Importance of platinum-free interval in second-line chemotherapy for advanced or recurrent endometrial cancer

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Summary

Purpose: To investigate the effectiveness of platinum-based combination chemotherapy as second-line chemotherapy for patients with advanced or recurrent endometrial cancer treated initially by platinum-based combination chemotherapy. *Materials and Methods:* Subjects were patients who had received platinum-based combination chemotherapy as second-line chemotherapy: 56 patients with recurrent disease who had previously received postoperative adjuvant platinum-based combination chemotherapy (Category 1) and 21 patients who had received first-line chemotherapy but not adjuvant chemotherapy for advanced or recurrent disease (Category 2). Patients' records were searched for the response to second-line chemotherapy and survival, particularly in relation to the platinum-free interval (PFI). *Results*: A PFI over 12 months was a predictor of response (64.7%) and overall survival time (23 months) in Category 1 patients. A PFI of less than three months was a negative predictor of response (0%) and overall survival (nine months) in Category 2 patients. *Conclusion:* Platinum-based combination chemotherapy appears to be effective as second-line chemotherapy for endometrial cancer if the PFI is sufficiently long.

Key words: Second-line chemotherapy; Advanced and recurrent endometrial cancer; Platinum-free interval.

Introduction

Chemotherapy has held an important position in the treatment of recurrent and advanced endometrial cancer. Although most patients with isolated vaginal recurrence are treated by vaginal brachytherapy alone, patients with metastases at multiple sites or distant metastasis are usually treated by repeat chemotherapy. First-line chemotherapy for recurrent and advanced endometrial cancer has been well-documented in a series of Gynecologic Oncology Group (GOG) randomized trials [1-4], which yielded a strategy for a proper first-line chemotherapy regimen. However, an optimum strategy for second-line chemotherapy has not yet been determined.

With respect to ovarian cancer, the established strategy for selecting a chemotherapy regimen is based on the treatment-free interval (TFI) [5]. The response to platinum rechallenge increases with a TFI, which refers to a platinum-free interval (PFI) in most cases of recurrent ovarian cancer. In cases of advanced or recurrent endometrial cancer, however, the time to recurrence (TTR) after primary chemotherapy is considered to be predictive of survival after recurrence, as was shown in the ancillary data analysis of the GOG trials [6]. The analysis also pointed to the TFI as an important indicator when single agents are used as second-line chemotherapy for endometrial cancer. These findings raise the possibility that the TFI or PFI can be used in selecting a second-line chemotherapy regimen for patients with endometrial cancer. Thus, the authors investigated the effectiveness of platinum-based combination chemotherapy as second-line chemotherapy for patients with advanced or recurrent endometrial cancer who had been treated initially by platinum-based combination chemotherapy.

Materials and Methods

After obtaining approval from the institutional review board, the authors obtained clinical records of the Cancer Institute Hospital (Tokyo) to identify patients treated for recurrent endometrial cancer between January 1999 and December 2009. Because the aim of the study was to determine the effectiveness of second-line chemotherapy for recurrent endometrial cancer, clinical records of all patients who had received any second-line chemotherapy were reviewed. No patient in the series had been treated with radiotherapy. At the present institution, platinum-based combination chemotherapy is used for both first-line and second-line chemotherapy of endometrial cancer. If the PFI between first-line and second-line chemotherapy is six months or more, the same drug combination used for first-line chemotherapy is used for second-line chemotherapy. If the PFI is less than six months, a different drug combination is used for second-line chemotherapy. The platinum-based combinations include paclitaxel and carboplatin (TC), docetaxel and carboplatin (DC), adriamycin and cisplatin (AP), ifosfamide, epirubicin, and cisplatin (IEP), docetaxel and cisplatin (DP), paclitaxel and cisplatin (TP), and irinotecan and nedaplatin (CPT-11/NDP).

Patients were identified as falling in one of two categories (Figure 1). Category 1 comprised patients who received postoperative adjuvant chemotherapy as first-line chemotherapy in the apparent absence of residual disease and received second-line

