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ORIGINAL ARTICLE

What is an appropriate second-line regimen for recurrent endometrial cancer? Ancillary analysis of the SGSG012/GOTIC004/Intergroup study

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Abstract

Purpose We previously reported that the concept of "platinum sensitivity" could be applied to recurrent endometrial cancer. We conducted an ancillary analysis to determine an appropriate second-line regimen for patients who received a platinum agent as first-line chemotherapy.

Methods We extracted and reanalyzed data of patients treated with doxorubicin and cisplatin (AP), paclitaxel and carboplatin (TC), or docetaxel and carboplatin (DC) as first- and second-line chemotherapies from the SGSG012/GOTIC004/Intergroup study.

Results We identified 216 patients: 38 received AP as first-line chemotherapy, of which 36 received TC or DC (Tax-C) as second-line chemotherapy; and 178 received Tax-C as first-line chemotherapy, of which 51 received AP and 127 received Tax-C as second-line chemotherapy. Median progression-free survival (PFS) and overall survival (OS) after second-line chemotherapy decreased in the order of Tax-C followed by Tax-C (10 and 48 months, respectively), AP followed by Tax-C (9 and 23 months, respectively), and Tax-C followed by AP (3 and 12 months, respectively). Median PFS and OS after second-line

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chemotherapy for platinum-resistant patients receiving Tax-C as first-line chemotherapy were longer in Tax-C than in AP (7 and 23 vs. 3 and 10 months, respectively) as second-line chemotherapy [hazard ratio (HR) 3.255, 95 % confidence interval (CI) 1.908–5.555, $p < 0.0001$; HR 3.179, 95 % CI 1.835–5.507, $p < 0.0001$, respectively]. Median PFS and OS after second-line chemotherapy for platinum-sensitive patients receiving Tax-C as first-line chemotherapy were almost equivalent to those receiving Tax-C or AP as second-line chemotherapy.

Conclusions For platinum-resistant recurrent endometrial cancer patients, Tax-C may be preferred over AP as second-line chemotherapy.

Keywords Recurrent endometrial cancer · Second-line chemotherapy · Platinum sensitivity · AP therapy · TC therapy

Introduction

Recently, in our exploratory retrospective SGSG012/GOTIC004/Intergroup study, we indicated that the concept of "platinum sensitivity" could be applied to recurrent endometrial cancer [1]. The probability of response to second-line platinum-based chemotherapy tended to be higher with longer platinum-free intervals (PFIs). In addition, progression-free survival (PFS) and overall survival (OS) were prolonged with extended PFIs. Particularly, the prognoses of patients with PFIs > 12 months were relatively good. Thus, PFI is a predictive factor of response to second-line platinum-based chemotherapy and survival after recurrence in patients with endometrial cancer who previously received a platinum agent.

The concept of "platinum sensitivity" was originally applied to the recurrence of epithelial ovarian cancer. Women with epithelial ovarian cancer and a PFI > 6 months are classified as "platinum sensitive," and these patients usually undergo platinum-based second-line chemotherapy, resulting in a response of 27–65 % and median survival of 12–24 months [2, 3]. On the other hand, patients with a PFI < 6 months are classified as "platinum resistant," often achieve a median survival period of 6–9 months, and have a 10–30 % probability of response to second-line chemotherapy. Therefore, patients with platinum-sensitive recurrence often receive combination chemotherapy of carboplatin with paclitaxel (TC therapy), whereas those with platinum-resistant recurrence typically receive a single-agent therapy with an agent other than platinum [4].

To date, the most appropriate regimen for treating recurrent endometrial cancer remains unclear. Therefore, we conducted an ancillary analysis of a dataset derived from the SGSG012/GOTIC004/Intergroup study. The purpose of this study was to determine an appropriate second-line platinum-based regimen for patients with a history of receiving platinum-based first-line chemotherapy and, particularly, to evaluate whether alternations to second-line chemotherapy regimens are reasonable.

Patients and methods

Data extraction

The protocol of this ancillary analysis was approved by the protocol committee of Sankai Gynecologic Study Group. It was approved by the Institutional Review Board of Hyogo Cancer Center and complied with the Declaration of Helsinki.

