's expertise in addition to imaging diagnoses in clinical practice.

### What is the optimal goal of IDS?

Most studies emphasized that the greatest advantage of NACT is a higher rate of optimal surgery in IDS. These studies uniformly used the same definition of optimal surgery in IDS as that in PDS. The meaning of residual disease after PDS and IDS is naturally different because chemoresistance may be altered by NAC and the planned number of postsurgical chemotherapy may be different. Thus, the definition of optimal surgery in IDS should be stricter than in PDS to indicate similar good survival from viewpoints of chemoresistance and remaining chemotherapy. In many retrospective studies and some prospective studies, a high proportion of optimal surgeries in IDS, based on the same definition, did not influence the survival of patients treated with NACT [4–6,9,12,15,16,20]. For example, Vrščaj *et al.* demonstrated higher optimal debulking in the IDS group compared with the PDS group (60 vs 22%, respectively; p = 0.001) but not improved survival (25 vs 26 months, respectively; p = not significant) [9]. Everett *et al.* reported similar observations of a higher proportion of optimal debulking in the IDS group than the PDS group (86 vs 54%, respectively; p < 0.001), but comparable survival (33 vs 42 months, respectively; p = not significant) [12]. Lee *et al.* presented an improved rate of optimal surgery (78% for IDS vs 46% for PDS; p = 0.04) without improving survival (53 months for IDS vs 55 months for PDS; p = not significant) [20]. These results support our idea.

As far as we know, there have been few studies addressing the definition of optimal surgery for IDS during NACT. Although it was not a direct analysis, we related the size of the residual tumor and survival after interval look or debulking surgery during PDS-CT based on the assumption that chemotherapy after interval surgery is identical between NACT and PDS-CT [48]. Interval look and debulking surgeries were performed after three or four cycles of chemotherapy for patients with optimal and suboptimal PDS, respectively. The 5-year survival of patients with no residual tumor after interval surgery was comparable with that of patients with minimal residual tumor (<2 cm) after PDS (47 vs 40%, respectively), while the 5-year survival of patients with minimal residual tumor after interval surgery is much worse (0%). Colombo *et al.* analyzed the prognostic factors in patients treated with NACT. They found that the size of the residual tumor is a significant prognostic factor (p = 0.014), and the 5-year survival of patients with no residual tumor, <1 cm tumor or >1 cm tumor was 33, 11 or 0%, respectively [16]. Mazzeo *et al.* reported similar results among patients treated with NACT [49]. The median survival of patients with no residual tumor at IDS is significantly better than that of patients with any residual tumor (41 vs 23 months, respectively; p = 0.0062). Almost 50% of patients with no residual tumor survived for 4 years, whereas no patients with residual tumor survived longer than 4 years. For long-term survival, surgery leaving even minimal residual tumor is not optimal.

Pölcher *et al.* addressed the definition of optimal surgery at IDS [35]. They performed a multivariate analysis of prognostic factors and found that no residual tumor was independently associated with good survival (hazard ratio: 0.33; p < 0.001).

They stated that optimal debulking after NAC should be defined as no gross residual disease. Although this suggestion may be based on a somewhat aggressive standpoint, it also supports our opinion. Without addressing the definition of optimal debulking, Kuhn *et al.* also demonstrated by multivariate analysis (relative risk: 14.3; p = 0.02) [18] and Schwartz *et al.* demonstrated by univariate analysis (p < 0.001) that macroscopic residual tumor is a significantly worse prognostic factor for OS [7]. Le *et al.* [50] and Le *et al.* [51] demonstrated a significant association between macroscopic residual tumor and PFS by multivariate analysis (p = 0.003 and 0.04, respectively). All of these studies support our opinion from an aggressive standpoint.

On the basis of these studies, we can say that the definition of optimal debulking in IDS should be stricter than in PDS and that the definition should be no residual tumor in IDS, even though the definition of optimal surgery in PDS remains <1-cm residual tumors.

### *How frequently can we achieve optimal IDS following NAC with platinum and taxane?*

Bristow *et al.* [22] and Kang *et al.* [23] reported that the weighted mean rate of optimal debulking was 65.0 and 70.0%, respectively, in their meta-analyses. Regrettably, these results may not be in accordance with current clinical practice. For example, these studies used the definition of optimal surgery as defined for each cohort, which is, in the majority of cases, residual tumors of <2 cm. In addition, these studies include cohorts treated with NAC regimens other than platinum–taxane combinations. Table 6 summarizes the performance rate and results of IDS among cohorts treated with a NAC regimen composed of platinum and taxane [4,17,18,20,27,35,50–53].

The median performance rate of IDS after three or four cycles of NAC ranged from 62 to 100% in each cohort base, and the average performance rate was 91% (695 out of 763). IDS resulted in residual disease with <2 cm residual tumors (i.e., the older definition of optimal surgery) in 80% (193 out of 242) of patients (range: 59–84% in each cohort base). Similarly, IDS resulted in residual disease with <1 cm residual tumors (i.e., present definition of optimal surgery) in 67% (430 out of 640) of patients (range: 45–74% in each cohort base). Finally, complete resection of all tumors (i.e., recommended definition of optimal surgery) was achieved in 42% (288 out of 687) of patients (range: 26–55% in each cohort base). Although these cohorts still include various selection criteria for NACT, different decision criteria for performing IDS and different target goals for surgery, as well as include retrospective studies, this information may be useful in order to predict an ordinary course of treatment.

As an average course of NACT for advanced-stage ovarian cancer by using a standard platinum–taxane combination regimen, IDS is possible in approximately 91% of patients, optimal debulking according to the present definition (<1 cm residual tumor) is possible in approximately 67% of patients, and complete resection can be achieved in approximately 42% of patients.

### *Should we exclude patients with clear-cell or mucinous histology from NACT?*

One of the important questions is whether we should avoid performing NACT for advanced-stage ovarian cancer with chemoresistant histology, such as clear-cell or mucinous adenocarcinoma. In principle, NACT does not seem beneficial for patients with chemoresistant histology. Current publications seldom discuss differences in histology.

Inciura *et al.* reported on a retrospective, comparative study between NACT (n = 213) and PDS-CT (n = 361) [13]. The number of patients with serous, mucinous, endometrioid, and other types were 84, 48, 49 and 32, respectively, in the NACT group and 135, 67, 118 and 41, respectively, in the PDS-CT group. There was no statistical difference in OS between NACT and PDS-CT in serous (p = 0.396), endometrioid (p = 0.197) and mucinous (p = 0.256) histology. We can find no apparent demerits of NACT for patients with mucinous adenocarcinoma in this study.

Ongoing Phase III studies [24,25] and a recently published EORTC study [4] set the criteria for tumor marker CA125 and CEA in eligibility. These criteria may work not only to exclude the malignancy of digestive tracts but also to decrease the enrollment of patients with clear-cell adenocarcinoma or mucinous histology. Actually, patients with clear-cell adenocarcinoma or mucinous adenocarcinoma enrolled in the EORTC study was only 4.3% (29 out of 670).

Accumulation of data may be necessary in order to determine whether we should avoid selecting NACT for patients with clear-cell adenocarcinoma or mucinous adenocarcinoma, although, in principle, NACT would not seem beneficial for patients with such chemoresistant histology.

## Expert commentary

When NACT was an alternative treatment for patients with advanced ovarian, tubal, or peritoneal cancer, selection of patients with primarily unresectable tumors was one of most important issues before initiating treatment. For this purpose, some investigators proposed the criteria of unresectablity using CT or MRI results [36–38], while others used or recommended diagnostic laparoscopy [39–41] to select such patients, as previously mentioned. Now that NACT is a standard treatment option, the roles of these criteria may change. How to diagnose ovarian, tubal or peritoneal malignancy and diagnose the advanced stage of these diseases (i.e., diagnose as adequate disease for NACT) without wasting time is a very important issue before starting NACT. As discussed previously, cytology may be a useful tool for this purpose. Although we cannot diagnose all patients with ovarian, tubal or peritoneal cancer correctly by cytological diagnosis alone, we can correctly select patients with these diseases by cytology in combination with imaging diagnosis and serum tumor markers. However, it is noteworthy that malignancies of other origins, such as breast and digestive tract, were carefully ruled out by some other criteria in the setting of clinical study. Similar careful diagnosis is necessary to use cytological diagnosis at clinical practice.

