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A feasibility study of carboplatin and weekly paclitaxel combination chemotherapy in endometrial cancer: A Kansai Clinical Oncology Group study (KCOG0015 trial)

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ABSTRACT

Objectives. The optimal chemotherapy regimen for women with endometrial cancer has not been established. We assessed the feasibility, toxicity and clinical efficacy of combination triweekly carboplatin and weekly paclitaxel in women with endometrial cancer.

Methods. Eligible patients had histologically confirmed primary advanced or recurrent endometrial cancer (Group A), or had localized high-risk features (Group B). All were treated with paclitaxel 80 mg/m^2 (days 1, 8 and 15) and carboplatin AUC 5 (day 1) each 21-day cycle. A minimum of 3 cycles was planned; if 75% or more of patients were able to receive at least 3 cycles with acceptable toxicity, the regimen was declared "feasible."

Results. Forty patients were enrolled and administered 163 cycles of therapy; 38 (95%) were chemo-naive. No patients received radiation previously. Group A (measurable disease) contained 15 patients (5 with recurrent disease, 7 receiving neo-adjuvant chemotherapy, and 3 treated adjuvantly following suboptimal cytoreduction). Group B (non-measurable disease) contained 25 patients (primary stage I:10, II:5, III:8, IV:1 and relapse 1). Hematological toxicities(G3/G4) were neutropenia (31%/33%) and thrombocytopenia (6%/0%). Reversible G3 hypersensitivity (5%) and G2 cardiotoxicity (3%) was uncommon. Thirty-one patients (78%) completed ≥3 cycles (median 4, range: 1–9). Thirteen of 15 (87%) measurable patients responded (3CR, 10PR). Eighty-seven percent of measurable patients were not progressive at 6 months. In Group A, QOL scores were significantly improved after 3 cycles of chemotherapy ($p = 0.037$), and at the completion of chemotherapy ($p = 0.045$). QOL scores in Group B did not change during therapy.

Conclusions. This combination chemotherapy is feasible and effective for endometrial cancer patients.

Introduction

Endometrial cancer is among the common gynecologic malignancies in Japan, accounting for over 7000 new cases annually and, as documented in other developed countries, is increasing in incidence, now occurring in over 11/100,000 women [1]. Fortunately, most women diagnosed with this disease will be identified with organ-confined disease where long-term survival is expected. Nonetheless, observations from longitudinal clinical studies suggest even these good-prognosis patients may be stratified into cohorts of differential recurrence risks. For instance, advancing age, lymphovascular invasion, outer third myometrial invasion and high grade were factors identified in Gynecologic Oncology Group (GOG) Protocol 99 that increased the risk for recurrence. While just one-third of patients entered into that study met "high intermediated risk" criteria, they accounted for nearly two-thirds of the recurrences [2]. This has led investigators to evaluate strategies to reduce this risk, although an optimal regimen or intervention has not been standardized and is the focus of worldwide investigation.

Similarly, the standard treatment for advanced and recurrent patients with endometrial cancer is still evolving. Over the past 2 decades, methodical randomized clinical trials conducted in large part, but not limited to the GOG, have established the efficacy of doxorubicin, cisplatin and paclitaxel in single agent and combination regimens. Owing to concerns of observed toxicities, investigators have begun to evaluate alternatives to these agents. Several studies have shown that chemotherapy with paclitaxel and carboplatin in a 4-week regimen gives an excellent response rate (63–78%) with acceptable

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toxicity [3,4]. Weekly paclitaxel administration may broaden the therapeutic index further as this infusion schedule has been associated with a lower incidence of myelosuppression and neurotoxicity, with equivalent efficacy compared to every 3-week administration in patients with recurrent ovarian cancer [5]. Therefore we carried out a prospective study of weekly paclitaxel and every 3-week carboplatin in endometrial cancer patients to assess its feasibility, toxicity and preliminary efficacy.

Patients and method

Patient eligibility

Given the potential differential impact of this therapy in our treatment population, we defined two cohorts: Group A included patients with measurable and pathologically confirmed primary bulky FIGO (1988) Stage IIB–IV endometrial cancer or recurrent endometrial cancer; and Group B, which included and patients without measurable disease treated adjuvantly for the presence of high risk postoperative factors such as, G3 histology, lymphovascular space involvement, completely resected nodal disease, adnexal metastases or poor prognosis histological types such as serous, adenosquamous, clear cell, or undifferentiated cancer. Patients treated adjuvantly after complete surgical resection of recurrent tumor were also included in Group B. All eligible patients also (1) had an interval of 4 or more weeks after completion of the previous chemotherapy, if applicable; (2) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or less; (3) were aged 15 to 75 years; (4) had adequate end-organ function (neutrophil count $\geq$ 1000 mm^{-3}, platelet count $\geq$100,000 mm^{-3}, hemoglobin level $\geq$9 g/dl, AST/ALT less than or equal to twice normal, bilirubin level less than or equal to 2 mg/dl, serum creatinine level less than or equal to 1.5 mg/dl); (5) no other active malignancy; (6) a life expectancy of 3 months or more; and (7) provided written informed consent. This trial was reviewed and approved by the Protocol Review Committee of the Kansai Clinical Oncology Group (KCOG, KCOG0015 trial) and the Institutional Review Boards of each of the participating institutions.