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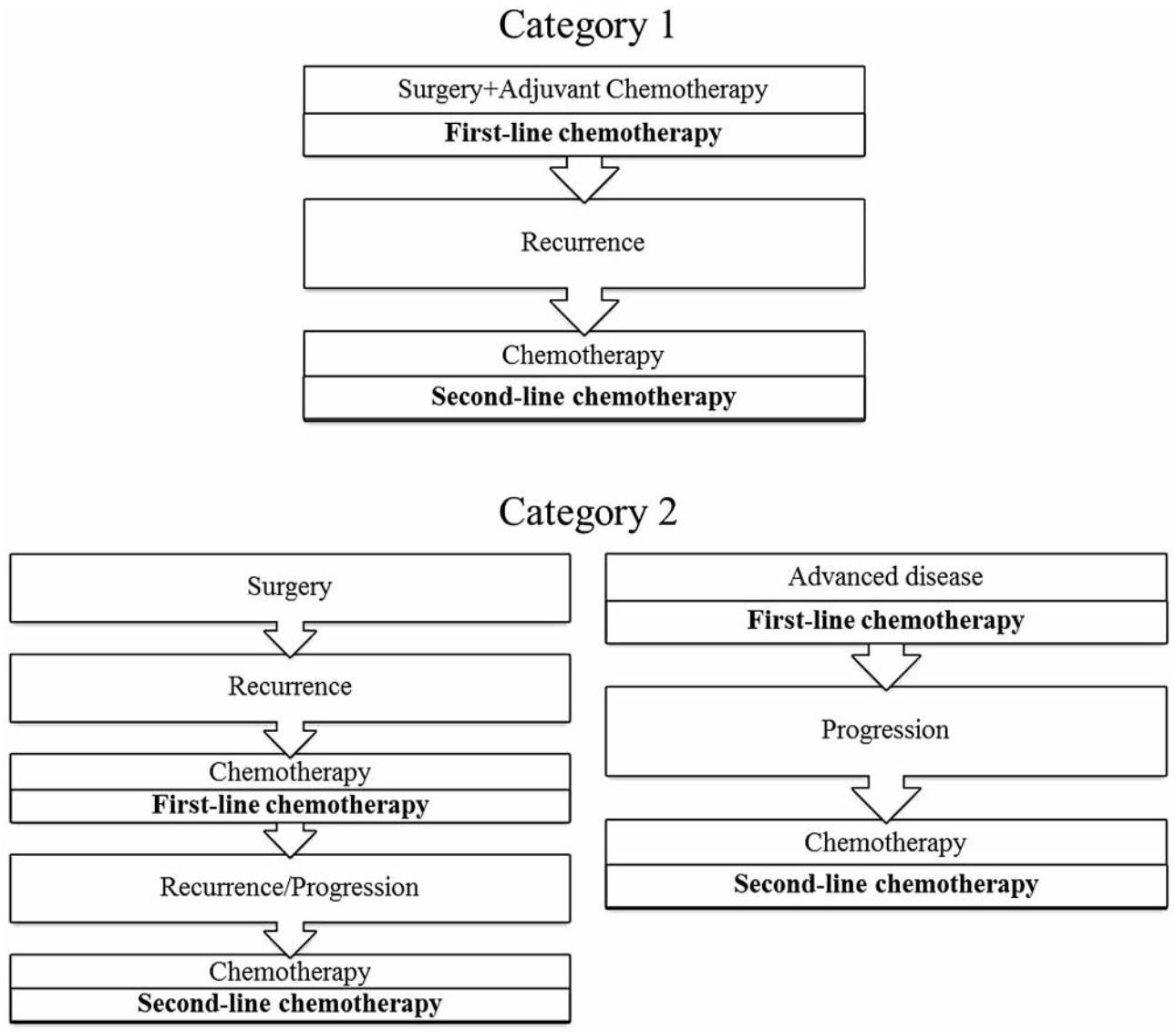

Figure 1. — Patient categories for study of second-line chemotherapy for recurrent or advanced endometrial cancer.

chemotherapy for recurrent disease. Category 2 comprised patients with either advanced or recurrent disease who received both first-line and second-line chemotherapy. For patients in this category, the first-line chemotherapy was performed not as adjuvant chemotherapy but for recurrent or residual disease. Responses to second-line chemotherapy were examined, and response rates were determined for each group. Response rates were also determined in relation to the PFI in both categories. Among Category 1 patients, overall survival (OS) after recurrence was determined in relation to the PFI, which was taken as the interval between the end of adjuvant chemotherapy and the start of second-line chemotherapy for disease recurrence, and among Category 2 patients, OS after the start of second-line chemotherapy was determined in relation to the PFI, which was taken as the time between the end of first-line chemotherapy and the start of second-line chemotherapy. Survival curves were drawn according to the Kaplan-Meier method.

Results

Seventy-seven patients with advanced or recurrent endometrial cancer were treated at the Cancer Institute Hospital during the period noted above. Fifty-six of these patients fell into Category 1, and 21 fell into Category 2. All had measurable disease.