Once again, when NACT was an alternative treatment for patients with more advanced-stage ovarian, tubal or peritoneal cancer with primarily unresectable tumors, achievement of optimal surgery with <1 cm residual tumors in IDS might have been very positive because the prognoses of these patients were deemed to be poor. Now that NACT is a standard treatment option for all patients with stage III/IV, NACT should be selected with the expectation of the best outcomes for patients. We should perform IDS in NACT with the aim of complete resection of all macroscopic tumors, taking into consideration that leaving even minimal residual disease makes prognoses of the patients poor.

Along with the change in the role of NACT, we should also change the management of patients regarding diagnosis before treatment and IDS.

## Five-year view

Mature, long-term, follow-up results from all or most of the ongoing Phase III studies will probably be available in order to help establish a role for NACT. The role of NACT itself and new strategies of chemotherapy in NACT will be a focus of research. In the setting of PDS-CT, the strategies of intraperitoneal (IP) chemotherapy; a combination regimen of CBDCA and dose-dense, weekly PTX; and a combination of molecular-target therapy, are candidates for replacing an intravenous, tri-weekly combination of platinum and taxane based on the results of Phase III studies [54–56]. All of these strategies can be combined with NACT, and several studies of these treatments have been performed or are in progress.

The Southwest Oncology Group (SWOG) performed a Phase II study of NAC and IDS followed by intravenous/IP chemotherapy in women with stage III/IV ovarian, tubal or peritoneal cancer with bulky disease [53]. NAC consisted of three cycles of intravenous CBDCA and PTX. Postsurgical chemotherapy for optimally cytoreduced patients consisted of six cycles of intravenous and IP PTX and IP CBDCA. In total, 26 out of 58 enrolled patients underwent optimal IDS and received postsurgical intravenous/IP chemotherapy. PFS and OS for 26 patients who received intravenous/IP chemotherapy is 29 and 34 months, respectively. They concluded that these results compare favorably with other studies of suboptimally debulked patients and that randomized comparisons are necessary to make conclusions regarding the toxicity and efficacy of their intravenous/IP regimen. The University Health Network in Canada started a Phase I/II study of NAC and IDS followed by IP CDDP and intravenous PTX in February 2007 (ClinicalTrials.gov identifier: NCT00889733 [101]). The Clinical Trial Group of the National Cancer Institute of Canada also started a randomized Phase II/III study in September 2009 to compare three post-IDS chemotherapy arms, including an intravenous PTX and intravenous CBDCA arm, intravenous/IP PTX and IP CDDP arm, and intravenous/IP PTX and IP CBDCA arm (ClinicalTrials.gov identifier: NCT00993655 [101]).

Pölcher *et al.* performed a Phase II study of NACT using a molecular target agent to assess activity and tolerability [57]. The regimen was a combination therapy of tri-weekly CBDCA and PTX with the multi-target, tyrosine kinase inhibitor, sorafenib (400 mg twice daily). The planned protocol treatment was two cycles of NAC and IDS followed by four cycles of postsurgical chemotherapy and maintenance, single-agent oral sorafenib through 1 year. Unfortunately, the study was terminated early because all four enrolled patients suffered severe toxicities after NAC and IDS. Although the regimen was not feasible, the authors conclude that further evaluations of sorafenib are warranted. Wright *et al.* initiated a Phase II study of neoadjuvant CBDCA, PTX and bevacizumab in May 2010 (ClinicalTrials.gov identifier: NCT01146795 [101]). The treatment schedule includes three cycles of NAC and IDS followed by six cycles of postsurgical chemotherapy.

The new strategies of NACT using a wide variety of schedules or agents will be assessed for efficacy and toxicity with great enthusiasm. It is expected that such strategies will contribute to further improvements in the outcome of patients with advanced ovarian, tubal or peritoneal cancer.

## Key issues

- Retrospective or nonrandomized prospective studies demonstrated that neoadjuvant chemotherapy-setting treatment (NACT) seemed to greatly reduce surgical invasiveness without compromising the survival of patients with advanced ovarian, tubal or peritoneal cancer.
- NACT is expected to become a standard treatment for unselected patients with advanced ovarian cancer when favorable results are confirmed by Phase III studies and several problems are resolved.
- Cytological examination of ascites, pleural effusion or tumor, in addition to imaging diagnosis and tumor markers, may be necessary before NACT can be used for accurate diagnosis of target diseases, unless we select diagnostic laparotomy or laparoscopy.
- Although further evaluation is necessary, three or four cycles may be the most likely optimal amount, and two cycles may be a reasonable option for the optimal number of neoadjuvant chemotherapy cycles.
- The definition of optimal debulking in interval debulking surgery should be stricter than in primary debulking surgery and it should mean no residual tumor, even though the definition in primary debulking surgery remains <1-cm residual tumors.
- As an average course of NACT for advanced ovarian cancer by using a standard platinum–taxane combination regimen, interval debulking surgery is possible in approximately 91% of patients, optimal debulking (<1-cm residual tumor) is possible in approximately 67% of patients, and complete resection can be achieved in approximately 42% of patients.
- Accumulation of data may be necessary in order to determine whether we should avoid selecting NACT for patients with chemoresistant histology, such as clear-cell adenocarcinoma or mucinous adenocarcinoma.

**Financial & competing interests disclosure**

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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- •• of considerable interest

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### *Website*

101 ClinicalTrials.gov http://clinicaltrial.gov

# Retrospective study comparing irinotecan and pegylated liposomal doxorubicin in treatment of recurrent platinum-refractory/resistant epithelial ovarian cancer

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**Summary**

*Purpose:* The standard regimen for platinum-resistant/refractory recurrent epithelial ovarian cancer (EOC) remains to be determined. In this study, we retrospectively compared the effect of irinotecan (CPT-11) and pegylated liposomal doxorubicin (PLD) in the treatment of platinum-resistant recurrent EOC. *Methods:* Thirty patients who received salvage chemotherapy with CPT-11 or PLD were included in the study. CPT-11 (100 mg/m²) was administered intravenously on days 1, 8 and 15 every four weeks. PLD (50 mg/m²) was administered on day 1 every four weeks. Treatment was repeated, provided that no disease progression or intolerable toxicity occurred. *Results:* Response rate in the CPT-11 group and PLD group showed no difference at 26.7% ($p = 0.66$) in both, while non-PD rate was 73.3% vs 33.3% ($p < 0.05$), respectively. Progression-free survival after CPT-11 treatment and PLD treatment was 28.4 weeks and 16.8 weeks ($p = 0.07$), respectively. Hand-foot syndrome and mucositis were more common in the PLD group than in the CPT-11 group ($p < 0.05$). *Conclusions:* The results indicate that CPT-11 is a promising drug for the treatment of platinum-resistant recurrent EOC.

*Key words:* Ovarian cancer; Recurrence; Platinum-resistant; Irinotecan; Liposomal doxorubicin.

## Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, accounting for approximately 8,000 new diagnoses and 4,000 deaths annually in Japan [1]. Patients are usually treated with cytoreductive surgery, followed by platinum/taxane chemotherapy, and the initial response rate for these treatments exceeds 70% [2]. Despite such a good initial response, however, the majority of patients experience a relapse, with a median disease-free interval of 18 to 24 months. Recurrent cases are classified into three categories: platinum-sensitive (relapse after ≥ 6 months of initial platinum therapy); platinum-resistant (relapse within 6 months of initial platinum therapy); or platinum-refractory (stable disease or progressive disease during initial platinum therapy). According to guidelines issued by the National Comprehensive Cancer Network (NCCN), while platinum-based combination therapy should be considered in recurrent cases classified as platinum-sensitive, non-platinum monotherapy is recommended in recurrent cases classified as platinum-resistant/refractory [3]. The standard regimen, however, remains to be determined. Pegylated liposomal doxorubicin (PLD) is approved by the US Food and Drug Administration for use in patients with EOC whose disease has progressed or recurred after platinum-based chemotherapy, and PLD has become a commonly used treatment option for patients with recurrent platinum-resistant/refractory EOC. Irinotecan (CPT-11), a semi-synthetic derivative of camptothecin and topoisomerase I inhibitor, is widely used for platinum-resistant EOC in Japan [4]. In this retrospective study, we compared the effect of CPT-11 and PLD in the treatment of platinum-resistant recurrent EOC.

## Materials and Methods

### *Patients*

We retrospectively reviewed the medical records of women with platinum-refractory/resistant recurrent EOC who received CPT-11 or PLD.

