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Therapeutic Efficacy of Platinum Re-administration for Recurrent Endometrial Cancer

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Aim : In recent years, molecularly targeted drugs and immune checkpoint inhibitors (ICIs) have become available for recurrent endometrial cancer. Recommended treatments for recurrent endometrial cancer with a history of platinum-containing therapy were changed from cytotoxic chemotherapy to treatments including pembrolizumab, an ICI, in the Japan Society of Gynecologic Oncology clinical practice guidelines for endometrial cancer in 2023. Some studies reported the efficacy of platinum re-administration in patients with recurrent endometrial cancer who had a history of platinum-containing therapy ; however, further evidence is needed. Therefore, we investigated the therapeutic effects of platinum re-administration in patients with recurrent endometrial cancer and unresectable lesions at our department.

Patients and Methods : Thirty-eight patients with endometrial cancer, who recurred with unresectable lesions during the follow-up after an initial treatment at Shinshu University Hospital from 2012 to 2022, were enrolled in the present study. The therapeutic effects of platinum re-administration were retrospectively examined from medical records.

Results : No significant differences were observed in the response rate, disease control rate, progression-free survival, or overall survival between patients with or without a history of platinum-containing therapy.

Conclusion : It is important to select the optimal treatment for each patient. Since some patients cannot be treated with molecular targeted drugs or ICIs, platinum re-administration for patients with recurrent endometrial cancer and a history of platinum-containing therapy has potential as a treatment option. *Shinshu Med J 74 : 175—182, 2026*

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Key words : endometrial cancer, recurrent, platinum re-administration

I Introduction

Few drug therapy options were previously available for patients with recurrent endometrial cancer. The Japan Society of Gynecologic Oncology clinical practice guidelines for endometrial cancer in 2018 recommended platinum-based doublet therapy, either paclitaxel plus carboplatin therapy (TC) or doxorubicin plus cisplatin therapy (AP), or platinum single-agent therapy for recurrent endometrial cancer[1)]. However, in recent years, molecularly targeted drugs and immune checkpoint inhibitors (ICIs) have become available. Progression-free survival (PFS) and overall survival (OS) were shown to be significantly longer with lenvatinib, an oral multikinase inhibitor, plus pembrolizumab, an ICI, than with single-agent chemotherapy in patients with advanced or recurrent endometrial cancer who had previously received platinum-containing therapy in the phase III Study 309/KEYNOTE-775[2)]. In 2021,

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lenvatinib plus pembrolizumab (LP) therapy started to be covered by the national health insurance system of Japan for "unresectable, advanced, or recurrent endometrial cancer that has progressed after cancer chemotherapy". In addition, recommended treatments for recurrent endometrial cancer were changed to TC therapy for patients with no history of platinum-containing therapy, and to treatments including pembrolizumab for patients with a history of platinum-containing therapy in the Japan Society of Gynecologic Oncology clinical practice guidelines for endometrial cancer in 2023[3]. In the phase III Study 309/KEYNOTE-775, the therapeutic effects of LP therapy and single-agent chemotherapy without platinum agents were compared in patients with recurrent endometrial cancer; therefore, LP therapy was not directly compared with platinum-containing therapy[2]. Some studies reported the efficacy of platinum re-administration in patients with recurrent endometrial cancer; however, further evidence is needed[4)5)]. Until 2021, platinum re-administration was performed for patients with recurrent endometrial cancer, regardless of the platinum-free interval (PFI) or a history of platinum-containing therapy, at Shinshu University Hospital. Therefore, we investigated the therapeutic effects of platinum re-administration in patients with recurrent endometrial cancer and unresectable lesions at our department.

Ⅱ Patients and Methods

Patients with endometrial cancer who recurred with unresectable lesions during the follow-up after an initial treatment at Shinshu University Hospital between January 2012 and December 2022 were enrolled in the present study. The therapeutic effects of platinum-containing therapy after recurrence were retrospectively examined from medical records. According to RECIST version 1.1, treatment efficacy was evaluated using the response rate (RR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS). The impact of PFI on second-line chemotherapy and the effects of local treatments, such as surgery and definitive radiation therapy, after platinum re-administration for patients with a history of platinum-containing therapy were also investigated.

All statistical analyses were performed with EZR version 1.68 (Jichi Medical University, Tochigi, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[6]. The Mann-Whitney U test and Fisher's exact test were examined, with a P value $<$ 0.05 being significant. This analysis did not correct for multiple comparisons, so there is a possibility that significant variables may contain Type I errors. Survival curves for OS and PFS were plotted using the Kaplan-Meier method, and significance was assessed using the Log-rank test.