Treatment schedule

Patients received paclitaxel 80 mg/m^2 on days 1, 8 and 15, and carboplatin AUC 5 day 1, each 21-day cycle. Paclitaxel was administered over 1-hour intravenously with standard premedication [6]. If a hypersensitive reaction did not occur in first cycle, we permitted a reduction in the dexamethasone dose to 8 mg at next cycle. Carboplatin dosing was calculated using the Calvert formula, estimating glomerular filtration rate (GFR) using the Jelliffe equation [7,8]. Patients were treated for a minimum of three cycles, unless this was precluded by unacceptable toxicity or rapid progression of disease. Patients treated adjuvantly were expected to receive at least 3 cycles.

Dose modification

Within a cycle, chemotherapy was delayed if the absolute neutrophil count was $<$1000 mm^{-3} and/or the platelet count was $<$50,000 mm^{-3} according to the blood count on the day of the scheduled treatment. Chemotherapy was resumed after confirmation of an absolute neutrophil count of $\geq$1000 mm^{-3} and a platelet count of $\geq$100,000 mm^{-3}, but the paclitaxel dose was reduced to half if there was grade 2 or greater neurotoxicity; subsequent courses were initiated if neurotoxicity recovered to grade 1 or less. Patients experiencing dose delays of 3 weeks or more due to hematologic or non-hematologic toxicity were removed from the study. Drugs to treat complications and/or adverse events were allowed, but prophylactic use of granulocyte colony stimulating factor (G-CSF) was prohibited.

Endpoints

The primary endpoint of this trial was feasibility, defined by the probability of receiving at least 3 cycles of protocol therapy without over 2-week treatment-delay or unacceptable toxicity. We defined the unacceptable toxicity as follows; (1) grade 4 neutropenia continued for 5 days, (2) febrile neutropenia, (3) grade 4 thrombocytopenia, (4) above grade 3 non-hematological toxicity (except of anorexia, nausea, vomiting and alopecia). For the purposes of this report, the treatment regimen was considered "feasible" if 75% or more of the treatment population could achieve this endpoint. Secondary endpoints included the antineoplastic effect of therapy (objective response rate for Group A), progression-free survival at 6 months and quality of life (QOL) assessment for patients obtained additional informed consent.

Clinical assessment

Baseline entry procedures included: a physical examination, electrocardiogram, chest x-ray, full blood count, biochemical profile, and abdominopelvic computed-tomography scan (CT) or magnetic resonance imaging (MRI). During chemotherapy, patients had a weekly physical examination, full blood count, biochemistry, and assessments of ECOG performance status. Efficacy (objective response rate, Group A) was assessed following every other cycle by CT or MRI. Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [9]. Best response to treatment was classified as complete response (CR) (no clinical and radiologic evidence of residual disease), partial response (PR) (30% decrease in the sum of the longest diameters of the target lesions), stable disease, and progression of disease (20% increase in the sum of the longest diameters of the target lesions). All responses were confirmed by an independent group extramural radiologists. Progression-free (PFS) and overall survival (OS) was calculated from the date of treatment initiation to the date of documented progression or death, respectively. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 3.0. Quality of life (QOL) was prospectively evaluated four times: before chemotherapy, after one and after three cycles of chemotherapy, and a month after the completion of chemotherapy, by use of the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire EORTC-QLQC30 [10].

Statistical design

This study was designed as a feasibility trial. The regimen was determined to be worthy of further study if the treatment was tolerated and if a majority (75%) of patients were able to finish chemotherapy without over 2-week treatment-delay and unacceptable toxicity [11]. We expected to observe 90% of the patients to finish three or more cycles of this regimen with acceptable toxicity. With a sample size of 40, the lower bound or the 95% confidence interval, 75%, would still be within the acceptable range. The Kaplan–Meier method [12] was used for statistical assessment of PFS and OS. Repeated measures of standardized QOL scores were analyzed statistically by paired *t* test using JMP6.0.3 (SAS Institute Inc. Cary, NC).

Results

Patient characteristics

A total of 40 patients were enrolled in this study from 13 collaborating institutions for two years from May, 2000 to May, 2002. Fifteen patients met Group A criteria; 25 patients met Group B criteria. All 15 patients in Group A were evaluable for response, and all

40 patients were evaluable for toxicity. The age, characteristics of each group, histology, prior therapy description, and ECOG PS are summarized in Table 1. Table 2 shows the FIGO stage of 34 patients enrolled with primary endometrial cancer. The FIGO stage of the 24 postoperative high risk patients who constituted major part of Group B were stage I ($N=10$), stage II ($N=5$) and stage IIIA–IV ($N=9$). Three patients in Group A with postoperative residual tumor were stage IIIC-IV. Neoadjuvant chemotherapy was administered to 7 patients (stage IIB–IV) considered to be at high operative risk or with extensive tumor burden.