Thirty patients in whom salvage chemotherapy was commenced between May 2006 and May 2010 were included in the study. All patients underwent initial surgery and primary chemotherapy consisting of a platinum/taxane regimen, and were followed-up at the Department of Obstetrics and Gynecology, Keio University Hospital, Tokyo. All treatments were performed by staff of the same gynecologic oncology group. Decisions with regard to the salvage chemotherapy were usually made by the attending clinician. Any regimen that contained a platinum or taxane drug was counted as one regimen. For example, if a patient received a platinum/taxane regimen as first-line chemotherapy and then, after recurrence, received another platinum/taxane regimen as second-line chemotherapy, the number of regimens was counted as two. Except one patient, none of the patients in the CPT-11 group had received prior treatment with CPT-11, topotecan (TOP) or some other topoisomerase I inhibitor, and none of the patients in the PLD group had been treated with anthracyclines, including PLD. Data were collected on age, International Federation of Gynecology and Obstetrics (FIGO) staging, histologic type, histologic grade, prior chemotherapeutic treatment, site of recurrence, interval between prior chemotherapy and date of recurrence and progression-free survival (PFS) after recurrence.

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*Definition of chemotherapy sensitivity of prior chemotherapy*

"Refractory," "resistant," and "sensitive" at first recurrence were defined as follows: refractory: progression, partial remission, or stable disease during primary chemotherapy; resistant: complete remission and relapse < 6 months of termination of primary chemotherapy; sensitive: complete remission and relapse ≥ 6 months after termination of primary chemotherapy.

*Treatment schedule, response evaluation and toxicity assessment.*

The treatment cycle consisted of four weeks. Irinotecan (100 mg/m$^2$) was administered intravenously over 90 min on days 1, 8 and 15 every four weeks. Pegylated liposomal doxorubicin (50 mg/m$^2$) was administered on day 1 every four weeks. Treatment was repeated for up to eight cycles, provided that no disease progression or intolerable toxicity occurred.

Response was based on 2-dimensional measurement of lesions based on computed tomography (CT) or magnetic resonance imaging (MRI). Complete response (CR) was defined as no evidence of disease on images obtained, with normalization of serum CA125 level. Partial response (PR) was defined as a > 50% decrease in tumor size. Progressive disease (PD) was defined as a > 25% increase in tumor size or the appearance of a new lesion. Stable disease (SD) was defined as neither sufficient shrinkage to qualify as PR, nor sufficient increase to qualify as PD. The CA125 response criteria were not used; however, the patients were considered as showing no PR or change if there was an increase in CA125. CT or MRI were performed every two to three cycles during chemotherapy and every three to six months after chemotherapy. Progression-free survival (PFS) was defined as the interval from the first day of administration of salvage chemotherapy to the day of disease progression.

All adverse effects were classified according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTC), version 3.

*Statistical analysis*

The Fisher exact test or chi-square test was used to compare clinical background and toxicity between the CPT-11 and PLD groups. The relationships between response rate or non-PD rate and age, histology, number of prior regimens and treatment-free interval (TFI) were analyzed with the Fisher exact test. Patients were categorized by age (< median vs ≥ median), histology (serous vs non-serous), regimen (CPT-11 vs PLD) and TFI (0-3 months vs 4-6 months). Factors influencing PFS were estimated by the Kaplan-Meier method and analyzed with the log-rank test. Statistical calculations were performed using the SPSS Statistics software package, version 17.0 for Windows (SPSS, Chicago, IL).

## Results

*Patients*

Median age at time of salvage chemotherapy was 63 years (range: 37-77 years). Clinical stage and histology were as follows: clinical stage (IIIa, 1; IIIb, 1: IIIc, 14; IV, 14); histology (serous, 18; clear cell, 4; endometrioid, 2; mucinous, 2; other, 4). Median TFI after prior chemotherapy was 3.3 months. Recurrent disease was solitary in five cases and multiple in 25. No patient underwent interval debulking surgery or secondary debulking surgery. Fifteen patients received monotherapy with CPT-11 and 15 with PLD. The clinical background in each regimen is shown in Table 1. No significant differences were observed between the CPT-11 group and the PLD group. The median number of prior chemotherapy regimens was 2.1 (range: 1-4) for CPT-11 and 2.1 (range: 1-5) for PLD. The median number of salvage chemotherapy cycles was 3.9 (range: 2-7) for CPT-11 and 4.1 (range: 2-8) for PLD.

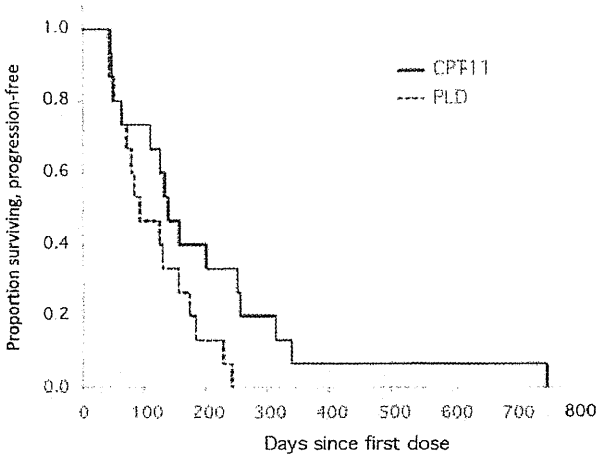


Figure 1. — Kaplan-Meier curve of estimated progression-free survival.

*Clinical effect of CPT-11 and PLD*

The relationships between clinical factors and response rate or non-PD rate with salvage chemotherapy are shown in Table 2. In total, response rate and non-PD rate in all cases were 26.7% (95% CI: 10.9%-42.5%) and 53.3% (95% CI: 35.4%-71.2%), respectively. PFS after salvage chemotherapy was 22.6 weeks (range: 6.0-107.4 weeks). Age, histology, disease site or TFI showed no association with response rate or non-PD rate in any case.

Response rate in the CPT-11 group and PLD group showed no difference at 26.7% (95% CI: 4.3%-49.1%) ($p$ = 0.66) in both, while the non-PD rate was 73.3% (95% CI: 50.9%-95.7%) vs 33.3% (95% CI: 9.5%-57.1%) ($p$ < 0.05), respectively. Non-PD rate was significantly better in the CPT-11 group than in the PLD group. PFS after CPT-11 treatment and PLD treatment was 28.4 weeks (range: 6.4-107.4 weeks) and 16.8 weeks (range: 6.0-34.7 weeks) ($p$ = 0.07), respectively (Figure 1).

*Toxicity*

A total of 59 cycles of CPT-11 was administered, and the CPT-11 dose on days 8 and 15 was skipped in 19% and 19% of patients, respectively. Forty-four cycles of CPT-11 were administered after the first cycle. In the

Table 1. — *Clinical background of salvage chemotherapy.*

| Factors | CPT-11 (n = 15) | PLD (n = 15) | *p* value |
|---|---|---|---|
| Median age in years | 63 (range: 42-71) | 62 (range: 37-77) | ns |
| Histology | | | ns |
| Serous | 9 | 9 | |
| Non-serous | 6 | 6 | |
| Endometrioid | 2 | 0 | |
| Mucinous | 1 | 1 | |
| Clear cell | 3 | 1 | |
| Other | 0 | 4 | |
| Disease | | | ns |
| Solitary | 3 | 2 | |
| Multiple | 12 | 13 | |
| TFI | | | ns |
| 0-3 months | 9 | 4 | |
| 4-6 months | 6 | 11 | |
| Prior regimen | 2.1 (range: 1-4) | 2.1 (range: 1-5) | ns |

TFI: treatment-free interval; ns: not significant

Table 2. — *Effect of CPT-11 treatment and PLD treatment.*

| Clinical factor | | CR+PR (8 cases) | CR+PR+SD (16 cases) |
|---|---|---|---|
| All cases (n = 30) | | | |
| Age | < Median | 3 | 9 |
| | ≥ Median | 5 | 7 |
| Histology | Serous | 3 | 8 |
| | Non-serous | 5 | 8 |
| Disease site | Solitary | 0 | 1 |
| | Multiple | 8 | 15 |
| TFI | 0-3 months | 3 | 8 |
| | 4-6 months | 5 | 8 |
| CPT-11 (n = 15) | | (4 cases) | (11 cases) |
| Age | < Median | 1 | 6 |
| | ≥ Median | 3 | 5 |
| Histology | Serous | 1 | 6 |
| | Non-serous | 3 | 5 |
| Disease site | Solitary | 0 | 1 |
| | Multiple | 4 | 10 |
| TFI | 0-3 months | 2 | 7 |
| | 4-6 months | 2 | 4 |
| PLD (n = 15) | | (4 cases) | (5 cases) |
| Age | < Median | 2 | 3 |
| | ≥ Median | 2 | 2 |
| Histology | Serous | 2 | 2 |
| | Non-serous | 2 | 3 |
| Disease site | Solitary | 0 | 0 |
| | Multiple | 4 | 5 |
| TFI | 0-3 months | 1 | 1 |
| | 4-6 months | 3 | 4 |

TFI: treatment-free interval.

