

Second-line chemotherapy for advanced or recurrent endometrial carcinoma previously treated with paclitaxel and carboplatin, with or without epirubicin

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Abstract

Purpose A combined chemotherapy of taxane and platinum, with or without anthracycline, has been used as a standard first-line regimen. The purpose of this study was to investigate the effectiveness of second-line chemotherapy for treatment of advanced or recurrent endometrial carcinoma previously treated with a combined chemotherapy of taxane and platinum, with or without anthracycline.

Methods During the 2000–2008 study period, 723 patients were diagnosed with endometrial cancer at the Departments of Obstetrics and Gynecology of the Osaka University and the Osaka Rosai Hospitals, Osaka, Japan. The subset of these cases that eventually required treatment by second-line chemotherapy was retrospectively analyzed.

Results Response rate to second-line chemotherapy was 25%. Treatment-free interval (TFI) of \geq or $<$ 6 months was demonstrated to be significantly associated with the response to second-line chemotherapy ($P = 0.0026$),

progression-free survival ($P = 0.0003$) and overall survival ($P = 0.025$). The second-line chemotherapy similar to the first-line regimen was ineffective in all the 7 cases (100%) whose TFI was shorter than 6 months. Multivariate analysis showed that TFI was the most significantly important factor predicting the effectiveness of second-line chemotherapy (the adjusted hazard ratio of TFI on PFS and OS: 3.482, 95% CI, 1.641–7.388, $P = 0.0012$, and 2.341, 95% CI, 1.034–5.301, $P = 0.042$, respectively).

Conclusions Our present study provides, for the first time, evidence that the majority of refractory or recurrent diseases, if they occur within 6 months of a first-line chemotherapy using taxane and platinum with or without anthracycline, are non-responsive to the current regimens of second-line chemotherapy.

Keywords Endometrial cancer · Second-line chemotherapy · Response · Treatment-free interval · Progression-free survival · Overall survival

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Abbreviations

CR	Complete response
HR	Hazard ratio
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RR	Response rate
SD	Stable disease
TFI	Treatment-free interval
CAP	Cisplatin, Adriamycin and cycloPhosphamide
MPA	MedroxyProgesterone Acetate

TAP or AP	Anthracycline (doxorubicin) plus Platinum (cisplatin) (with, or without, the Taxane, paclitaxel)
TEC or TC	Taxane paclitaxel and Carboplatin (with, or without, the anthracycline, Epirubicin)
TEP	Taxane (paclitaxel), Epirubicin and the Platinum, cisplatin
TCw, TCm, TECm	TC or TEC administered on a weekly or monthly regimen

Introduction

The incidence of endometrial carcinoma, already the most common malignancy of the female pelvis and the fourth most common cancer among women in the United States, has been increasing steadily during the last three decades [1]. In approximately 75% of patients, the tumor is still confined to the uterus at diagnosis (FIGO stage I), and thus, there is a good prognosis [2]. However, the prognosis for advanced endometrial carcinomas, with extra-pelvic metastatic dissemination, is extremely poor, and the 5-year survival rate is a mere 5–32% [1]. Irradiation was usually performed as post-operative adjuvant therapy for early cases considered being at risk of recurrence and for most advanced cases [3]. Recently, systemic adjuvant chemotherapy, compared to adjuvant irradiation, was reported to significantly improve the prognosis of these cases [4, 5].

About one-fourth of those patients, treated for what was thought to be an early-stage endometrial cancer, go onto develop a recurrence. Unfortunately, 3–19 years after treatment for the recurrence, only 7.7% of the patients were alive and without evidence of disease [3]. Recurrences, restricted to the vaginal vault, are relatively better treated with radiotherapy. However, in most cases of relapse, the disease had spread to other sites, including pelvic and para-aortic lymph nodes, the peritoneum of the pelvis and abdominal cavity, and the lungs. For these cases, systemic chemotherapy is usually required.

