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Effectiveness of third-line chemotherapy in recurrent ovarian cancer patients

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Summary

Objective: Despite recent advances in the treatment of recurrent ovarian cancer, little evidence exists describing the benefit of third-line chemotherapy. The present authors previously reported that the treatment-free interval (TFI) after second-line chemotherapy may predict a survival benefit of third-line chemotherapy, however the length of TFI was uncertain due to limited cases. In this study, the authors evaluated the length of TFI, which is correlated with the effectiveness of third-line chemotherapy and a prognostic factor of third-line chemotherapy. *Materials and Methods:* The authors reviewed the medical records of 85 women with recurrent ovarian cancer who received third-line chemotherapy after a paclitaxel/carboplatin (PC) regimen as first-line chemotherapy. *Results:* The response rate [complete response (CR) + partial response (PR)] and clinical benefit rate [(CBR): CR + PR + stable disease (SD)] during the TFI after second-line chemotherapy for 0–3 months, 3–6 months, and 6–12 months and ≥ 12 months were 9.8%, 0%, 0%, 43.8% and 15.7%, 50%, 66.7%, and 93.8%, respectively. The median overall survival (OS) from the onset of third-line chemotherapy was longer for TFI ≥3 months than for TFI 0–3 months (795 days *vs.* 281 days, $p < 0.001$). Finally, according to univariate (HR = 0.256; $p < 0.001$) and multivariate (HR = 0.264; $p < 0.001$) analyses, TFI was the independent significant prognostic factor for OS. *Conclusions:* TFI less than three months after second-line chemotherapy may predict little survival benefit of third-line chemotherapy.

Key words: Epithelial ovarian cancer; Recurrent ovarian cancer; Third-line chemotherapy.

Introduction

At present, there are no effective screening methods for epithelial ovarian cancer, ultimately resulting in the vast majority of patients being identified during advanced stages. International Federation of Obstetricians and Gynecologists (FIGO) Stage III or IV patients usually relapse in more than 70% patients, indicating difficulties in achieving complete cure. Ovarian cancer is the ninth most common disease in women and the fifth leading cause of cancer death [1]. Thus, the goal of primary treatment is to cure, and on recurrence, life extension or palliation of cancer-related symptoms is the objective for better quality of life (QoL). There is concern regarding whether treatment of relapsed patients is beneficial or whether multiple chemotherapies threaten QoL. The present authors previously reported that the treatment-free interval (TFI) after second-line chemotherapy may predict a survival benefit of third-line chemotherapy [2]; however, the length of TFI was uncertain because of limited patients. In this study, the authors performed retrospective analysis of 85 patients of recurrent ovarian cancer who received paclitaxel/carboplatin (PC) as first-line therapy, particularly evaluating the patients who benefited from third-line chemotherapy.

Materials and Methods

Patients

The authors retrospectively reviewed the medical records of women with recurrent ovarian cancer who received third-line chemotherapy. Eighty-five patients who started to receive third-line chemotherapy between July 1997 and December 2009 were included. Among then, 40 patients were also included in the present authors' previous study [2]. All patients underwent initial debulking surgery. They received primary chemotherapy consisting of PC regimen and second-line chemotherapy after the first relapse. The patients who underwent surgery at relapse were excluded. All patients were followed up at the Department of Obstetrics and Gynecology, Keio University Hospital. Treatment decisions regarding third-line chemotherapy were usually made by the attending clinician. Data were collected on age, FIGO staging, histologic type, extent and outcome of surgery, prior chemotherapeutic treatments and disease responses, intervals between primary, secondary, and tertiary treatments, and overall survival (OS) after receiving the third-line drug.

Definition of sensitivity of primary chemotherapy

"Refractory," "resistant," and "sensitive" in first recurrence were defined as follows: refractory, progression, partial remission, or stable disease at the time of primary chemotherapy, resistant, complete remission, and relapse less than six months after primary chemotherapy, and sensitive, complete remission, and relapse six months or more after discontinuing primary chemotherapy. TFI before third-line chemotherapy was defined as the interval between the last day of second-line chemotherapy and the first day of third-line chemotherapy.