CPT-11 group, 12 of 44 (27%) cycles were delayed, and median delay per one cycle was 3.8 days. Forty-six cycles of PLD were administered after the first cycle. In the PLD group, 17 of 46 (37%) cycles were delayed, and median delay per one cycle was 4.4 days.

The adverse events in the CPT-11 and PLD groups are shown in Table 3. No significant differences were observed in hematologic toxicities between the two groups. Hand-foot syndrome (HFS) and mucositis were significantly more common in the PLD group ($p < 0.05$). Although diarrhea and nausea were more common in the CPT-11 group than in the PLD group, the differences were not significant.

## Discussion

Despite a high clinical complete remission rate, EOC patients still exhibit a high rate of recurrence and require chemotherapy. According to guidelines issued by the NCCN, while platinum-based combination therapy should be considered in recurrent cases classified as platinum-sensitive, non-platinum monotherapy is recommended in recurrent cases classified as platinum-resistant/refractory [3]. A number of randomized phase III studies on PLD, TOP, gemcitabine (GEM) and paclitaxel (PTX) for recurrent EOC have been reported [5-8]. Ten Bokkel *et al.* compared TOP and PTX in 235 recurrent EOC cases and reported that TOP showed a level of efficacy at least equivalent to that of PTX, as manifested by an increased response rate and significantly longer time to progression [8]. Gordon *et al.* performed a randomized phase III study to compare the effect of TOP and PLD in 474 recurrent EOC cases and concluded that PLD yielded comparable efficacy, a favorable safety profile and convenient dosing, thus supporting its candidacy as a valuable treatment option in recurrent EOC [6]. However, the subset analysis of platinum-refractory/resistant EOC showed a trend in favor of TOP over PLD in terms of PFS ($p = 0.733$), with a median of 13.6 vs 9.1 weeks, respectively, and overall survival (OS) ($p = 0.455$), with a median of 41.3 vs 35.6 weeks, respectively [6]. Mutch *et al.* performed a randomized phase III trial comparing GEM with PLD in 195 platinum-refractory/resistant recurrent EOC cases and reported that median PFS was 3.6 vs 3.1 months, median OS was 12.7 vs 13.5 months and overall response rate was 6.1% vs 8.3% in the GEM and PLD groups, respectively [7]. From these results, it remains difficult to determine the standard monotherapy regimen for platinum-refractory/resistant recurrent EOC.

Irinotecan is a topoisomerase I inhibitor, and is widely used in platinum-refractory/resistant recurrent EOC in Japan. Matsumoto *et al.* retrospectively analyzed the effect of CPT-11 in 28 platinum-refractory/resistant recurrent EOC patients and reported that response rate (CR+PR) was 29% and that median time to progression was 17 weeks [4]. These results are believed to be promising.

In this study, we compared the effect of CPT-11 and PLD in platinum-refractory/resistant recurrent EOC, retrospectively. Although the response rate was comparable, both non-PD rate and PFS were better in the CPT-11 group than in the PLD group at 73.3% vs 33.3% ($p < 0.05$) and 28.4 weeks vs 16.8 weeks ($p = 0.07$), respectively. Both CPT-11 and TOP are topoisomerase I inhibitors, and this type of drug may be effective for platinum-refractory/resistant recurrent EOC.

Table 3. — *Toxicity of CPT-11 treatment and PLD treatment.*

| | CPT-11 (n = 15) | | | | | | PLD (n = 15) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | All grades | G3 + 4 | G1 | G2 | G3 | G4 | All grades | G3 + 4 |
| Hematologic | | | | | | | | | | | | |
| WBC | 3 | 9 | 2 | 0 | 14 (93%) | 2 (13%) | 2 | 6 | 6 | 1 | 15 (100%) | 7 (47%) |
| ANC | 1 | 5 | 6 | 0 | 12 (80%) | 6 (40%) | 1 | 3 | 6 | 4 | 14 (93%) | 10 (67%) |
| Hb | 4 | 6 | 3 | 0 | 13 (87%) | 3 (20%) | 4 | 6 | 2 | 1 | 13 (87%) | 3 (20%) |
| Plt | 3 | 0 | 0 | 0 | 3 (20%) | 0 (0%) | 6 | 1 | 2 | 0 | 9 (60%) | 2 (13%) |
| Non-hematologic | | | | | | | | | | | | |
| Total bilirubin | 0 | 0 | 0 | 0 | 0 (0%) | 0 (0%) | 0 | 0 | 0 | 0 | 0 (0%) | 0 (0%) |
| AST | 2 | 0 | 0 | 0 | 2 (13%) | 0 (0%) | 5 | 0 | 0 | 0 | 5 (33%) | 0 (0%) |
| ALT | 1 | 1 | 0 | 0 | 2 (13%) | 0 (0%) | 3 | 0 | 0 | 0 | 3 (20%) | 0 (0%) |
| Creatinine | 3 | 1 | 0 | 0 | 4 (27%) | 0 (0%) | 3 | 0 | 0 | 0 | 3 (20%) | 0 (0%) |
| Diarrhea | 5 | 1 | 1 | 0 | 7 (47%) | 1 (7%) | 2 | 0 | 0 | 0 | 2 (13%) | 0 (0%) |
| Nausea | 8 | 3 | 1 | 0 | 12 (80%) | 1 (7%) | 7 | 1 | 0 | 0 | 8 (53%) | 0 (0%) |
| HFS | 0 | 0 | 0 | 0 | 0 (0%)* | 0 (0%) | 6 | 3 | 0 | 0 | 9 (60%)* | 0 (0%) |
| Mucositis | 2 | 1 | 0 | 0 | 3 (20%)* | 0 (0%) | 6 | 4 | 0 | 0 | 10 (67%)* | 0 (0%) |

* $p < 0.05$.

One of the important purposes of salvage chemotherapy is palliation of symptoms and maintenance of quality of life (QOL). Therefore, toxicity is an important consideration in choice of chemotherapy regimen. In this study, no significant difference was observed in hematologic toxicities or most non-hematologic toxicities between the CPT-11 and PLD groups. However, HFS and mucositis were more common in the PLD group. Finally, tolerability was equivalent between the two groups. Assessment of QOL will be an essential factor in choice of drug.

## Conclusion

In conclusion, the results indicate that CPT-11 is a promising drug for the treatment of platinum-resistant recurrent EOC. Further randomized phase III studies are required to elucidate the efficacy of CPT-11 in the treatment of platinum-refractory/resistant recurrent EOC in comparison with PLD.

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# Phase II study of S-1, an oral fluoropyrimidine, in patients with advanced or recurrent cervical cancer

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**Background:** S-1 is an oral fluoropyrimidine. This phase II study was designed to evaluate the efficacy and safety of S-1 in patients with advanced or recurrent uterine cervical cancer.

**Patients and methods:** S-1 35 mg/m$^2$ was given twice daily for 28 days repeated every 6 weeks. Eligible patients were women aged 20–74 years, who had Eastern Cooperative Oncology Group performance status of zero or one, who had stage IVB or recurrent uterine cervical cancer, and who had received no more than one platinum-containing chemotherapy regimen for stage IVB or recurrent disease. The primary end point was overall response rate (ORR) determined by RECIST.

**Results:** A total of 37 patients were enrolled in the trial and 36 were eligible. The median number of cycles administered was 4. The confirmed ORR was 30.6% (95% confidence interval 15.5% to 45.6%). The response rate for patients who had received platinum-based treatment including chemoradiotherapy was 31.8% (7 of 22). After a median follow-up duration of 25 months, the median time to progression and the median survival time were 5.2 and 15.4 months, respectively. The most frequent grade 3 or 4 adverse events were anemia (16%), anorexia (16%), and diarrhea (22%).

**Conclusions:** This phase II study of S-1 in cervical cancer suggests a promising response rate and a contribution toward prolonging survival, with modest toxic effects. Phase III studies of S-1 in patients with advanced or recurrent cervical cancer are thus warranted.