Category 1

Clinicopathologic characteristics, including treatment details, of the 56 Category 1 patients are summarized in Table 1. Median age was 58 years. At the time of adjuvant chemotherapy, disease stages were as follows: Stage I (n=7), Stage II (n=2), Stage III (n=26), and Stage IV (n=11). Twenty-one patients had endometrioid adenocarcinoma grade 1-2,

Table 1. — *Clinicopathologic characteristics of Category 1 patients (n=56).*

Age	
Median	58 years
Range	35-78 years
Disease stage (before first-line chemotherapy)	
I	7
II	2
III	26
IV	11
Histology	
Endometrioid adenocarcinoma G1-2	21
Endometrioid adenocarcinoma G3	8
Carcinosarcoma	15
Serous	6
Clear	1
Mixed	5
Site of recurrence	
Distant	39
Local	8
Both	9
First-line chemotherapy	
IEP	24
TC/DC	30
AP	2
Second-line chemotherapy	
IEP	12
TC/DC	35
AP	5
DP	4

Number of patients is shown unless otherwise indicated.
IEP: ifosfamide-epirubicin-cisplatin; TC: paclitaxel-carboplatin; DC: docetaxel-carboplatin; AP: adriamycin-cisplatin; DP: docetaxel-cisplatin

Table 2. — *Response to second-line chemotherapy and overall survival of Category 1 patients per PFI.*

Response rate (total)	44.6% (10 CR, 15 PR)
PFI ≥ 12 months (n=29)	64.7
PFI 6-11 months (n=13)	38.4
PFI < 6 months (n=14)	0.0
Overall survival (median months)	13.1
PFI ≥ 12 months (n=29)	23.0
PFI 6-11 months (n=13)	5.6
PFI < 6 months (n=14)	5.4
Outcome (n)	6 NED, 12 AWD, 38 DOD

PFI: platinum-free interval; CR: complete response; PR: partial response; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease.

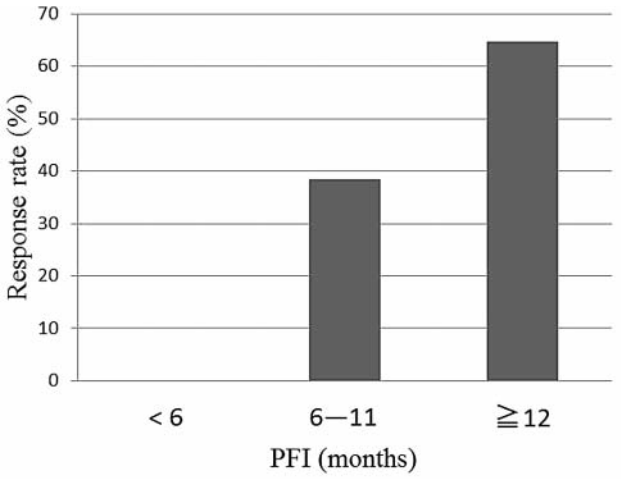

Figure 2. — Responses of Category 1 patients to second-line chemotherapy per platinum-free interval (PFI). Responses are shown as total percentages of patients with complete or partial response.

eight had endometrioid adenocarcinoma grade 3, and 15 had carcinosarcoma. There was no residual disease in these patients after surgery. The following adjuvant chemotherapy drug combinations were given, IEP (n=24), TC (n=30), and AP (n=2). Upon recurrence, these patients received IEP (n=12), TC or DC (n=35), AP (n=5), or DP (n=4).

The response to second-line chemotherapy in this group was 44.6%, with ten complete responses and 15 partial responses. Response rates differed markedly in relation to PFI (Figure 2). The response rate was 0% when PFI was less than six months, 38.4% when PFI was six to 11 months, and 64.7% when PFI was over 12 months. With a PFI of less than six months, median OS after recurrence was 5.4 months. With a PFI of six to 11 months, median OS was 5.6 months, and with a PFI of 12 months or more, median OS was 23.0 months (Table 2). Kaplan-Meier curves for survival of Category 1 patients after recurrence are shown per PFI in Figure 3.

Category 2

Clinicopathologic characteristics, including treatment details, of the 21 Category 2 patients are summarized in Table 3. Median age was 65 years. Initial disease stages in this group were as follows: Stage I (n=1), Stage III (n=4), and Stage IV (n=16). Four patients had endometrioid adenocarcinoma grade 1-2, 4 had grade 3 endometrioid adenocarcinoma, and nine had carcinosarcoma. The following first-line chemotherapy drug combinations were given: IEP (n=10) and TC or DC (n=11). Second-line chemotherapy drug combinations consisted of the following: IEP (n=4) and TC or DC (n=10).