We conducted an ancillary analysis using a dataset from the SGSG012/GOTIC004/Intergroup study [1]. In our previous study, consecutive patients with histologically confirmed endometrial cancer or uterine carcinosarcoma, who received second-line platinum-based chemotherapy between January 2005 and December 2009, were registered (histological confirmation of recurrence was not required). All patients had received primary platinum-based chemotherapy. Concurrent chemoradiation therapy was not regarded as platinum-based chemotherapy, even if it included a platinum-based agent. Patients were excluded if they had uterine sarcoma or any other concurrent invasive cancer. In this ancillary analysis, from the dataset, we extracted data of patients who received doxorubicin and cisplatin combination chemotherapy (AP therapy), TC therapy, or docetaxel and carboplatin combination chemotherapy (DC therapy) as first- and second-line chemotherapy regimens.

Data analysis

Background factors of patients were analyzed using the one-way ANOVA with Tukey's multiple comparison test or Chi-squared test. Associations between a first- and/or second-line chemotherapy regimen and response to second-line chemotherapy, PFS, or OS after second-line chemotherapy were compared. PFS or OS curves were constructed using the Kaplan–Meier method and evaluated for statistical significance using the log-rank test. For survival analysis, TC therapy and DC therapy were integrated into taxane and carboplatin combination therapy (Tax-C therapy) because those had similarities in some characteristics including less toxic and convenient. We set the threshold of the platinum sensitivity as 12 months based on the results of our primary analysis [1]. The Cox proportional hazards model was used to investigate the significance of first- and second-line chemotherapy on outcome, controlling for all

Table 1 First- and second-line chemotherapy ($N = 216$)

First-line chemotherapy	Second-line chemotherapy	*N* (%)
AP		38 (17.6)
	AP	2 (0.9)
	TC	29 (13.4)
	DC	7 (3.2)
TC		172 (79.6)
	AP	49 (22.7)
	TC	101 (46.8)
	DC	22 (10.2)
DC		6 (3.8)
	AP	2 (0.9)
	TC	2 (0.9)
	DC	2 (0.9)

AP: doxorubicin and cisplatin combination chemotherapy; TC: paclitaxel and carboplatin combination chemotherapy; DC: docetaxel and carboplatin combination chemotherapy

other parameters found significant in univariate analysis. The two-tailed test was applied in all statistical analysis, and a p value <0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 6.0e or IBM® SPSS Statistics version 22 statistical software.

Results

First- and second-line chemotherapy regimens

A total of 216 patients were identified from the dataset (Table 1) [1]. As first-line chemotherapy, 48, 172, and 6 patients received AP, TC, and DC therapies, respectively. Most patients (94.7 %, 36/38) who received AP therapy as first-line chemotherapy were switched to Tax-C therapy as second-line chemotherapy. The remaining 2 patients who received AP therapy as both first- and second-line chemotherapies were excluded from further analysis, because these were apparently exceptional cases. Usually, reuse of doxorubicin is not employed with the fear of cardiac toxicity. On the other hand, 51 (29 %) of 178 patients who received Tax-C therapy as first-line chemotherapy were switched to AP therapy as second-line chemotherapy. The remaining 127 patients (71 %) received Tax-C therapy as both first- and second-line chemotherapies.

Response

The response rates of second-line chemotherapy in patients with evaluable lesion are presented in Table 2. Patients were classified according to the first- and second-line regimen and further classified as "platinum resistant" (PFI < 12 months) or "platinum sensitive" (PFI ≥ 12 months). For patients with platinum-resistant recurrence, AP therapy as second-line chemotherapy achieved a notably lower response rate (15 %) than Tax-C therapy (71 and 40 %). On the other hand, patients with platinum-sensitive recurrence achieved relatively good response rates (67 % in AP therapy, 84 and 67 % in Tax-C therapy) regardless of the second-line chemotherapy regimen.