**Key words:** cervical cancer, chemotherapy, phase II trial, relapse, S-1

## introduction

Cancer of the uterine cervix is the main cause of death from gynecologic malignancy in emerging countries. In the developed world as well, a third of women with cervical cancer die of uncontrolled disease. Although a number of chemotherapeutic agents have been investigated in patients with advanced or recurrent cervical cancer, the prognosis of those patients remains poor. Identification of new agents with activity in cervical cancer is needed.

S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is an oral fluoropyrimidine consisting of tegafur [a prodrug that is metabolized to 5-fluorouracil (5-FU) in blood, largely by the cytochrome P450 system in the liver], gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1 : 0.4 : 1 [1]. S-1 is known to be active against gastric, head and neck, colorectal, lung, breast, pancreatic, and biliary tract cancers [2–9]. This phase II study was designed to evaluate the efficacy and safety of S-1 in patients with uterine cervical cancer and is the first exploration of S-1 for the treatment of any gynecologic cancer. S-1 has also shown activity for cervical cancer in preclinical study (data are available only in investigator's brochure); phase II study of S-1 in patients with cervical cancer has been launched to evaluate the usefulness of S-1 in those patients.

## patients and methods

### eligibility criteria

Eligible patients were aged between 20 and 74 years, had Eastern Cooperative Oncology Group performance status of zero or one, and had histological documented primary stage IVB or recurrent cervical carcinoma.

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All patients had measurable disease according to the RECIST [10]. Measurable lesions defined unit dimensionally were ≥20 mm using conventional imaging or ≥10 mm with spiral computed topographic scan. Patients had not received more than one prior chemotherapy regimen since diagnosis of metastatic or recurrent disease. Patients who were administered in conjunction with radiation were not counted under prior chemotherapy. Four weeks from prior chemotherapy or radiotherapy were required before study entry. Adequate organ function was required for study entry: neutrophil count ≥2000/μl; platelet count ≥100 000/μl; hemoglobin ≥8.0 g/dl; serum bilirubin level ≤1.5 times upper limit of the institutional normal (ULN); asparate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels ≤2.5 times ULN; and serum creatinine level ≤ ULN. Only patients who could swallow tablets were eligible. Patients with any of the following conditions were excluded from the study: active infection, severe heart disease, interstitial pneumonitis, history of hypersensitivity, malignant or benign effusions requiring drainage, active brain metastasis, or active concomitant malignancy. Patients receiving drugs with potential interactions with S-1 (flucytosine, warfarin, and phenytoin) were excluded. All patients gave informed consent before entering this study, which was approved by the institutional review boards at all participating institutions.

### treatment schedule

Patients received two oral doses of S-1 35 mg/m$^2$ daily for 4 weeks of a 6-week cycle. As S-1 is provided in 20 or 25 mg tablets, the actual dosage of S-1 was decided according to the patient's body surface area as follows: patients with a body surface area of less than 1.25 m$^2$ received 40 mg; those with a body surface area of 1.25–1.5 m$^2$ received 50 mg; and those with a body surface area of more than 1.5 m$^2$ received 60 mg. The schedule was repeated until the occurrence of disease progression, unacceptable toxic effects, or patient's refusal. If a grade 3 or higher hematological toxicity or a grade 2 or higher nonhematological toxicity was observed, the dose was reduced from 60 to 50 mg, 50 to 40 mg, or temporary interruption of S-1 administration was recommended. Patients whose toxic effects necessitated a rest period of >4 weeks were withdrawn from treatment. When initial dose was 40, 50, or 60 mg, dose escalation could be allowed to 50, 60, and 75 mg for subsequent cycles, unless adverse events were observed.

### response and toxicity evaluation

The tumor response was assessed according to the guidelines of RECIST. Target lesions included all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total. Target lesions were included the lesions with previously irradiated area. Complete response (CR) was defined as the complete disappearance of all target and nontarget lesions, with no development of new disease. Partial response (PR) was defined as a reduction by ≥30% in the sum of the longest diameter of target lesions. CRs or PRs were confirmed by repeat assessments carried out no <4 weeks after the criteria for response were first met. Progressive disease (PD) was defined as an increase ≥20% in the sum of the longest diameter of all target lesions or the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. Stable disease (SD) was defined as neither sufficient lesion shrinkage to qualify for PR nor sufficient increase to qualify for PD. Best response was defined as the most CR achieved by a patient (thus, each patient had a single best response: CR, PR, SD, or PD), and the date of best response was the date it was first detected. Radiological studies were repeated every two cycles. If a patient was documented as having a CR or a PR, the response was confirmed at least 4 weeks after the first evidence of response. An independent response review committee (IRRC) evaluated all tumor responses after the investigators had completed their judgment.

Toxic effects were evaluated with respect to incidence and severity using Common Terminology Criteria of Adverse Events (version 3.0) (www.cancer.gov/).

### statistical consideration

The primary end point of this study was to assess the overall response rate determined by the IRRC. The secondary end points were to assess duration of response, time to response, time to progression (TTP), overall survival, and adverse events. Assuming a response rate of 20%, the study was designed with 80% power such that the lower limit of the 95% confidence interval (CI) for the estimate of the response rate was >0.05. A sample size of 32 assessable patients was required. The Kaplan–Meier method was used to determine the TTP and median survival time (MST) in the assessable population. TTP was defined as the time from the first medication to the date of a PD event or death (due to cervical cancer or study drugs).

## results

### patient population

A total of 37 patients were entered into the study from July 2005 to September 2007 and 36 patients were eligible and assessable. One patient had a lack of absolute neutrophil count for eligibility criteria. All 37 patients were evaluated for safety. Patient characteristics are listed in Table 1. More than half of the patients had distant diseases. Seventeen patients (8 for neoadjuvant chemotherapy, 3 for metastatic disease, and 6 for both) received prior chemotherapy (not including chemoradiotherapy): 14 received platinum-containing regimen and 3 received oral 5-FU derivative drug alone. Thirteen

**Table 1.** Patient characteristics

| Characteristic | No. of patients |
|---|---|
| No. of patients entered | 37 |
| No. of patients eligible | 36 |
| Age (years) | |
| Median | 57 |
| Range | 33–72 |
| Performance status | |
| 0 | 26 |
| 1 | 10 |
| Histology | |
| Squamous cell carcinoma | 29 |
| Adenocarcinoma | 2 |
| Adenosquamous | 4 |
| Small cell carcinoma | 1 |
| Site of disease | |
| Pelvic | 23 |
| Distant | 26 |
| Both | 13 |
| Prior therapy | |
| Prior radiotherapy | 22 |
| Prior chemotherapy[a] | 17 |
| Prior chemoradiotherapy | 13 |
| Prior platinum therapy | 22 |

[a]Not included chemoradiotherapy.

patients (36%) received chemoradiotherapy. Prior platinum therapy including chemotherapy or chemoradiotherapy was administered for 22 patients.

A total of 167 treatment cycles (median 4, range 1–19) were administered. Nineteen patients (53%) were subjected to dose reduction owing to adverse events. The median relative dose intensity was 0.83 (range 0.45–1.04).

### antitumor activity

Table 2 describes the response assessment. The objective response rate assessed by IRRC was 30.6% (95% CI 15.5% to 45.6%). The median duration of response was 134 days (range 73–553 days). The investigators identified one CR and nine PRs. One clinical responded patient who had CR was downgraded to PR, two clinical responded patients who had PR were downgraded to SD and PD, respectively, and three patients who had SD were upgraded to PR by the judgment of IRRC. Therefore, a total of 11 patients were judged PR. Responses according to prior therapy are listed in Table 2. Patients who received chemotherapy alone had a response of 17.6%, patients who received chemoradiotherapy 53.8%, and patients who received platinum-containing chemotherapy or chemoradiotherapy 31.8%. Eighteen patients had target lesions with previously irradiated area and five (27.8%) of them were responded.

After a median follow-up duration of 25 months, the median TTP was 5.2 months (95% CI 4.5–6.6 months; Figure 1) and the MST was 15.4 months (95% CI 11.5–17.8 months; Figure 2). One-year survival was 58.3%.

### safety

All 37 patients were assessed for safety. Four patients were discontinued due to toxic effects. Adverse events are listed in Table 3. Grade 3 or 4 hematologic toxic effects were anemia (16%), neutropenia (8%), and thrombocytopenia (5%). Among grade 3 or 4 nonhematologic toxic effects, the most frequent were anorexia (16%) and diarrhea (22%). All other grade 3 or 4 toxic effects were recorded in <10% of patients.