The present study was approved by the Ethical Committee for Medical and Biological Research of Shinshu University School of Medicine (approval number 6055).

Ⅲ Results

A Patient characteristics

Thirty-eight patients were registered: nine with no history of platinum-containing therapy were classified as Group A and 29 with a history of platinum-containing as Group B. Of the group who received platinum re-administration, 27 patients (93.1 %) relapsed before molecularly targeted drugs and ICIs became available in Japan. **Table 1** summarizes patient characteristics. No significant differences were observed in age, BMI, CA125, histological type, or time to recurrence ($P>0.05$) between the two groups. PFI in Group B was 13 months (range: 3-44). The percentage of patients with stages III-IV was markedly higher in Group B than in Group A ($P=0.005$). Six patients in Group A did not receive chemotherapy even though they were classified as having an intermediate or higher risk of recurrence and were generally recommended additional postoperative treatment. The reasons for this were that radiation therapy was performed as adjuvant therapy in four patients and adjuvant chemotherapy after surgery was not administered to two. Chemotherapy or radiation ther-

Table 1 Characteristics in Groups A and B

		Group A : with no history of platinum administration (n = 9)	Group B : with a history of platinum administration (n = 29)	P value
Age (years)		71 (51-83)*1	62 (42-81)*1	0.092
BMI (kg/m^2)		25.0 (18.7-36.9)*1	25.1 (17.8-33.8)*1	0.876
CA125 (U/ml)		16.5 (2.8-293.0)*1	26.5 (4.1-474.4)*1	0.768
Stage III-IV		3 (33.3%)	25 (86.2%)	0.005
High-grade histological types		4 (44.4%)	21 (72.4%)	0.226
Time to recurrence (months)		12 (1-26)*1	10 (1-42)*1	0.796
PFI (months)			13 (3-44)*1	
First-line chemotherapy regimens	TC		20 (69.0%)	
	DC		9 (31.0%)	
	wTC		2 (6.9%)	
	wDC		1 (3.4%)	
	CPT/N		1 (3.4%)	
Second-line chemotherapy regimens	TC	3 (33.3%)	12 (41.4%)	
	DC		5 (17.2%)	
	wTC	7 (77.8%)	6 (20.7%)	
	wDC	1 (11.1%)	4 (13.8%)	
	CPT/N		1 (3.4%)	
	AP		2 (6.9%)	
	Carboplatin		1 (3.4%)	
Cycles of second-line chemotherapy		6 (3-9)*1	5 (2-9)*1	0.38

*1 : mean (range)

PFI : platinum-free interval TC : paclitaxel + carboplatin DC : docetaxel + carboplatin

wTC : weekly paclitaxel + carboplatin wDC : weekly docetaxel + carboplatin CPT/N : irinotecan + nedaplatin

AP : anthracycline + cisplatin

apy are generally considered to be additional postoperative treatments for endometrial cancer ; however, in Japan, chemotherapy alone is selected at most facilities[1].

B Chemotherapy

Table 1 shows the first- and second-line chemotherapy regimens. In the second-line chemotherapy regimen, only one patient (2.6 %) received platinum single-agent therapy ; the remaining patients received platinum-based doublet chemotherapy.

C Responses and survival

No significant differences were observed in RR or DCR between Groups A and B. Furthermore, no significant differences were noted in PFS or OS **(Table 2, Fig. 1 A, B)**.

D Impact of PFI on second-line chemotherapy

To investigate whether responses to second-line platinum-based chemotherapy increased with longer PFI, Group B was divided into those with PFI <12 months and ≥ 12 months **(Table 3)**. No significant differences were observed in age, BMI, CA125, histological type, or the percentage of patients with stages III-IV between the two groups ($P>0.05$). A significant difference was noted in PFI between the two groups ($P<0.001$), but not in RR, DCR, PFS, or OS **(Table 3, Fig. 1 C, D)**.