Cisplatin and doxorubicin were shown to be the most effective drugs for both advanced and recurrent endometrial carcinomas; paclitaxel was also reported to be useful [6, 7]. A Gynecologic Oncology Group's (GOG) study showed that a tripartite regimen of the Taxane paclitaxel, plus the Anthracycline doxorubicin and the Platinum drug cisplatin (TAP), provided a better response, as measured by progression-free and overall survival rates, than without the taxane (AP). However, there were significant adverse side effects in the TAP group [8]. A modified TAP regimen, with the Taxane paclitaxel and Epirubicin (a semi-synthetic

stereoisomer of doxorubicin) plus the Platinum drug cisplatin (TEP), was a more effective combination chemotherapy, with a 73% response rate for advanced endometrial carcinomas, suggesting a possible future role of TEP therapy as the first-line treatment for advanced endometrial carcinomas [9]. A combination chemotherapy of the Taxane paclitaxel and Carboplatin (TC), which is a standard regimen for ovarian carcinoma, was also shown to be a well-tolerated, active adjuvant therapy regimen for advanced endometrial carcinomas [10]. More recently, a combination chemotherapy of the Taxane paclitaxel, Epirubicin and Carboplatin (TEC) was demonstrated to be active and tolerable in patients with advanced metastatic and recurrent endometrial carcinomas [11].

Based on these findings, a combined chemotherapy of taxane and platinum, with or without anthracycline, has been used as a standard first-line regimen for both unresected and recurrent endometrial carcinomas and also as an adjuvant therapy for resected cases with a high risk of recurrence. However, a second-line regimen for the treatment of advanced or recurrent endometrial carcinoma previously treated with a combined chemotherapy of taxane and platinum, with or without anthracycline, has yet to be established. We hoped our findings would change that. In our current study, the effectiveness of second-line chemotherapy and the various clinical factors that associate with the prognosis of advanced or recurrent endometrial carcinoma previously treated with a combination chemotherapy of taxane and platinum, with or without anthracycline, were retrospectively investigated.

Materials and methods

Materials

Patients' characteristics

During the 9-year study period of 2000–2008, we diagnosed 723 endometrial carcinomas in Japanese women at the Departments of Obstetrics and Gynecology of the Osaka University and the Osaka Rosai Hospitals, Osaka, Japan. Traditionally, our department has used either a monthly delivered combination of Taxane (paclitaxel) and Carboplatin (with, or without, the anthracycline Epirubicin, TEC or TC, respectively) or a weekly administered TC regimen as the first-line adjuvant therapy for resected endometrial carcinomas and also as the first-line salvage therapy for unresected and recurrent diseases. Patients were enrolled in the present study, after obtaining their written informed consent, if they were treated by a second-line chemotherapy for their recurrent disease, after first having an initial first-line adjuvant or salvage TEC or TC therapy.

In the initial first-line monthly TEC (TECm) treatment, paclitaxel (150 mg/m^2), carboplatin ($\text{AUC} = 4$) and epirubicin (50 mg/m^2) were administered intravenously every 3–4 weeks. The dose of chemotherapy drugs appropriate for our Japanese population was determined in phase I/II studies we had previously conducted (to be described in detail elsewhere). In the monthly TC (TCm) therapy, paclitaxel (175 mg/m^2) and carboplatin ($\text{AUC} = 5$) were also administered intravenously every 3–4 weeks, based on previous reports [12, 13]. In the weekly TC regimen (TCw), paclitaxel (80 mg/m^2) and carboplatin ($\text{AUC} = 2$) were administered intravenously on days 1, 8 and 15 on a 4-week cycle [14, 15].

The clinicopathological features of these cases, including the age of the patient, the histology and initial stage of the disease and the regimen of the first and second-line chemotherapies, were retrospectively reviewed utilizing their clinical records, including physical examination notes, radiological reports, operative records and histopathology reports. The histological diagnoses were made by authorized pathologists from the Department of Pathology of the Osaka University and the Osaka Rosai Hospitals.