## discussion

The prognosis of patients with advanced or recurrent cervical cancer remains poor and there is an urgent need for novel therapeutic agents. This current study was designed to determine the efficacy and tolerability of an oral agent of S-1 for advanced or recurrent cervical cancer and demonstrated a higher response rate of 30.6% with modest toxic effects: grade 3 or 4 anemia (16%), anorexia (16%), and diarrhea (22%).

The most extensively studied agent in the treatment of advanced cervical cancer is cisplatin, which has been used as a single agent, in combination chemotherapy, or with radiotherapy. The eligibility criteria of our study included

**Table 2.** Responses to S-1 according to the patient characteristics

| | *n* | CR | PR | SD | PD | Response rate (95% CI) |
|---|---|---|---|---|---|---|
| Overall | 36 | 0 | 11 | 18 | 7 | 30.6 (15.5–45.6) |
| Prior therapy | | | | | | |
| Chemotherapy | 17 | 0 | 3 | 9 | 5 | 17.6 (0–35.8) |
| Chemoradiotherapy | 13 | 0 | 7 | 5 | 1 | 53.8 (26.7–80.9) |
| Platinum therapy | 22 | 0 | 7 | 10 | 5 | 31.8 (12.4–51.3) |
| No platinum therapy | 14 | 0 | 4 | 8 | 7 | 28.6 (14.9–52.2) |

CR, complete response; PR, partial response; SD, stable disease; PD, Progressive disease; CI, confidential interval.

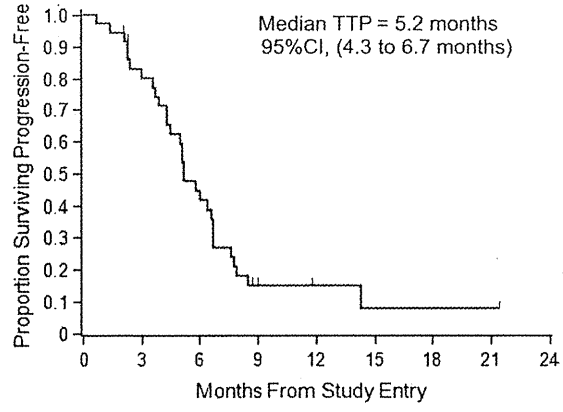


**Figure 1.** Kaplan–Meier plot for time to progression (TTP; $n = 36$). CI, confidence interval.

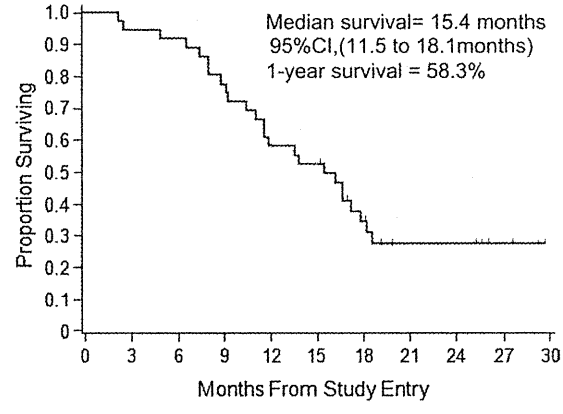


**Figure 2.** Kaplan–Meier plot for overall survival ($n = 36$). CI, confidence interval.

**Table 3.** Adverse events ($n = 37$)

| Toxicity | Grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | Grade 3–4(%) |
| Anemia | 6 | 11 | 5 | 1 | 16 |
| Leukopenia | 5 | 13 | 2 | 0 | 5 |
| Neutropenia | 6 | 9 | 3 | 0 | 8 |
| Thrombocytopenia | 6 | 1 | 1 | 1 | 5 |
| Stomatitis | 18 | 2 | 0 | 0 | 0 |
| Anorexia | 14 | 7 | 6 | 0 | 16 |
| Nausea | 21 | 4 | 1 | 0 | 3 |
| Vomiting | 12 | 2 | 1 | 0 | 3 |
| Diarrhea | 13 | 10 | 8 | 0 | 22 |
| Hyperpigmentation | 31 | 1 | 0 | 0 | 0 |
| Skin rash | 7 | 4 | 1 | 0 | 3 |
| Fatigue | 12 | 11 | 2 | 0 | 5 |


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patients with prior chemotherapy or chemoradiotherapy. Twenty-two of the 36 patients (61%) had previously received platinum therapy including chemoradiotherapy. There may be drug resistance to cisplatin in such patients; however, objective responses were seen in patients who had received prior platinum therapy. Therefore, it is suggested that S-1 is a noncross resistant drug for cisplatin.

Several non-platinum agents, such as paclitaxel [11–13], topotecan [14, 15], irinotecan [16, 17], vinorelbine [18–20], capecitabine [21, 22], and ifosphamide [23–25] were found to have moderate activity in patients with metastatic cervical cancer. However, none of the previously reported phase II studies of non-platinum single-agent chemotherapy for patients with advanced cervical cancer have reported >30% response rate, except paclitaxel and ifosphamide [26]. Paclitaxel is an active agent for cervical cancer and has been evaluated in randomized trial. GOG 0204 compared doublets of paclitaxel, vinorelbine, and gemcitabine plus cisplatin with the combination of topotecan plus cisplatin, and there was a trend favoring treatment with cisplatin/paclitaxel for response rate, progression-free survival (PFS), overall survival, and quality of life [27]. Ifosphamide in combination with cisplatin was tested in randomized trial comparing cisplatin alone and showed a better response rate and PFS but not overall survival and including severe toxic effects. Although our study examined a small number of patients and the CI was wide, notable objective responses were achieved in this single-agent chemotherapy.

Combinations of 5-FU and cisplatin yield synergistic in preclinical studies [28, 29]. A combination therapy of S-1 and cisplatin has been studied in other malignancies, including gastric cancer, lung cancer, and head and neck cancer [30–32]. Phase III trial comparing S-1 in combination with cisplatin versus S-1 alone in advanced gastric cancer demonstrated a significant benefit for combined S-1 plus cisplatin in response rate, PFS, and overall survival [33]. Based on the promising activity of S-1 in the present phase II study, and the experience with S-1 plus cisplatin in other malignancies, we have started phase III trial of S-1 plus cisplatin compared with single-agent cisplatin for metastatic cervical cancer in an Asian trial, including Japan, Korea, and Taiwan.

In conclusion, S-1 is active in patients with metastatic cervical cancer and well tolerated. S-1 plus cisplatin has now entered a prospective randomized phase III trial.

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# Dose-dense therapy is of benefit in primary treatment of ovarian cancer? In favor

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Paclitaxel and carboplatin given every 3 weeks is the current standard treatment in first-line chemotherapy regimens for ovarian cancer. The concept of 'dose-dense therapy' is based on the hypothesis that a shortening interval of the doses of cytotoxic agents will be more effective for tumor-cell kill. Recently published phase III trials in breast cancer have shown that dose-dense weekly paclitaxel improves response and survival. The Japanese Gynecologic Oncology Group reported a phase III study comparing the conventional 3-weekly paclitaxel and carboplatin schedule versus dose-dense weekly paclitaxel and 3-weekly carboplatin for advanced epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. The progression-free survival, as the primary endpoint of this study, was significantly prolonged with the dose-dense treatment [28 versus 17.2 months; hazard ratio (HR): 0.71; 95% confidence interval (CI): 0.58–0.88; $P = 0.0015$], as was the overall survival at 3 years (72.1% versus 65.1%; HR 0.75; 95% CI: 0.57–0.98; $P = 0.03$). Dose-dense weekly paclitaxel plus carboplatin represents a new treatment option in women with advanced epithelial ovarian cancer.

**Key words:** advanced epithelial ovarian cancer, dose-dense therapy, paclitaxel

## introduction

Currently, the combination of paclitaxel and carboplatin (TC) is the standard first-line chemotherapy for ovarian cancer. In its most recent consensus statements on the management of ovarian cancer during the Fourth International Ovarian Cancer Consensus Conference, the Gynecologic Cancer InterGroup (GCIG) confirmed this. GCIG recommended the use of 175 mg/m$^2$ paclitaxel, given intravenously (i.v.) over 3 h, followed by carboplatin as an i.v. infusion over 30–60 min at a dose adjusted to produce an area under the plasma concentration–time curve (AUC) of 5–6 mg·ml/min and to repeat this every 3 weeks for six cycles [1]. Moreover, GCIG considered intraperitoneal therapy in patients with small-volume residual disease and dose-dense weekly paclitaxel in combination with 3-weekly carboplatin acceptable treatment options.