E Effects of local treatments after platinum re-administration

Six patients in Group B received local treatments for residual disease after platinum re-administration **(Table 4)**, while the remaining 23 did not. Of the patients who received local treatment, all had stage III

Table 2　Treatment results in Groups A and B

	Group A : with no history of platinum administration (n = 9)	Group B : with a history of platinum administration (n = 29)	P value
CR PR SD, Non-CR/Non-PD PD	1 (11.1%) 6 (66.7%) 2 (22.2%)	1 (3.4%) 11 (37.9%) 10 (34.5%) 7 (24.1%)	
RR	77.8%	41.4%	0.124
DCR	100%	75.9%	0.164
PFS (months)	12	12	0.329
OS (months)	not reached	27	0.201
Observation period (months)	26 (6-107)*1	19 (7-80)*1	0.208

*1 : mean (range)
CR : complete response PR : partial response SD : stable disease PD : progressive disease
RR : response rate DCR : disease control rate PFS : progression-free survival OS : overall survival

Table 3　Comparison of PFI in Group B

	PFI ＜12 (n = 16)	PFI ≥12 (n = 13)	P value
Age (years)	60.5 (52-80)*1	63.0 (42-81)*1	0.715
BMI (kg/m^2)	24.8 (19.4-32.6)*1	25.4 (17.8-33.8)*1	1.000
C125 (U/ml)	41.4 (4.1-474.5)*1	26.0 (7.7-220.9)*1	0.751
Stage III-IV	14 (87.5%)	11 (84.6%)	0.617
High-grade histological types	10 (62.5%)	11 (84.6%)	0.183
PFI (months)	8 (3-11)*1	20 (12-44)	＜0.001
CR PR SD, Non-CR/Non-PD PD	1 (6.2%) 5 (31.2%) 7 (43.8%) 3 (18.8%)	 6 (46.1%) 3 (23.0%) 4 (30.8%)	
RR	37.5%	46.1%	0.912
DCR	81.3%	69.2%	0.423
PFS (months)	10	12	0.583
OS (months)	27	45	0.843
Observation period (months)	17.5 (7-72)*1	20 (8-80)*1	0.65

*1 : mean (range)
PFI : platinum-free interval CR : complete response PR : partial response SD : stable disease PD : progressive disease
RR : response rate DCR : disease control rate PFS : progression-free survival OS : overall survival

with high-grade histological types, and the therapeutic effects of platinum re-administration were assessed as PR in four and non-CR/non-PD in two. Local treatments were surgery in three patients and definitive radiation therapy in three. PFS and OS were significantly longer in the local treatment group (P = 0.004 and 0.004, respectively) **(Table 5, Fig. 1 E, F)**.