Methods

In order to evaluate the therapeutic effect of second-line chemotherapy, previously described standard criteria from the World Health Organization [16] and others (Pectasides et al. [17–19]) were used. The tumors were assessed with a CT scan and/or MRI at baseline and every three treatment courses thereafter. A complete response (CR) was defined as the disappearance of all known disease, 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.

Progression-free survival (PFS) was measured from the date of the last administration of chemotherapy to the date of the radiological or pathological relapse or to the date of the last follow-up. Overall survival (OS) was defined as the period from the start of chemotherapy to the patient's disease-specific death or to the date of the last follow-up, as previously described [10]. Treatment-free interval (TFI) was defined as the period between the last administration of first-line chemotherapy and the initiation of the second-line chemotherapy, as previously described [20].

Second-line chemotherapy

Some patients received TECm or TCw (as described above) as second-line chemotherapy. Others were given docetaxel (30 mg/m^2) and CPT-11 (60 mg/m^2) (docetaxel + CPT) on days 1 and 8, on a 3–4-week cycles, or daily oral medroxyprogesterone acetate (MPA) ($400\text{--}600 \text{ mg/day}$). The dose and schedule of administration of docetaxel + CPT appropriate for our Japanese population was also determined in our previous phase I/II study (to be described in detail elsewhere).

Statistical analysis of effect of second-line chemotherapy

The association between sensitivity to second-line chemotherapy and sensitivity to a TFI was analyzed by Fisher's exact test. PFS curves determined by a TFI were constructed using the Kaplan–Meier method and were evaluated for statistical significance by the log-rank test. The multivariate Cox proportional hazards model was used to calculate the significant factors contributing to PFS after second-line chemotherapy. Results were considered to be significant when the P value was <0.05 .

Results

Clinical characteristics of the study cases

During the 9-year study period, 40 patients required a second-line chemotherapy treatment against a recalcitrant or recurrent disease, after having first received an adjuvant or salvage first-line chemotherapy using TECm, TCm or TCw. The clinicopathological characteristics of these 40 patients are shown in Table 1. Eighty percent (32 out of 40 cases) of the patients received first-line TECm therapy; the other eight cases underwent either monthly or weekly TC (TCm or TCw) therapy, prior to the second-line chemotherapy. No cases were canceled due to second-line chemotherapy toxicity.

Outcome of the patients after second-line chemotherapy

Among the 40 patients, 24 patients received second-line TECm, TCm or TCw, 3 received docetaxel + CPT, 7 received oral MPA therapy, and 6 received oral Etoposide therapy (Table 2). The overall response rate for second-line chemotherapy was 25% (0–38%). The PFS was 3.5 months (0–20 months), and the OS was 10 months (2–44 months). The response rate, PFS, and OS were not significantly different among the TECm/TCm/TCw, docetaxel + CPT, MPA and Etoposide groups.

Table 1 Clinical characteristics of the study cases

Characteristics	Patients (<i>n</i> = 40)	
	Number	%
Age (years)		
<60	18	45
≥60	22	55
Histology		
Endometrioid	32	80
Serous	4	10
Clear cell	1	3
Others	3	8
Initial stage		
I	10	25
II	6	15
III	19	48
IV	5	13
First-line chemotherapy		
TEC	32	80
TC	7	18
Weekly TC	1	3

All patients received first-line chemotherapy using taxane and carboplatin (with or without epirubicin, TC/TEC)

TECm monthly administration of taxane (paclitaxel), epirubicin and carboplatin, *TCm* monthly administration of paclitaxel and carboplatin, *TCw* weekly administration of paclitaxel and carboplatin

Table 2 Outcome of the patients after second-line chemotherapy

	Cases	Response rate (%)	PFS (months)	OS (months)
TEC/weekly TC	24	38	5.5 (2–20)	13 (3–44)
Docetaxel + CPT-11	3	33	4 (0–5)	6 (4–10)
MPA (oral)	7	0	1 (0–3)	5 (2–22)
Etoposide (oral)	6	0	2 (1–8)	9 (4–11)
Total	40	25	3.5 (0–15)	10 (2–44)