## the concept of dose-dense therapy

'Dose-dense therapy' is a strategy to enhance antitumor activity and prolong the survival of patients. The theoretical basis for this dose-dense chemotherapy strategy is derived from the Gompertzian model, which is based on Norton–Simon's hypothesis [2, 3]. In the Gompertzian model, smaller tumors grow faster and so tumor regrowth between treatment cycles is more rapid when cell kill is greatest. Increased dose density is achieved by reducing the interval between each dose of chemotherapy. The cumulative drug dose remains constant, but the same amount of drug is administered over a shorter period. Mathematical models of tumor growth have provided the basis for the clinical application of dose-dense chemotherapy. The Norton–Simon model suggests that increasing the dose density of chemotherapy will increase efficacy by minimizing the opportunity for regrowth of tumor cells between cycles of chemotherapy. This concept has been applied in adjuvant therapy, in sequential administration of chemotherapy and in dose-dense administration of chemotherapy, in particular for breast cancer. The Cancer and Leukemia Group B C9344 study demonstrated that the sequential use of paclitaxel following doxorubicin and cyclophosphamide as adjuvant therapy for breast cancer improved survival [4]. Weekly paclitaxel as compared with every-3-weeks administration of paclitaxel improved survival in two phase III trials of breast cancer [5, 6]. A meta-analysis of dose-dense chemotherapy in non-metastatic breast cancer demonstrated a better overall and disease-free survival [7].

## dose-dense paclitaxel for ovarian cancer

The weekly administration of paclitaxel has been investigated from preclinical studies to clinical trials. The results from some *in vitro* studies indicate that increasing the number of short paclitaxel infusions results in a greater response rate than the normal 24-h administration period [8]. Preclinical studies have suggested that the duration of exposure is an important determinant of the cytotoxic activity of paclitaxel [9]. Adequate cytotoxicity can be achieved at relatively low concentrations of paclitaxel, provided that the exposure is prolonged [9, 10]. It

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has also been suggested that in addition to its microtubule-stabilizing action, paclitaxel may have other cytotoxic effects, such as inducing apoptosis and inhibiting angiogenesis, which are even observed at very low concentration levels of paclitaxel and even under weekly administration [11].

A phase I study conducted at the Memorial Sloan Kettering Cancer Center by Leiser et al. [12], included 16 relapsed ovarian cancer patients. Weekly paclitaxel escalating dose of 50–80 mg/m$^2$ and carboplatin AUC 4–6 every 3 weeks were administered. Febrile neutropenia and grade 4 thrombocytopenia according to the National Cancer Institute common toxicity criteria were the dose-limiting toxicities at dose levels 3 and 4 with no mucositis, nausea, vomiting or peripheral neuropathy observed greater than grade 2. They recommended weekly paclitaxel 80 mg/m$^2$ in combination with carboplatin AUC 5 every 3 weeks for further study. Kikuchi et al. [13] conducting a similar phase I trial, in Japanese patients with advanced non-small cell lung cancer, recommend a dose of weekly paclitaxel 100 mg/m$^2$ on days 1, 8, and 15 in combination with carboplatin AUC 6 every 4 weeks.

Several phase II clinical trials of dose-dense weekly paclitaxel and carboplatin administration have shown promising efficacy and favorable tolerability in women with ovarian cancer [14–16]. We reported a phase II study of 80 mg/m$^2$ paclitaxel and carboplatin AUC 2, which were administered every week in recurrent ovarian cancer patients [14]. The objective response rate was 67% (22/33). Grade 3–4 leukopenia was observed in 25% of patients and grade 3–4 neutropenia in 57% of patients. However, no patient was given granulocyte-colony stimulating factor. Febrile neutropenia was not observed. Grade 3 neurotoxicity was observed in 4% of patients. All patients were treated in the outpatient clinic. In another study, Sehouli et al. [16] reported weekly administration of 100 mg/m$^2$ paclitaxel and weekly carboplatin AUC 2, and showed substantial activity and tolerability of this regimen when treating patients in the primary disease setting. A treatment delay of only 2.8% was observed and the incidence of grade 3 neurotoxicity was even lower than that in our study. In addition, Pignata et al. reported that weekly carboplatin at a dose of AUC 2 and weekly paclitaxel at a dose of 60 mg/m$^2$ on days 1, 8 and 15, every 4 weeks, had a favorable toxicity profile in elderly ovarian cancer patients, when treated in first line [17].

## randomized phase III trial of dose-dense weekly paclitaxel in combination with carboplatin for advanced ovarian cancer

The Japanese Gynecologic Oncology Group (JGOG) conducted a randomized phase III trial of dose-dense weekly paclitaxel in combination with 3-weekly carboplatin for advanced ovarian cancer [JGOG 3016; New Ovarian Elaborate (NOVEL) trial] [18].

Patients with stage II–IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer were randomly assigned to receive six cycles of either paclitaxel plus carboplatin, given on day 1 of a 21-day cycle [conventional TC (c-TC)] or dose-dense paclitaxel, given on days 1, 8 and 15, plus carboplatin given on day 1 of a 21-day cycle [dose-dense TC (dd-TC)]. Both groups received carboplatin at a dose calculated to produce an AUC of 6 mg·ml/min on day 1 of each 21-day cycle. Carboplatin was given as an i.v. infusion over 1 h. The conventional therapy group received paclitaxel given as a 3 h i.v. infusion at a dose of 180 mg/m$^2$ body surface area on day 1. In the dose-dense therapy group, paclitaxel was given as a 1 h i.v. infusion at a dose of 80 mg/m$^2$ body surface area on days 1, 8 and 15. The dose of carboplatin was calculated with the Calvert formula [19], using the creatinine clearance instead of the glomerular filtration rate (GFR). The creatinine clearance was calculated with the Jelliffe formula [20]. The treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or a complete response received three additional cycles of chemotherapy. The primary endpoint was progression-free survival. Secondary endpoints were overall survival, response rate and adverse

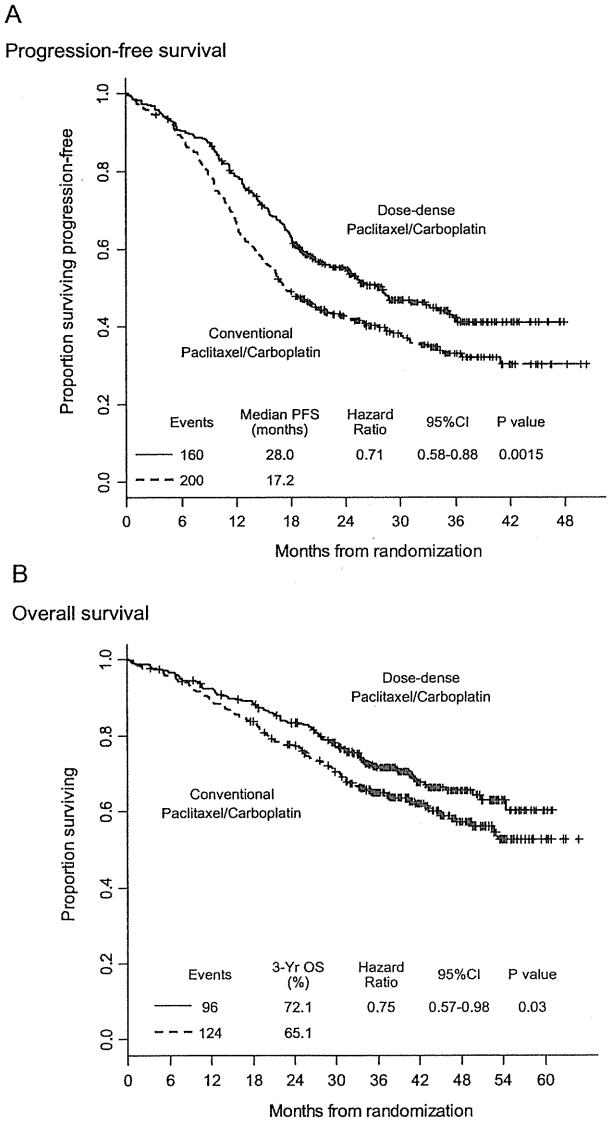


**Figure 1.** Progression-free and Overall Survival.

events. A total of 600 patients were required to detect a 5-month prolongation of progression-free survival with an 80% power, using a two-sided log-rank test, with an $\alpha$ level of 0.05, an accrual period of 3 years and a follow-up period of 1.5 years.