Survival

Estimates of PFS and OS by the Kaplan–Meier method after the administration of second-line platinum-based chemotherapy for patients classified according to the first-line chemotherapy regimen are shown in Fig. 1. There were no significant differences in PFS and OS among patients who received either AP therapy or Tax-C therapy [median PFS 9 vs. 7 months, hazard ratio (HR) 0.913, 95 % confidence interval (CI) 0.624–1.335, $p = 0.638$, log-rank test; median OS 23 vs. 25 months, HR 1.275, 95 % CI 0.818–1.988, $p = 0.284$, log-rank test]. PFS and OS after second-line chemotherapy according to the combination of first- and second-line regimens are shown in Fig. 2. Although the

Table 2 Response rate at second-line chemotherapy ($N = 201$)

Platinum-free interval	<12 months			≥12 months		
First-line regimen	AP	TC/DC	TC/DC	AP	TC/DC	TC/DC
Second-line regimen	TC/DC	AP	TC/DC	TC/DC	AP	TC/DC
Complete response	3	0	9	4	3	25
Partial response	7	6	12	12	3	19
Stable disease	3	5	18	1	0	11
Progression disease	1	30	13	2	3	11
Response rate (%)	71	15	40	84	67	67

AP: doxorubicin and cisplatin combination chemotherapy, TC: paclitaxel and carboplatin combination chemotherapy, DC: docetaxel and carboplatin combination chemotherapy

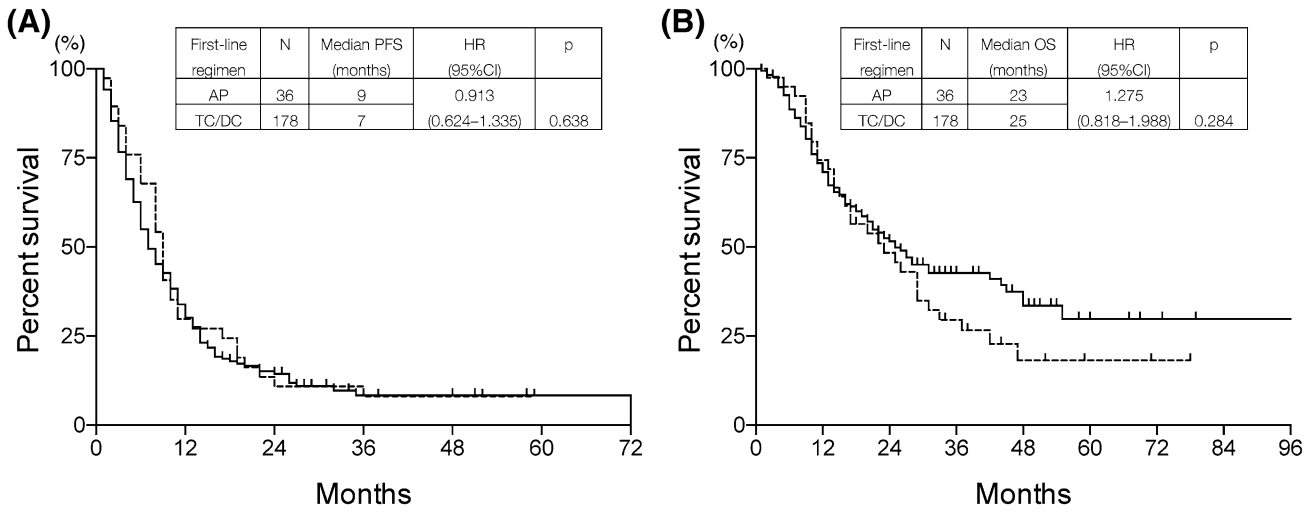

Fig. 1 Estimates of progression-free survival (**a**) and overall survival (**b**) after second-line chemotherapy by the Kaplan–Meier method for patients who received doxorubicin and cisplatin combination chemotherapy (*dotted line*) or taxane (paclitaxel or docetaxel) and carboplatin combination chemotherapy (*solid line*) as first-line chemotherapy