Ⅳ　Discussion

In recent years, treatment options for recurrent en-

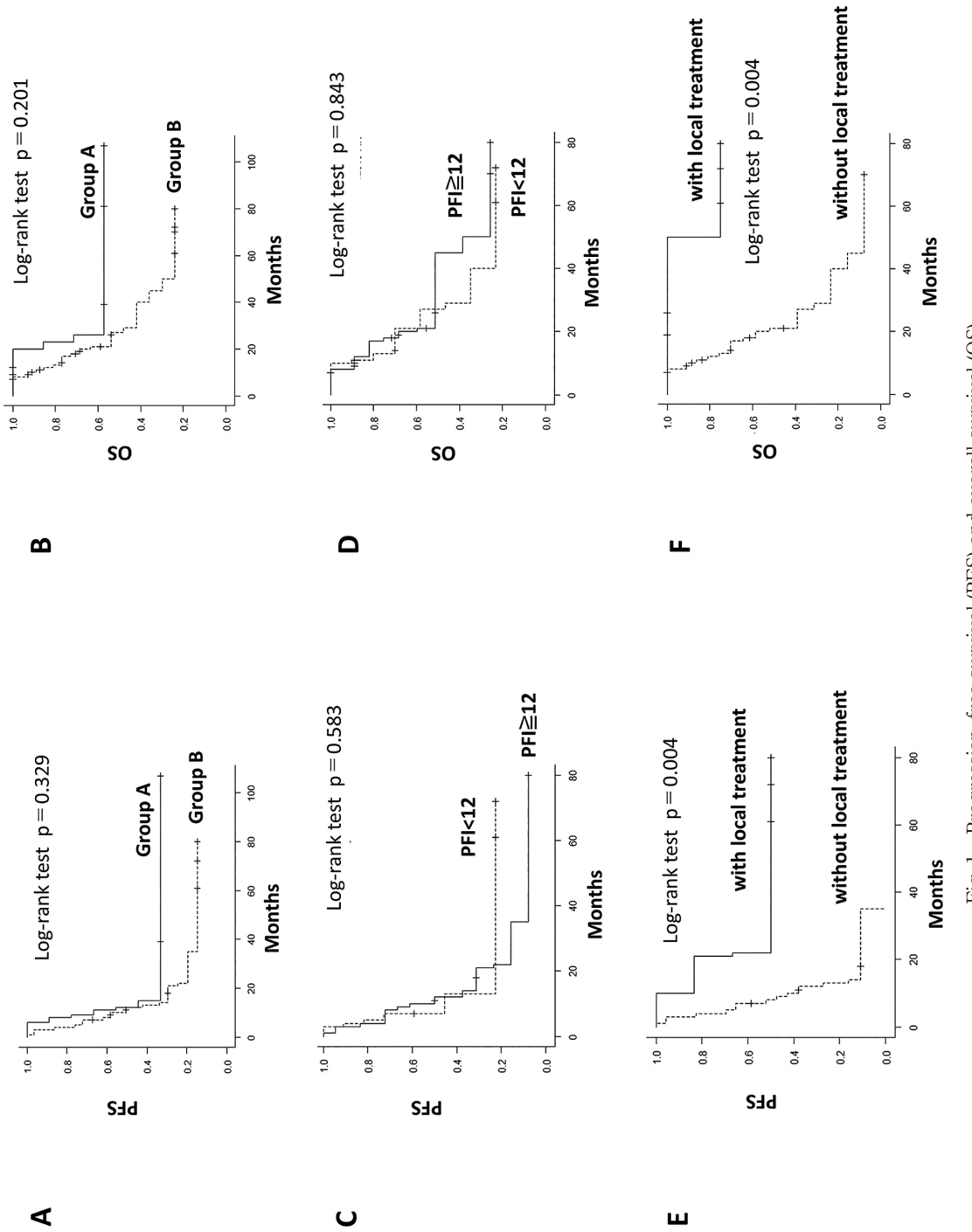

Fig. 1 Progression-free survival (PFS) and overall survival (OS)

A : PFS in Groups A and B.
B : OS in Groups A and B.
C : PFS for a platinum-free interval (PFI) <12 and ≥12 in Group B.
D : OS for PFI <12 and ≥12 in Group B.
E : PFS of patients with and without local treatments in Group B.
F : OS of patients with and without local treatments in Group B.

Table 4　Characteristics of patients who received local treatments in Group B

case	age (years)	stage	pathology	site of recurrence	PFI (months)	response to platinum agent	local treatment	PFS (months)	OS (months)	survival data
1	44	IIIC2	endometrioid G3	PAN, ILN	21	PR	RT	22	50	DOD
2	70	IIIC2	serous	dissemination	14	PR	ST	80	80	NED
3	61	IIIC2	clear	dissemination	6	PR	ST	61	61	NED
4	69	IIIB	SCNEC carcinosarcoma	PAN, PEN	11	Non-CR/ Non-PD	ST	72	72	NED
5	65	IIIC2	clear	PAN, SCLN	34	PR	RT	10	19	AWD
6	57	IIIC2	serous	lung, PEN	16	Non-CR/ Non-PD	RT	21	26	AWD

SCNEC : small cell neuroendocrine carcinoma PAN : paraaortic lymph node PEN : pelvic lymph node ILN : inguinal lymph node
SCLN : supraclavicular lymph node PFI : platinum-free interval CR : complete response PR : partial response
PD : progressive disease RT : radiation therapy ST : surgical therapy PFS : progression-free survival OS : overall survival
DOD : died of disease NED : no evidence of disease AWD : alive with disease

Table 5　Comparison of whether local treatments were received in Group B

	with local treatment (n = 6)	without local treatment (n = 23)	P value
Age (years)	63 (44-77)*1	61 (42-81)*1	0.957
BMI (kg/m^2)	25.9 (23.3-33.8)*1	24.7 (17.8-33)*1	0.262
C125 (U/ml)	17.4 (5.7-91.1)*1	33 (4.1-474.5)*1	0.427
Stage III-IV	6 (100%)	19 (82.6%)	0.553
High-grade histological types	6 (100%)	15 (65.2%)	0.148
PFI (months)	15 (6-34)*1	13 (3-44)*1	0.829
CR PR SD, Non-CR/Non-PD PD	 4 (66.7%) 2 (33.3%)	1 (4.3%) 7 (30.4%) 8 (34.8%) 7 (30.4%)	
RR	66.7%	34.8%	0.198
DCR	100%	69.6%	0.289
PFS (months)	22	8	0.004
OS (months)	not reached	20	0.004
Observation period (months)	55.5 (19-80)*1	17 (7-70)*1	0.005

*1 : mean (range)
PFI : platinum-free interval CR : complete response PR : partial response SD : stable disease PD : progressive disease
RR : response rate DCR : disease control rate PFS : progression-free survival OS : overall survival

dometrial cancer have become more diverse, with an increasing number of cases receiving molecular targeted drugs and ICIs, such as LP therapy. However, LP therapy has a number of side effects, such as hypertension and hypothyroidism[2], and there are some cases in which a dose reduction, treatment interruption, or treatment discontinuance is needed. In the Phase III trial 309/KEYNOTE-775, LP therapy was interrupted or discontinued in 69.2 % and 33.0 % of patients, respectively, due to treatment-emergent adverse events[2]. On the other hand, the discontinuation rate of TC therapy was previously reported to be 12-18 % ; therefore, LP therapy is more likely to be discontinued than platinum-containing therapy[7][8].