A total of 637 patients were randomized either to the dd-TC arm with 312 eligible patients or to the c-TC arm with 319 eligible patients. The overall response rate evaluated by classical World Health Organisation criteria was not significantly different in both arms (56% versus 53%; $P = 0.72$). Progression-free survival was substantially improved in the dd-TC arm (28 versus 17.2 months; hazard ratio: 0.71; 95% confidence interval: 0.58–0.88; $P = 0.0015$; Figure 1). The overall survival was immature because of lacking sufficient events at the time of presentation at the American Society of Clinical Oncology meeting in 2008 [18]; however, the 2-year overall survival was better in the dd-TC arm than in the c-TC arm of the study (83.6% versus 77.7%; $P = 0.049$) . Updated overall survival with a median follow-up of 42 months was significantly better in the dd-TC arm (72.1%) than in the c-TC arm (65.1%) ($P = 0.03$ by the log-rank test) (Figure 1) [21]. Early discontinuation of treatment occurred in 165 patients in the dose-dense regimen group and in 117 patients in the conventional regimen group. Withdrawal because of toxicity was higher in the dose-dense regimen group (113 versus 69), but reasons for dropout were otherwise balanced between the groups. Neutropenia was the most frequently observed adverse event [dose-dense regimen, 286 (92%) of 312 patients; conventional regimen, 276 (88%) of 314 patients]. Compared with the conventional treatment group, the dose-dense treatment group had a higher frequency of grade 3 and 4 anemia [214 (69%) versus 137 (44%); $P < 0.0001$]. Other toxic effects, including neuropathy, occurred with similar frequencies in both groups.

## carboplatin for Japanese patients

Hematologic toxicity was more frequently observed in the JGOG trial than in previous trials using the same chemotherapy doses in Western countries [22, 23]. There are well-known discrepancies in the observed toxicity of carboplatin-based chemotherapy between Japanese and Western patients [24], which can be explained in part by the different techniques used to assay creatinine. Two techniques are commonly used to measure serum creatinine levels: (i) the kinetic Jaffe method; and (ii) the enzymatic peroxidase–antiperoxidase (PAP) method. The creatinine clearance measured by the PAP method overestimates the GFR in subjects with normal renal function [25], and most clinical laboratories in Japan use the PAP method. Therefore, the carboplatin dose calculated with the Calvert formula using the PAP method would be overdosed in the JGOG trial and induce more myelotoxicity. Several methods to estimate GFR more accurately from serum creatinine have been proposed [26–29]; however, there is no global consensus on the best method for assessing renal function as the basis for determining the dosage of carboplatin. One should be cautious in interpreting carboplatin-induced toxicities and take into account the method used to determine serum creatinine concentrations when using creatinine clearance estimations with the Calvert formula.

## summary

In conclusion, dose-dense TC is an effective treatment with improved progression-free survival in patients with advanced ovarian cancer. Confirmatory studies are ongoing in Western countries. GOG 262 (trial registration: NCT01167712; Figure 2) is comparing carboplatin AUC 6 plus 175 mg/m$^2$ paclitaxel given every 3 weeks with carboplatin AUC 6 plus weekly 80 mg/m$^2$paclitaxel given every 3 weeks for suboptimal stage III or IV ovarian cancer. Additional bevacizumab is an option in the study. MITO 7 (trial registration: NCT00660842; Figure 3) is comparing carboplatin AUC 5 plus 175 mg/m$^2$ paclitaxel with weekly carboplatin AUC 2 plus weekly 60 mg/m$^2$ paclitaxel. ICON 8 is preparing to start a three-armed randomized trial comparing carboplatin AUC 5 plus 175 mg/m$^2$ paclitaxel with carboplatin AUC 5 plus weekly 80 mg/m$^2$ paclitaxel and with weekly carboplatin AUC 1.67 plus weekly 80 mg/m$^2$ paclitaxel for stage IC to IV ovarian cancer. It is reasonable to conclude that if these studies confirm the Japanese phase III trial data, then weekly paclitaxel administration is an appropriate strategy to consider in the standard treatment of advanced ovarian cancer.

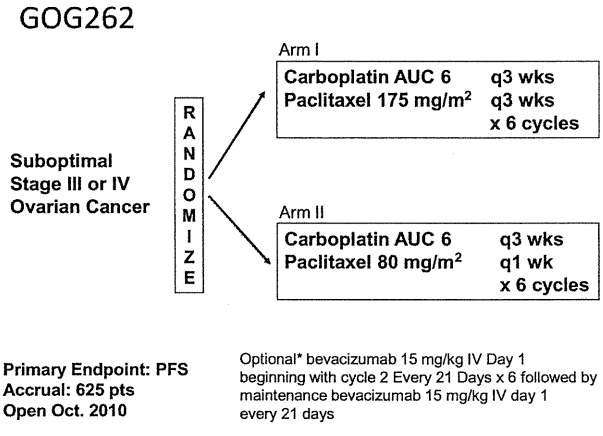


Figure 2. The GOG 262 study.

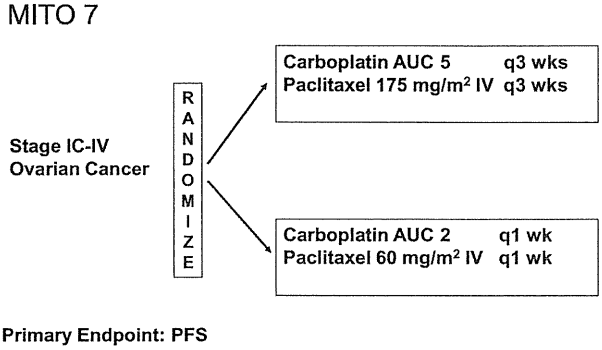


Figure 3. The MITO 7 study.

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**Clinical Trial Note**

# Phase II Study of Oral Etoposide and Intravenous Irinotecan for Patients with Platinum-resistant and Taxane-pretreated Ovarian Cancer: Japan Clinical Oncology Group Study 0503

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A single-arm Phase II study evaluating combination chemotherapy utilizing oral etoposide and irinotecan for platinum-resistant and taxane-pretreated ovarian cancer has started. The aim of this study is to evaluate the efficacy and safety of this regimen as a test arm regimen in a subsequent Phase III trial. Patients with platinum-resistant and taxane-pretreated ovarian cancer are given etoposide at 50 mg/m$^2$ p.o. from days 1 to 21 and irinotecan 70 mg/m$^2$ i.v. at days 1 and 15, repeated every 28 days, up to six cycles. A total of 60 patients will be enrolled at 36 institutions. The primary endpoint is response rate. The secondary endpoints include adverse events and progression-free and overall survival.

*Key words: Chemo-Gynecology – Gynecol-Med – clinical trials*

## INTRODUCTION

Ovarian cancer is one of the most lethal gynecologic cancers in Japan. The first-line standard chemotherapy regimen is carboplatin plus paclitaxel (1,2). Although first-line chemotherapy is very effective, more than 60% of the patients with an advanced stage will die of recurrent disease. After relapse, the choice of second line chemotherapy depends on 'platinum-free interval (PFI)', which is prognostic and predictive for the effect of repeating platinum agents. Usually, the cut-off point of PFI is regarded as 6 months. Patients recurred within 6 months after first-line chemotherapy are regarded as 'platinum-resistant' and receive second-line chemotherapy with single agent such as pegylated liposomal doxorubicin (3), topotecan (3) and gemcitabine (4) as the standard treatment. Many single cytotoxic agents have shown activity against recurrent ovarian cancer; however, response rates generally have been low, such as 6–12% (3,4), and of short duration because of emerging resistance to the monotherapy regimens. Combination chemotherapy may circumvent this resistance and halt progression of disease, because lower dose of two drugs with different mechanism may reduce the toxicity and enhance the efficacy (5).

Irinotecan, a semi-synthetic derivative of camptothecin, is a prodrug with little inherent topoisomerase inhibitory activity and is converted by carboxylesterases to its more active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin). *In vitro*, SN-38 is 250–1000 times more potent than irinotecan as an inhibitor of topoisomerase. For platinum-resistant patients, irinotecan has shown modest activity (6–8) as monotherapy in weekly, every 2-week and every 3-week schedules.

Etoposide is a semi-synthetic glycosidic derivative of podophyllotoxin (9). Intravenous dosing of etoposide has been tested in two Phase II studies and shown relatively low response rates (10,11) (0 and 8.3%). On the contrary, oral etoposide has shown better efficacy, whose response rate was 26.8% for patients with platinum-resistant relapse (12).