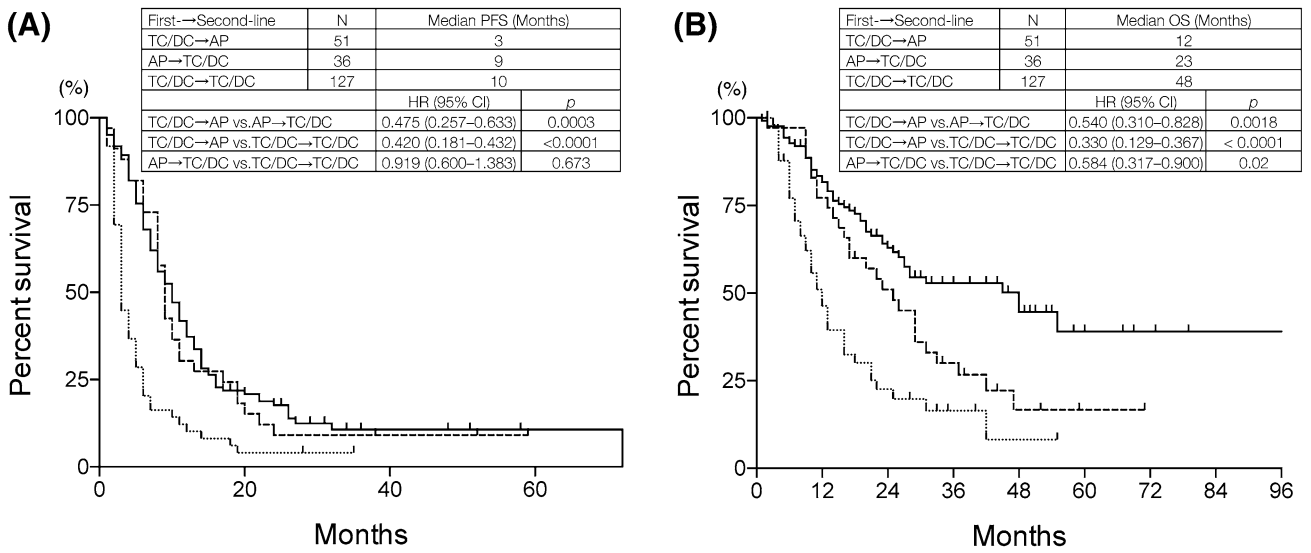

Fig. 2 Estimates of progression-free survival (**a**) and overall survival (**b**) after second-line chemotherapy by the Kaplan–Meier method according to the combination of first- and second-line regimens. Taxane (paclitaxel or docetaxel) and carboplatin combination chemotherapy (Tax-C therapy) followed by doxorubicin and cisplatin combination chemotherapy (AP therapy): *short dotted line*. AP therapy followed by Tax-C therapy: *dotted line*. Tax-C therapy followed by Tax-C therapy: *solid line*

difference of PFS between AP followed by Tax-C therapy and Tax-C followed by Tax-C therapy was not significant, both PFS and OS tended to be longer in patients who received Tax-C followed by Tax-C therapy, AP followed by Tax-C therapy, and Tax-C followed by AP therapy.

Table 3 presents patient characteristics according to the combination of first- and second-line regimens. Among the three groups, significant differences were found only in PFI, although differences in age at recurrence were marginally significant. PFI tended to be longer in patients who received Tax-C followed by Tax-C therapy or AP followed by Tax-C therapy compared with Tax-C followed by AP therapy ($p < 0.0001$).

PFS and OS after second-line platinum-based chemotherapy of 178 patients who received Tax-C therapy as first-line chemotherapy are shown in Fig. 3. Patients were classified according to the second-line chemotherapy regimen and further classified as platinum-resistant recurrence

Table 3 Patient characteristics ($N = 214$)

First-line chemotherapy	AP	TC/DC	TC/DC	
Second-line chemotherapy	TC/DC	AP	TC/DC	
	($N = 36$)	($N = 51$)	($N = 127$)	
Age (range) (years)	60 (50–69)	61 (48–78)	65 (37–80)	$p = 0.040$
FIGO stage				
I	4 (11 %)	8 (16 %)	15 (12 %)	
II	4 (11 %)	4 (8 %)	11 (9 %)	
III	20 (56 %)	23 (45 %)	49 (39 %)	
IV	8 (22 %)	16 (31 %)	52 (41 %)	$p = 0.443$
Histology				
Endometrioid	31 (86 %)	31 (61 %)	64 (50 %)	
Grade 1	9	5	19	
Grade 2	12	14	22	
Grade 3	8	10	20	
Squamous diff.	1	0	5	
Not determined	1	2	3	
Serous	1 (3 %)	6 (12 %)	21 (17 %)	
Clear cell	1 (3 %)	3 (6 %)	7 (6 %)	
Carcinosarcoma	3 (8 %)	9 (18 %)	13 (10 %)	
Others	0	2 (4 %)	17 (13 %)	$p = 0.095$
Residual tumor at primary surgery				
Yes	13 (36 %)	21 (41 %)	37 (29 %)	
No	23 (64 %)	30 (59 %)	90 (71 %)	$p = 0.356$
Radiation therapy				
Done	3 (8 %)	5 (10 %)	7 (6 %)	
Not done	33 (92 %)	46 (90 %)	120 (94 %)	$p = 0.799$
Platinum-free interval				
<6 months	8 (22 %)	31 (61 %)	21 (17 %)	
6≤, <12 months	7 (19 %)	11 (22 %)	34 (27 %)	
12≤, <24 months	10 (28 %)	7 (14 %)	38 (30 %)	
24 months≤	11 (31 %)	2 (4 %)	34 (27 %)	$p < 0.0001$