No significant difference was demonstrated among the four groups (TECm/TCm/TCw, docetaxel + CPT, MPA and Etoposide)

TECm monthly administration of paclitaxel, epirubicin and carboplatin, *TCw* weekly administration of paclitaxel and carboplatin, *TCm* monthly administration of paclitaxel and carboplatin, *MPA* oral daily medroxyprogesterone acetate, *Etoposide* oral daily Etoposide, *PFS* progression-free survival, *OS* overall survival

Association between TFI and sensitivity to second-line chemotherapy

The effect of a TFI, after first-line chemotherapy using TC/TEC, on the tumor's sensitivity to second-line chemotherapy was evaluated. Among the 24 patients whose TFI was equal to or longer than 6 months, CR or PR was achieved in 10 patients (42%). However, all 16 cases (100%) whose TFI was shorter than 6 months exhibited

either SD or PD against the second-line chemotherapy. This association between TFI and sensitivity to a second-line chemotherapy was statistically significant ($P = 0.0026$ by Fisher's exact test). These results are tabulated in Table 3.

Association between TFI and sensitivity to second-line chemotherapy using taxane and platinum, with or without anthracycline, was, next, analyzed. Among the 17 patients whose TFI was equal to or longer than 6 months, CR or PR was achieved in 9 patients (53%). However, all 7 cases (100%) whose TFI was shorter than 6 months exhibited either SD or PD against the second-line chemotherapy. This association between TFI and sensitivity to a second-line chemotherapy was statistically significant ($P = 0.015$ by Fisher's exact test). These results are tabulated in Table 4.

PFS and OS after second-line chemotherapy by TFI

The differences by TFI in the effectiveness of second-line chemotherapy regimens were investigated. The median PFS was 7 months (1–20 months) for the 26 patients whose TFI was equal to or longer than 6 months, which

Table 3 Association between TFI and effectiveness of second-line chemotherapy

	CR/PR	SD/PD
TFI ≥ 6 months	10 (42%) ^a	14 (58%)
TFI < 6 months	0 (0%)	16 (100%) ^a

Forty-two percent (10 out of 24 cases) of the patients whose TFI was equal to or longer than 6 months exhibited sensitivity to second-line chemotherapy; however, all cases whose TFI was shorter than 6 months were resistant to second-line chemotherapy. This association was statistically significant ($P = 0.0026$ by Fisher's exact test)

TFI treatment-free interval, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

^a $P = 0.0026$

Table 4 Association between TFI and sensitivity to second-line chemotherapy using taxane and platinum, with or without anthracycline

	CR/PR	SD/PD
TFI ≥ 6 months	9 (53%) ^a	8 (47%)
TFI < 6 months	0 (0%)	7 (100%) ^a

Fifty-three percent (9 out of 17 cases) of the patients whose TFI was equal to or longer than 6 months exhibited sensitivity to second-line chemotherapy; however, all cases whose TFI was shorter than 6 months were resistant to second-line chemotherapy. This association was statistically significant ($P = 0.015$ by Fisher's exact test)

TFI treatment-free interval, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

^a $P = 0.015$

was significantly longer than the 2 months (0–9 months) for the 14 whose TFI was shorter than 6 months ($P = 0.0003$ by log-rank test) (Fig. 1). The median OS was 13 months (3–22 months) for the 26 patients whose TFI was equal to or longer than 6 months, which was significantly longer than the 5.5 months (2–44 months) for the 14 whose TFI was shorter than 6 months ($P = 0.025$ by log-rank test) (Fig. 1).

Multivariate Cox proportional hazards analysis for effectiveness of second-line chemotherapy on PFS and OS

In order to further support our finding that a TFI was significantly associated with the effectiveness of second-line chemotherapy, the multivariate Cox proportional hazards model was utilized. The results are listed in Table 4. The adjusted hazard ratio (HR) of TFI (≥ 6 months versus < 6 months) on PFS was 3.482 (95% CI, 1.641–7.388) and that of TFI on OS was 2.341 (95% CI, 1.034–5.301). TFI was demonstrated to be a significant factor in predicting for PFS and OS ($P = 0.0012$ and $P = 0.042$, respectively, based on the multivariate Cox proportional hazards model) (Tables 5 and 6).