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Table 1. — *Patient characteristics of third-line chemotherapy (n = 85).*

Age (years) median	56 (32-76)
FIGO Stage	
I	6
II	3
III	52
IV	24
Histological subtype	
Serous	47
Clear	17
Endometrioid	11
Mucinous	3
Mixed/undifferentiated/others	7
Debulking status	
Complete	24
Incomplete/optimal	61
Platinum sensitivity of first relapse	
Sensitive	40
Refractory/resistant	45
TFI of 2nd to 3rd chemotherapy	
0 - 3m	51
3 - 6m	6
6 m - 12 m	12
≥ 12 m	16
Chemotherapy regimen of third-line setting	
Single agent	45
Taxane	21
PLD	9
Irinotecan/topotecan	7
Other	8
Combination	40
Platinum/taxane	30
Cisplatin+doxorubicin+cyclophosphamide	4
Cisplatin+irinotecan	3
Other	3

Evaluating response of third-line chemotherapy

Response was based on two-dimensional measurements of the lesions based on computed tomographic images. A complete response (CR) was defined as no evidence of disease on imaging studies, with normalization of the serum CA125 level. Partial response (PR) was defined as >50% decrease in tumor size. Progressive disease (PD) was defined as >25% increase in tumor size or the appearance of a new lesion. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The CA125 response criteria were not used. OS was defined as the interval from the first day of administration of the third-line drug to the day of death or the last day of observation.

Statistical analysis

Patients were categorized by age (< median *vs.* ≥ median), debulking status (complete *vs.* incomplete), platinum sensitivity (sensitive *vs.* refractory/resistant), histology (serous *vs.* non-serous), FIGO staging (Stage I, II *vs.* Stage III, IV), and TFI (0–3 months *vs.* ≥ three months). Factors influencing OS were analyzed by Cox's proportional hazard test and the log-rank test. After investigation of multicollinearity of these factors, multivariate Cox's proportional hazard test was applied. *P*-value <0.05 was considered statistically significant. Statistical calculations were performed using SPSS Statistics software, version 20 for Windows.

Table 2. — *RR, CBR, and OS of third-line chemotherapy classified by TFI*

TFI (months)	RR (%)	CBR (%)	Median OS (days)
0-3	9.8	15.7	281 (182.1-379.9)
3-6	0	50	612 (0.0-1,415.6)
6-12	0	66.7	788 (442.0-1,134.0)
≥12	43.8	93.8	1110 (640.6-1,579.4)

RR: response rate (CR+PR), CBR: clinical benefit rate (CR+PR+SD).

Results

Patients

Median age at the onset of third-line chemotherapy was 56 years (range: 32–76). Clinical stage and histology were as follows: clinical Stage (I: 6; II: 3: III: 52; IV: 24); histology (serous: 47; clear cell: 17; endometrioid: 11; mucinous: three; undifferentiated: three; others: four). In the first recurrence, 40 patients were platinum-sensitive and 45 were platinum-resistant. Thirty-two patients received a platinum/taxane regimen, 18 received cisplatin + irinotecan, six received cisplatin + doxorubicin + cyclophosphamide, three received other combination therapies, 15 received irinotecan, five received taxan monotherapy, five received pegylated liposomal doxorubicin (PLD), and one received carboplatin as second-line chemotherapy.

The clinical background of the third-line settings are shown in Table 1. TFI from the last day of second-line chemotherapy to the first day of third-line chemotherapy was 0–3 months in 51 patients, 3–6 months in six patients, 6–12 months in 12 patients, and 12 months in 16 patients. Forty-five patients received single-agent chemotherapy (taxane: 21; irinotecan/topotecan: seven; liposomal doxorubicin: nine; other: eight) and 40 received combination chemotherapy (platinum/taxane: 30; cisplatin + irinotecan: three; cisplatin + doxorubicin + cyclophosphamide: four; other: three) as third-line chemotherapy.