AP: doxorubicin and cisplatin combination chemotherapy, TC: paclitaxel and carboplatin combination chemotherapy, DC: docetaxel and carboplatin combination chemotherapy

(PFI < 12 months) (Fig. 3a, b) or platinum-sensitive recurrence (PFI ≥ 12 months) (Fig. 3c, d). Of the patients with platinum-resistant recurrence, the median PFS of those who received Tax-C or AP therapy was 3 or 7 months, and the median OS was 10 or 23 months, respectively. Both PFS (HR 3.255, 95 % CI 1.908–5.555, $p < 0.0001$, log-rank test) and OS (HR 3.179, 95 % CI 1.835–5.507, $p < 0.0001$, log-rank test) were significantly longer in patients who received Tax-C therapy as second-line chemotherapy. For patients with platinum-sensitive recurrence, the median PFS of those who received Tax-C or AP therapy was 11 or 12 months, respectively. However, OS of neither regimen has been reached yet. There were no significant differences in PFS (HR 1.441, 95 % CI 0.609–3.410, $p = 0.406$, log-rank test) and OS (HR 1.320, 95 % CI 0.347–5.030, $p = 0.684$, log-rank test).

Factors associated with PFS or OS in univariate analysis included age, residual tumor at primary surgery, PFI (<12 or ≥12 months), and regimen of first- and second-line chemotherapy (Tax-C followed by Tax-C therapy, AP followed by Tax-C therapy, or Tax-C followed by AP therapy). However, in multivariable analysis, only PFI ($p < 0.0001$) and first- and second-line chemotherapy ($p < 0.0001$) were independent prognostic factors for PFS and OS.

Discussion

The results of the present study indicate that Tax-C therapy is more appropriate than AP therapy as second-line chemotherapy for the treatment of recurrent endometrial cancer irrespective of platinum sensitivity. For patients with platinum-resistant recurrence, the response rate, PFS, and OS were superior following Tax-C therapy than following AP therapy. Similarly, there was no improvement in the response rate or survival for patients with platinum-sensitive recurrence following AP therapy.

The most active individual therapeutic agents against endometrial cancer are platinum, taxanes, and anthracyclines, because each reportedly has a response rate of more than 20 % among patients with no history of prior chemotherapy [4]. However, the response rates of these agents are generally poor in second-line therapy settings. For example, the response rate of cisplatin as a second-line agent was only 4 % in a phase II study [5]. Additionally, in a small retrospective review of 17 patients who received TC therapy as first-line chemotherapy, none achieved an objective response to doxorubicin as second-line chemotherapy [6]. Only docetaxel (31 %) and weekly paclitaxel (27 %) administrations demonstrated a relatively high response rate following a single dose as second-line chemotherapy [7, 8]. In addition, reuse of TC therapy in patients with a history of TC therapy was reported to be effective [9]. In this study, 8 (42 %) of 19 patients with endometrioid histology and 6 (50 %) of 12 patients with serous histology achieved partial or complete response. The superior effectiveness of Tax-C therapy in the present study is consistent with the results of these previous reports.