Conclusions

Endometrial adenocarcinoma is increasingly the most common malignancy of the female pelvis in the United States [1]. Although early-stage endometrial carcinomas have a good prognosis [2], the prognoses for advanced or recurrent cases are extremely poor (except for recurrences limited to the vaginal vault, which can generally be treated successfully with surgery and radiation therapy) [3].

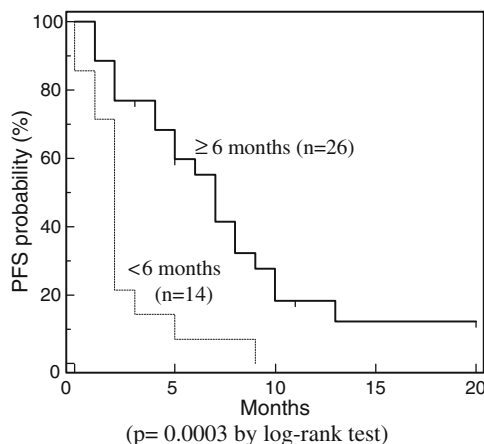


Fig. 1 PFS and OS after second-line chemotherapy by TFI. Progression-free probability and overall probability after second-line chemotherapy of the patients whose TFI was equal to or longer than

Table 5 Multivariate Cox proportional hazards analysis for effectiveness of second-line chemotherapy on PFS

Variable	Adjusted HR	95% CI	<i>P</i> value
Age (years)			0.14
<60	1		
≥ 60	0.573	0.274–1.197	
Histology			0.53
Endometrioid	1		
Non-endometrioid	1.331	0.546–3.247	
Initial stage			0.82
I/II	1		
III/IV	1.092	0.517–2.308	
TFI			0.0012
≥ 6 months	1		
< 6 months	3.482	1.641–7.388	

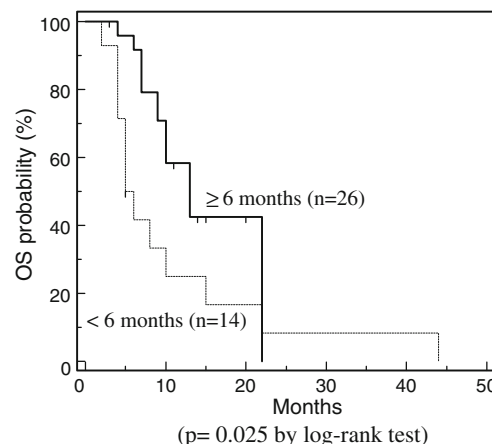
The adjusted HR of TFI < 6 months was 3.482 (95% CI, 1.641–7.388), compared to TFI ≥ 6 months, showing statistical significance ($P = 0.0012$)

HR hazard ratio, TFI treatment-free interval

Although a truly successful treatment for advanced or recurrent endometrial carcinomas has yet to be established, taxane and platinum (with or without anthracycline, TC/TEC) have demonstrated at least a partial efficacy [6–11].

Recently, based on these findings, the combined chemotherapy of TC/TEC has been used as a standard first-line regimen for unresected and recurrent endometrial carcinomas as well as an adjuvant therapy for resected cases with a high risk of recurrence. However, an effective second-line regimen for advanced or recurrent endometrial carcinomas previously treated with TC/TEC has not yet been established.