Relationships between TFI and RR or CBR of third-line chemotherapy

To evaluate the length of TFI, which can predict the benefit of third-line chemotherapy, the authors initially investigated RR and CBR of TFI 0–3 months, 3–6 months, 6–12 months, and ≥ 12 months, respectively (Table 2). RR was 0–3 months in 9.8%, 3–6 months in 0.0%, 6–12 months in 0.0%, and ≥ 12 months in 43.8% patients. CBR was 0–3 months in 15.7%, 3–6 months in 50.0%, 6–12 months in 66.7%, and ≥ 12 months in 93.8% patients.

Table 3. — *Univariate and multivariate analyses of the effect of various prognostic factors on OS.*

	Univariate analysis		Multivariate analysis	
	Hazard Ratio	*p*-value	Hazard Ratio	*p*-value
Age (< median *vs.* ≥ medin)	1.046 (0.609-1.795)	0.871	1.535 (0.838-2.812)	0.165
Debulking status (complete *vs.* incomplete)	1.096 (0.609-1.971)	0.761	1.719 (0.801-3.690)	0.164
Platinum sensitivity (sensitive *vs.* refractory/resistant)	2.847 (1.604-5.052)	<0.001	1.892 (0.977-3.666)	0.059
Histology (serous *vs.* non-serous)	1.147 (0.666-1.976)	0.620	1.270 (0.641-2.518)	0.494
FIGO staging (Stage I, II *vs.* Stage III, IV)	0.579 (0.260-1.288)	0.180	0.358 (0.127-1.008)	0.052
TFI (0-3 months *vs.* ≥ three months)	0.256 (0.139-0.470)	<0.001	0.264 (0.133-0.527)	<0.001

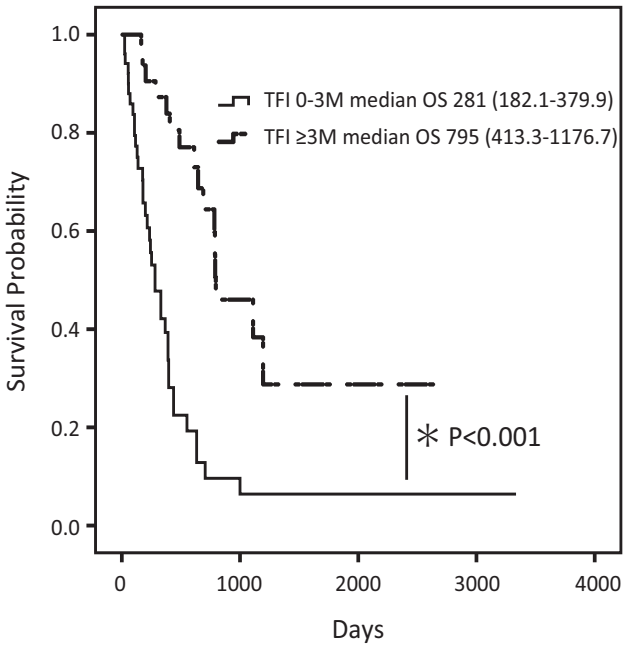

Figure 1. — Relationship between TFI from second-line chemotherapy and OS. The median OS of TFI 0–3 months is significantly shorter than that of TFI ≥ three months ($p < 0.001$).