Tax-C therapy is generally less toxic and more convenient to administer than AP therapy, although there have been no direct comparisons. Many women with endometrial cancer are elderly (peak age at diagnosis, 75–79 years), have a history of adjuvant therapy, including chemotherapy or pelvic radiation therapy, and often limited hematopoietic

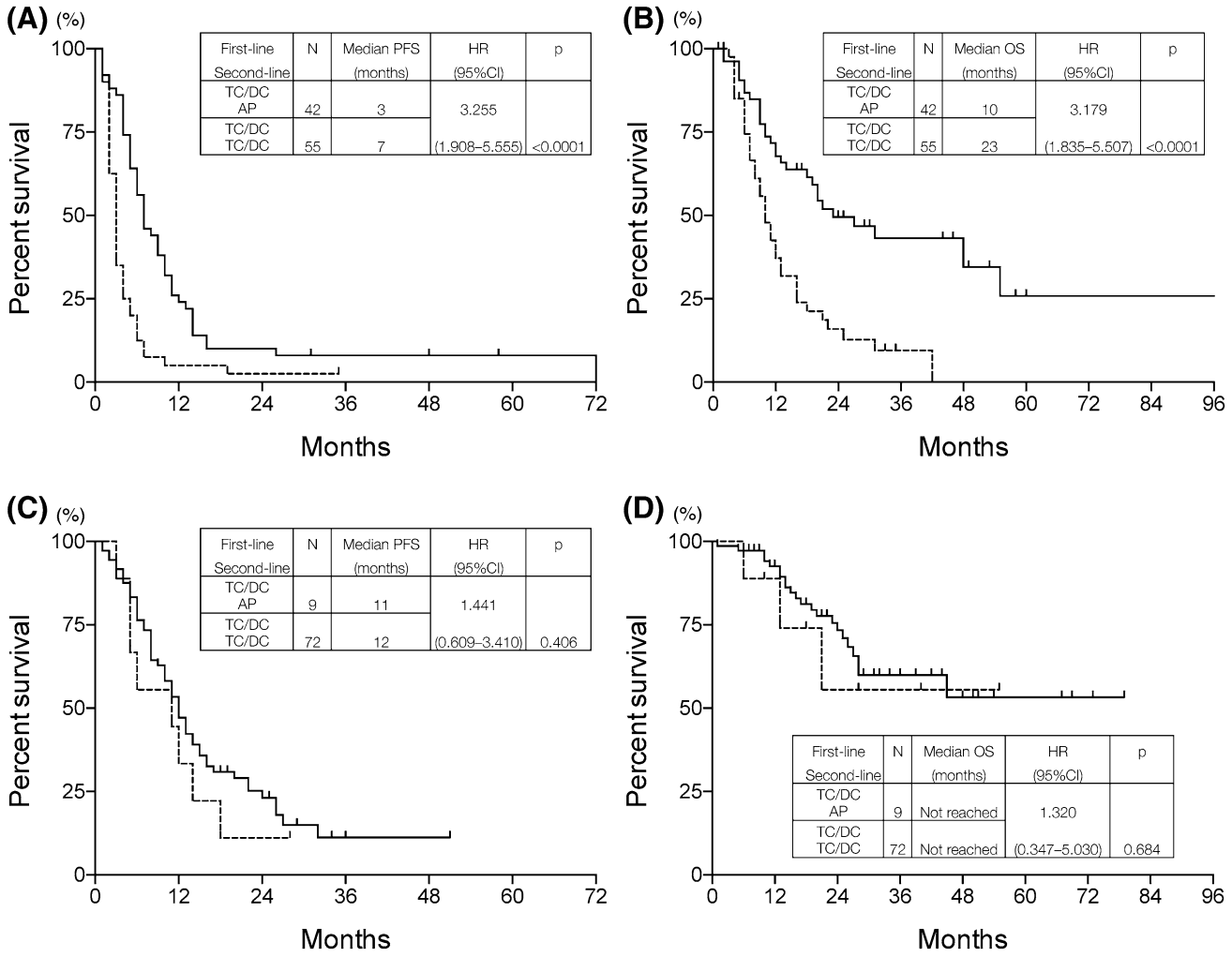

Fig. 3 Estimates of progression-free survival (PFS) and overall survival (OS) after second-line chemotherapy in patients who received Tax-C therapy as first-line chemotherapy, according to the regimen of second-line chemotherapy. **a** PFS in platinum-resistant recurrence. **b** OS in platinum-resistant recurrence. **c** PFS in platinum-sensitive recurrence. **d** OS in platinum-sensitive recurrence. Doxorubicin and cisplatin combination chemotherapy: *dotted line*. Taxane (paclitaxel or docetaxel) and carboplatin combination chemotherapy: *solid line*

function [10]. Therefore, it is essential to sufficiently consider toxicity and the quality of life when choosing an appropriate treatment for recurrent endometrial cancer. Therefore, it is reasonable to consider Tax-C therapy, if the efficacies of Tax-C therapy and AP therapy are equivalent.