Response to second-line chemotherapy in this group was 4.8% (with one partial response). Response rates differed markedly in relation to PFI (Figure 4). With a PFI of less than three months, the response rate was 0%, but with a PFI of three months or more, the response rate was 20.0%. Median OS after the start of second-line chemotherapy was nine months for patients with a PFI of less than three months, and 15.4 months for patients with a PFI of three months or more (Table 4). Kaplan-Meier curves for survival of Category 2 patients after the start of second-line chemotherapy are shown per PFI in Figure 5.

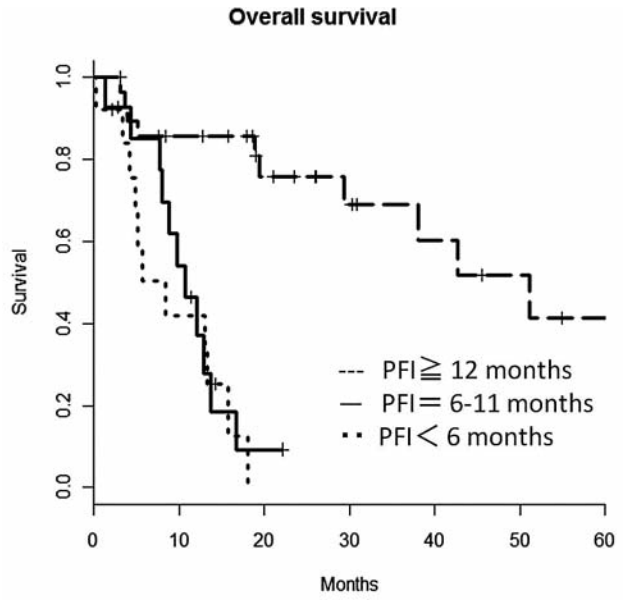

Figure 3. — Kaplan-Meier curves of overall survival of Category 1 patients after recurrence per platinum-free interval (PFI). A significant difference was noted between PFI ≥ 12 months and PFI < 12 months ($p < 0.001$).

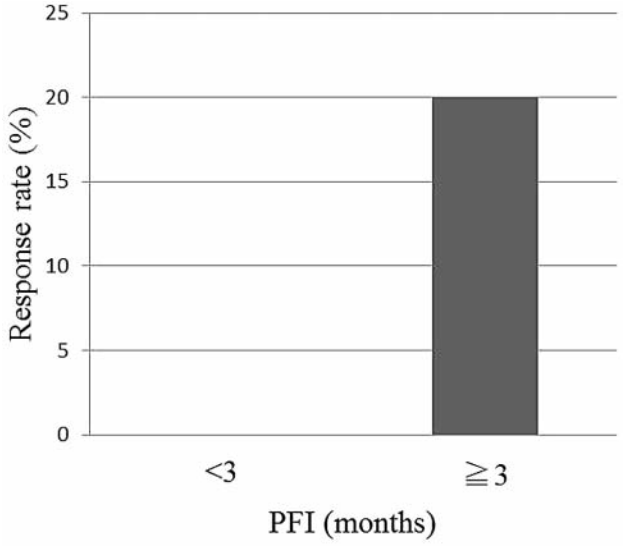

Figure 4. — Responses of Category 2 patients to second-line chemotherapy per platinum-free interval (PFI). Responses are shown as total percentages of patients with complete or partial response.

Table 3. — *Clinicopathologic characteristics of Category 2 patients (n=21).*

Age	
Median	65 years
Range	47-77 years
Disease stage (before first-line chemotherapy)	
I	1
II	0
III	4
IV	16
Histology	
Endometrioid adenocarcinoma G1-2	4
Endometrioid adenocarcinoma G3	4
Carcinosarcoma	9
Serous	0
Clear	1
Mixed	3
Site of recurrence	
Distant	9
Local	11
Both	1
First-line chemotherapy	
IEP	10
TC/DC	11
AP	0
Second-line chemotherapy	
IEP	4
TC/DC	10
AP	2
DP	3
TP	1
CPT-11/NDP	1

Number of patients is shown unless otherwise indicated.
IEP: ifosfamide-epirubicin-cisplatin; TC: paclitaxel-carboplatin; DC: docetaxel-carboplatin; AP: adriamycin-cisplatin; DP: docetaxel-cisplatin; TP: paclitaxel-cisplatin; CPT-11/NDP: irinotecan-nedaplatin

Table 4. — *Response to second-line chemotherapy and overall survival of Category 2 patients per PFI*