TFI less or more than three months can predict survival after third-line chemotherapy

Next, the authors evaluated the relevance of survival and each TFI. The median OS for all patients was 330 days (range, 24–3,335). Fifty-three patients died, 20 were alive with disease, and 12 were alive with no evidence of disease on the last day of August 2011. The median OS was 281 days in TFI 0–3 months, 612 days in TFI 3–6 months, 788 days in TFI 6–12 months, and 1110 days in TFI ≥ 12 months (Table 2). Based on these findings and the fact that CBR rather than RR associates with the effect of third-line chemotherapy, the authors divided all patients into two groups (TFI: 0–3 months, ≥ 3 months) and compared OS between the two groups (Figure 1). The median OS in the TFI 0–3 months group was significantly shorter than that in the TFI ≥ three months group (281 days *vs.* 795 days, $p < 0.001$).

TFI three months is the independent prognostic factor of third-line chemotherapy benefit

The authors next analyzed the prognostic significance of multiple factors such as age, debulking status, platinum sensitivity, histology, FIGO staging, and TFI. Among then, TFI is the single independent factor for determining the benefit of third-line chemotherapy by univariate (HR = 0.256, $p < 0.001$) and multivariate analysis (HR = 0.264, $p < 0.001$), although platinum sensitivity of the first relapse may also serve as a prognostic factor with a greater number of patients (univariate $p < 0.001$, multivariate $p = 0.059$) (Table 3).

Discussion

For almost two decades, the paclitaxel/platinum regimen has been the standard chemotherapy for ovarian cancer [3]. Despite improvement in the prognosis of ovarian cancer, it is still difficult to achieve complete remission, and effective therapy is needed. There are several reports describing the benefits of second-line chemotherapy; however, the clinical evidences regarding advantages of third-line chemotherapy are few.

In epithelial ovarian cancer, "platinum sensitivity" is the well-recognized clinical factor [4]. On second-line setting of platinum-sensitive relapse, platinum-based combination chemotherapy is recommended. In addition to the traditional PC treatment, carboplatin in combination with PLD [5] or gemcitabine [6] is a favorable regimen. On the other hand, regarding platinum-resistant relapse, single usage of PLD, topotecan, paclitaxel, or gemcitabine have shown similar activity, and six randomized trials failed to show superiority in outcomes for combination *vs.* single agent [7].

In the third-line setting, the concept of a platinum-free interval is not clear. However, in clinical situations, the decision to give third- or fourth-line chemotherapy to patients is often contemplated. In this study, platinum sensitivity of the first relapse was shown to help predict the efficacy of third-line chemotherapy, but this result was not significant. Furthermore, debulking status of operation, histology, or FIGO staging did not predict the efficacy of third-line chemotherapy. These data indicate that in cancers that are beyond second relapse, tumor characteristics

are more aggressive and can withstand chemotherapeutic damage. Hanker *et al.* reported optimal tumor debulking and platinum sensitivity of first-line chemotherapy as independent prognostic factors for PFS up to the third relapse, and maximum of three lines of subsequent relapse treatment seem to be beneficial [8]. Griffiths *et al.* reported that treatment efficacy declined rapidly with successive lines of therapy after platinum resistance and suggested that disease progression on two consecutive lines of therapy should be used as a guide to discontinue chemotherapy [9]. Hoskins *et al.* reported that an interval between two consecutive relapses measuring less than six months was a proposed marker for discontinuing further chemotherapy [10]. The present data indicates that populations with TFI < three months show little response to third-line therapy, which is mostly consistent with prior reports.

The present authors previously reported that TFI from second-line chemotherapy is the predictive marker of third-line chemotherapy; however, they were unable to determine the specific time window among the TFI three to six month group because of limited patients [2]. In this present study, the authors evaluated more patients with recurrent ovarian cancer who received the CP regimen in the first-line setting. According to RR and CBR of each TFI, CBR is thought to be the better indicator of third-line chemotherapy compared with RR, with RR of TFI <12 months being very low and difficult to evaluate. Overall, the authors determined TFI of three months to be a prognostic indicator of third-line chemotherapy. In the clinical situation, third-line chemotherapy for TFI < three months may have little-to-no clinical benefit or may actually threaten QoL.

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