In the present study, the efficacies of Tax-C therapy and AP therapy as second-line chemotherapies were almost equivalent among patients with platinum-sensitive recurrence (HR for recurrence and death 1.411; 95 % CI 0.609–3.410; HR 1.320; 95 % CI 0.347–5.030, respectively). Experience from ovarian cancer indicates that reuse of TC therapy is effective in a platinum-sensitive population [11]. Therefore, it may be reasonable to adopt a similar strategy in the treatment of endometrial cancer. In other words, it may not be logical to administer AP therapy as second-line chemotherapy in patients with platinum-sensitive recurrent endometrial cancer, despite equivalent efficacy and less toxicity of Tax-C therapy.

Tax-C therapy was significantly more effective than AP therapy in patients with platinum-resistant recurrence after adjuvant Tax-C therapy as a first-line treatment (median PFS and OS 3 vs. 7 and 10 vs. 23 months, respectively). However, the use of Tax-C therapy as second-line chemotherapy may be unjustified because the median PFS after Tax-C therapy was only 7 months, which cannot overcome the toxicities induced by combination chemotherapy. Additionally, there might have been a selection bias regarding the reuse of Tax-C therapy primarily in patients without residual tumors who had either previously responded to or been treated with this agent in an adjuvant therapy setting. These factors may have led to overestimation of the present study results. The administration of a single non-platinum

agent under the same conditions as those in patients with platinum-resistant recurrent ovarian cancer may be reasonable, although single therapy with doxorubicin may have minimal effectiveness, as mentioned above [6]. Therefore, the equivalency of Tax-C therapy versus single non-platinum agents should be further scrutinized.

This study has some limitations. First, we did not completely assess the impact of first-line chemotherapy regimens. The results of the present study suggested that Tax-C therapy followed by the reuse of Tax-C therapy resulted in improved survival compared with AP therapy followed by Tax-C therapy. However, as explained above, the superiority of Tax-C therapy followed by Tax-C therapy compared with that of AP therapy followed by Tax-C therapy likely resulted from the selection bias, because Tax-C therapy was reused only for patients without a residual tumor who had either previously responded to or been treated with this agent in an adjuvant therapy setting. Second, regarding platinum-resistant recurrence, we have no data of the use of non-platinum single therapies. Therefore, further retrospective and prospective studies to compare platinum combination therapy with non-platinum single therapy are required. Third, regarding platinum-sensitive recurrence, only 9 patients received AP therapy as second-line chemotherapy. Therefore, larger retrospective and prospective studies to confirm the non-inferiority of Tax-C therapy as second-line chemotherapy are warranted.

For the management of chemotherapy-naïve endometrial cancer patients, doxorubicin and cisplatin combination therapy with or without paclitaxel is considered the most effective regimen [12–14]. The triplet of cisplatin, doxorubicin, and paclitaxel (TAP therapy) was recently compared with TC therapy in a large phase III trial (GOG209 study) [15], which reported that PFS and OS following TC therapy were not inferior to PFS and OS following TAP therapy (HR 1.03 and 1.05; duration 13.5 vs. 13.3 and 40.3 vs. 36.5 months, respectively) at interim analysis. In addition, toxicity was preferable in TC therapy, which induced less sensory neuropathy. Thus, TC therapy is currently the most promising regimen in a first-line setting. Therefore, we propose that the superiority of the reuse of Tax-C therapy as second-line chemotherapy in patients with a history of Tax-C therapy as first-line chemotherapy is useful to develop a treatment strategy against recurrent endometrial cancer.

Our finding suggested that, as second-line chemotherapy, the utility of AP therapy is limited for patients with recurrent endometrial cancer after platinum-containing chemotherapy. Therefore, Tax-C therapy may be appropriate as second-line chemotherapy in such cases.

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Conflict of interest The authors declare that there are no conflicts of interest.

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