In our present study, we analyzed the outcomes of patients who, after having received a first-line TC or TEC



6 months were significantly longer than those whose TFI was shorter than 6 months ($P = 0.0003$ and $P = 0.025$, respectively, by the log-rank test)

Table 6 Multivariate Cox proportional hazards analysis for effectiveness of second-line chemotherapy on OS

Variable	Adjusted HR	95% CI	<i>P</i> value
Age (years)			0.081
<60	1		
≥60	0.497	0.228–1.085	
Histology			0.40
Endometrioid	1		
Non-endometrioid	1.497	0.590–3.800	
Initial stage			0.30
I/II	1		
III/IV	1.613	0.658–3.953	
TFI			0.042
≥6 months	1		
<6 months	2.341	1.034–5.301	

The adjusted HR of TFI < 6 months was 2.341 (95% CI, 1.034–5.301), compared to TFI ≥ 6 months, showing statistical significance (*P* = 0.042)

HR hazard ratio, TFI treatment-free interval

chemotherapy, received a variety of second-line chemotherapy against relapsed or recurrent tumors. The overall response rate to second-line chemotherapy was 25% (0–38%). The PFS was 3.5 months (0–20 months), and the OS was 10 months (2–44 months). The response rates, PFS and OS did not differ significantly by the regimen of second-line chemotherapy. Therefore, other factors associated with the response to second-line chemotherapy were investigated.

In the related field of ovarian carcinomas, a TFI has consistently been shown to be the most important factor in the prediction of the response to the second-line chemotherapy [21–24]. Patients with ovarian tumor who relapse within 6 months have a disease that is significantly more likely to be both resistant to the original drugs and to have a lower response rate to new chemotherapy; however, those who relapse after 6 months from a 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 [21].

However, comparable predictive factors for the response to second-line chemotherapy have not been established for endometrial carcinomas. It was yet to be determined whether TFI predicts a response to second-line chemotherapy, and if so, whether 6 months was a reasonable critical threshold that would suggest the clinical outcome after second-line chemotherapy. It was also unclear which current regimen is most effective as a second-line chemotherapy for endometrial carcinoma.

In our study, a TFI greater or less than 6 months was demonstrated to be significantly associated with the

tumor's likely responsiveness to a second-line chemotherapy (*P* = 0.0026 by Fisher's exact test). The current study also showed that the association between TFI and sensitivity to a second-line TECm, TCM or TCw was statistically significant (*P* = 0.015 by Fisher's exact test), indicating that second-line chemotherapy using taxane and platinum, with or without anthracycline, was not effective for those whose TFI was shorter than 6 months after initial treatment using taxane and platinum, with or without anthracycline.

PFS and OS were also shown to relate to a TFI ≥ or <6 months (*P* = 0.0003 and *P* = 0.025, respectively, by the log-rank test). As in ovarian tumors, multivariate analysis showed that the TFI for endometrial tumors was also the most significant factor for predicting the effectiveness of a second-line chemotherapy (the adjusted HR of TFI (≥6 months versus <6 months) on PFS: 3.482 (95% CI, 1.641–7.388), and that on OS: 2.341 (95% CI, 1.034–5.301)). TFI was demonstrated to be a significant factor in predicting for PFS and OS (*P* = 0.0012 and *P* = 0.042, respectively, based on the multivariate Cox proportional hazards model).

These results imply, for the first time, that the standard strategy for ovarian carcinoma second-line chemotherapy can now be applied to endometrial carcinoma as well. Endometrial carcinomas that relapse at least 6 months after first-line chemotherapy using TC/TEC have a significantly higher chance of responding to second-line chemotherapy. However, the tumors that relapse before 6 months are likely to be resistant. In fact, none of the currently popular regimens of chemotherapy (including the same as, or other than, the first-line regimen) were effective, and the PFS and OS were only 2 months (0–9 months) and 5.5 months (2–44 months), respectively (data not shown). Palliative care in these cases, rather than second-line chemotherapy, may for now be more appropriate.

Our present study provides, for the first time, good evidence that relapsed or recurrent diseases found within 6 months from a first-line chemotherapy regimen using taxane and platinum (with or without anthracycline) fail to respond to second-line chemotherapy. Further investigation is still required to establish an efficacious strategy for second-line chemotherapy for advanced or recurrent endometrial cancer.

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Conflicts of interest statement This study was approved by our Institutional Review Board and Ethics Committee. There are no conflicts of interest between the authors related to the research being reported.

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