Response rate (total)	4.8% (1 PR,1 SD)
PFI ≥ 3 months (n=5)	20.0%
PFI < 3 months (n=16)	0.0%
Overall survival (median months)	9.8
PFI ≥ 3 months (n=5)	15.4
PFI <3 months (n=16)	9.0
Outcome	1 NED, 20 DOD

PFI: platinum-free interval; PR: partial response; SD: stable disease
NED: no evidence of disease; DOD: died of disease

Discussion

The authors' overall study goal was to determine which drug combination should be selected for second-line chemotherapy in patients with advanced or recurrent endometrial cancer. First-line chemotherapy regimens are already established. Results of the GOG randomized trials made it clear that platinum-based combination chemotherapy should be selected for first-line chemotherapy in such cases. In the GOG-77 trial, addition of cisplatin to doxorubicin for advanced endometrial cancer improved survival [2]. Currently, AP is the standard chemotherapy combination for recurrent and advanced

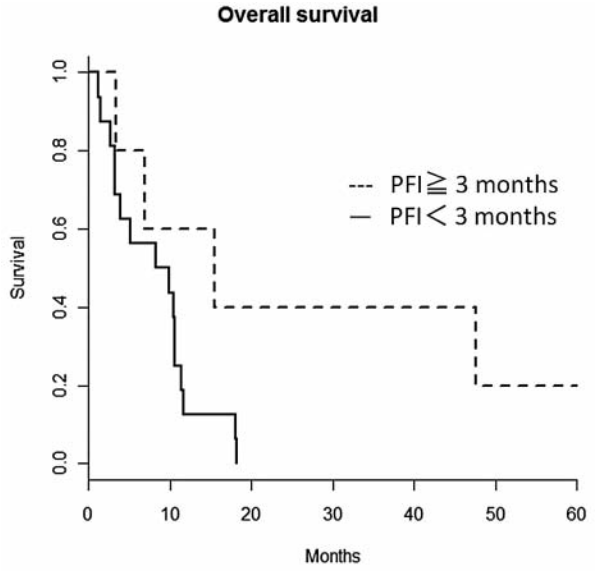

Figure 5. — Overall survival of Category 2 patients after the start of second-line chemotherapy per platinum-free interval (PFI). A significant difference was not noted, but a difference in trend was observed between PFI < 3months and PFI ≥ 3 months ($p = 0.06$).

endometrial cancer. In the GOG-163 trial, AP was compared with AT (adriamycin and paclitaxel), and it was clarified that cisplatin combination chemotherapy was superior to non-platinum-containing chemotherapy. In the GOG-177 trial, TAP (paclitaxel, adriamycin, and cisplatin) was shown to significantly improve response rate, progression-free survival, and OS, but severe side-effects are associated with TAP [4]. Thus, TAP was not recommended in place of AP [4]. GOG-209 is underway to determine whether TC is therapeutically equivalent to TAP with respect to survival.

The effectiveness of combination chemotherapy as second-line chemotherapy has been unclear. In the current study, patients who relapsed more than six months, especially more than 12 months, after adjuvant therapy and patients who relapsed more than three months after first-line chemotherapy for recurrent or advanced disease showed a good chance of response to rechallenge with platinum-based combination chemotherapy, which may translate to increased survival for similar patients. Conversely, in patients who relapse within six months after adjuvant therapy or within three months after first-line chemotherapy for recurrent or advanced disease, rechallenge with combination chemotherapy may be futile. In this situation, a different approach, such as single-agent chemotherapy, participation in a clinical trial, or hormonal therapy, may be recommended. Several phase II trials of single-agent regimens have been undertaken for second-line chemotherapy, but the response rates have been limited to 0-25% [7-15]. In addition, use of a single agent within three months after first-line chemotherapy is generally thought to be of little value [6].

Several molecular targeted agents have been recently investigated. Single agent VEGF inhibitor bevacizumab was tested in a GOG trial [16] in which more than half of the patients had been treated previously under one or two cytoxic regimens. The response rate was 13.5% [16]. The reported response rate for mTOR inhibitor temsirolimus is 14% in chemotherapy-naive patients [17]. Because the response was not enough to select a single molecular targeted agent for second-line treatment, combination bevacizumab and temsirolimus was studied in a phase II trial, but severe toxicity was reported, possibly because the combination therapy was tested in patients who had received prior cytotoxic chemotherapy [18].

In summary, the present authors report the possibility of platinum-based combination chemotherapy as second-line treatment for recurrent and advanced endometrial cancer. The effectiveness clearly depends on the PFI between first-line and second-line chemotherapy. The PFI is a key to successful chemotherapy for endometrial cancer after failure of first-line chemotherapy.

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