Depending on side effects and the patient's condition, platinum re-administration needs to be considered for some patients.

In the present study, the RR and DCR of patients treated with platinum re-administration and those who had not received platinum-containing therapy were 41.4 % vs. 77.8 % (p = 0.124) and 75.9 % vs. 100 % (p = 0.164), respectively, with no significant differences. Regarding the treatment outcomes of platinum re-administration in patients with recurrent endometrial cancer, RR was 38–50 % and DCR was 65–75 %[4)5)9)], which are consistent with the present results. In the randomized phase II study comparing docetaxel plus cisplatin (DP), docetaxel plus carboplatin (DC), and paclitaxel plus carboplatin (TC) in patients with advanced or recurrent endometrial carcinoma (JGOG2041), no significant differences in RR or toxic effects were observed among the groups[10)]. Furthermore, the phase III trial, GOG0209 demonstrated the non-inferiority of TC therapy to paclitaxel-doxorubicin-cisplatin (TAP) therapy in advanced and recurrent endometrial cancer[7)]. It is considered that there is little difference in platinum combination therapies for endometrial cancer depending on the type of platinum agent or the concomitant drugs, but it can be suggested that there is insufficient evaluation of whether the effectiveness differs depending on the drugs when platinum agents are re-administered. In the Phase III trial 309/KEYNOTE-775, RR and DCR of LP therapy were 31.9 % and 78.9 %, respectively[2)]. Although the present study cannot be directly compared with the Phase III trial 309/KEYNOTE-775, platinum re-administration may be a treatment option for patients with recurrent endometrial cancer who previously received platinum-containing therapy and for whom LP therapy is difficult.

In recurrent ovarian cancer, PFI ≥6 months is considered to be platinum-sensitive recurrence, while PFI <6 months is regarded as platinum-resistant recurrence. Non-platinum single-agent chemotherapy is generally administered for platinum-resistant recurrence[11)]. Although there is no concept of platinum sensitivity for recurrent endometrial cancer, platinum re-administration was shown to be less effective with PFI <6 or 12 months than with PFI >6 or 12 months[4)5)]. In the present study, the number of patients with PFI <6 months was small; therefore, we divided patients based on PFI <12 months and found no significant differences in treatment outcomes.

Previous studies reported the efficacy of local treatments, such as surgery and definitive radiotherapy, for recurrent endometrial cancer[12)13)]. However, these treatments may be difficult to perform due to the patient's general condition and the location and number of lesions, and, thus, drug therapy or palliative care are often preferred. At our institution, even for patients who are judged to require local treatments that are difficult at the time of recurrence and platinum re-administration is selected, we actively perform local treatments when recurrent lesions are reduced by platinum re-administration. Prognosis was significantly better in patients who received local treatments than in those who did not. On the other hand, to the best of our knowledge, there is currently no information on the advisability of local treatments for residual lesions after LP therapy. In cases of recurrent endometrial cancer with a history of platinum-containing therapy in which local treatments are initially difficult, they need to be actively implemented if platinum re-administration proves effective and local treatments become possible.

In November 2024, the combination of TC therapy with pembrolizumab or durvalumab, a human anti-human PD-L1 monoclonal antibody, was approved in Japan for advanced and recurrent endometrial cancer. In the phase III DUO-E trial and the NRG GY018 phase III randomized trial, which were suggested that a combination of platinum-based doublet therapy and ICIs was effective in advanced and recurrent endometrial cancer, patients received previous adjuvant chemotherapy were included if their chemotherapy-free interval was at least 12 months, and the rate was 21 and 25 %, respectively[14)15)]. Although a combination of platinum re-administration and ICIs may be also effective, further studies are needed to confirm that. Platinum agents are expected to continue to play an important role in the treatment of recurrent endometrial cancer. It is important to select the

optimal treatment for each patient, and platinum re-administration has potential as one of these treatment options.

This study has two major limitations. First, the sample size was small because of single-center study. Second, there may be selection and confounding bias in this study. Therefore, these results must be interpreted with caution, and further studies, such as randomized phase III trial, are needed to confirm the accuracy of our suggestion.

Conflict of interest statement

The authors have no conflicts of interest relevant to this article.

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