Treatment administration

A total of 163 cycles of treatment were administered (median/patient, 4; range, 1–9). Thirty-six of 40 patients completed more than 3 cycles therapy (Table 3). The remaining four patients did not complete three courses for the following reasons: ventricular arrthymia (one patient), paclitaxel hypersensitivity reaction (two patients), and shift to operation due to CR response after two cycles of chemotherapy (one patient).

Toxicity

Grade 4 neutropenia was observed in the first cycle in 4 patients (11%), in the second cycle in five patients (14%), and in the third cycle in three patients (8%). Twenty-three patients (64%) had grade 3 or 4 neutropenia, but no patients had febrile neutropenia. G-CSF was used in 17 patients (43%) for the treatment of observed toxicity. Chemotherapy was delayed mainly due to neutropenia during the first 3 cycles in 17 patients (43%) (median delay, 8 days; range, 3–32). Grade 3 thrombocytopenia was seen in two patients (6%) and anemia in four patients (11%). Three patients received red blood cell transfusions for grade 3 anemia.

Non-hematological toxicity (Table 4) was mild; peripheral neuropathy was observed in 9 patients (22.5%), but that did not exceed grade 1. One patient experienced a grade 2 ventricular arrythmia, and two other chemo-naïve patients experienced grade 3 hypersensitivity reactions to paclitaxel. These patients were removed from the study as outlined in the protocol. Treatment-related death did not occur.

Table 1
Patient characters ($n=40$).

Age (years)	30–70 (median 53)
Group A (measurable disease: $n=15$)	
Primary post-operative residual tumor	3
Primary neo-adjuvant	7
Recurrence	5
Group B (non-measurable disease: $n=25$)	
Primary post-operative high risk	24
After complete resection of recurrent tumor	1[a]
Histology	
Endometrioid adenocarcinoma	35
Adenosquamous carcinoma	4
Papillary serous adenocarcinoma	1
Prior chemo- and/or radiation therapy	
Naïve	38
Chemotherapy	2
Radiation	0
Performance status	
0	26
1	13
2	1

Data are years old or *n*.
[a] This patient underwent complete resection of recurrent disease in the abdominal wall fascia and sigmoid colon submucosa.

Table 2
FIGO stage (1988 criteria) of 34 primary (non-recurrent) patients[a].

		Postoperative high risk	Postoperative residual tumor	Neoadjuvant
Stage	IB	5		
	IC	5		
	IIA	4		
	IIB	1		1
	IIIA	2[b]		2[c]
	IIIB			1
	IIIC	6	1	1
	IV	1	2	2
Total		24	3	7

Data are *n*.
[a] Six recurrent patients are excluded from this table.
[b] Both cases of stage IIIA in postoperative high risk group were diagnosed by positive peritoneal cytology. But histological type of a case of them was serous papillary adenocarcinoma.
[c] Both cases of stage IIIA in neoadjuvant chemotherapy group showed adnexal invasion assessed by CT/MRI.

Response and survival

Fifteen patients in Group A were evaluable for response. CR was observed in three patients (20%) and PR in 10 patients (66.7%), yielding an overall response rate of 86.7% (95% confidence interval, 62.1–92.3%). In addition, SD was observed in 2 patients. 87% of patients in Group A were not progressive, and no patients in Group B relapsed at 6 months. The initial feasibility analysis was done in October, 2003, but these results have not been published. Because considerable time passed from initial analysis, we added the follow up survival data. Follow up survival analysis for all 40 patients was performed in March 2010 after a median follow-up of 95 months (range: 18–116 months). Median progression-free survival was 47+ months (range, 5–116+) and overall survival, 97+ months (range, 9–116+). In Group B, four patients relapsed, and three of those died after a median follow-up of 95 months. A stage IIIC patient relapsed with a localized lung metastasis after 27 months; this was completely resected. A stage IIIA patient with serous papillary adenocarcinoma, a stage IIIC patient and a stage IV patient with omental metastasis relapsed at 35, 23, 95 months and died at 36, 43, 96 months after primary treatment, respectively. When survival analysis was performed, 21 patients (84%) in Group B were alive with no evidence of disease.

Quality of life

Quality of life (QOL) data were obtained for 18 patients (10 patients in Group A, 8 patients in Group B) agreed this accompanying study, and consisted of 54 assessments. The QOL data were transponded to a 0–100 linear scale by setting the best QOL score to 100 and the worst QOL score to 0. Every answer on the EORTC-QLQ C30 was transported to a 0–100 linear scale, and the total of 30 answers was also transported to a 0–100. We assessed QOL four times: before chemotherapy, after one cycle of chemotherapy, after 3 cycles of chemotherapy, and a month after the

Table 3
Number of completed chemotherapy cycles.

Number of chemotherapy cycles	1	2	3	4	5	6	7	8	9	median
Group A										
Postoperative residual tumor ($n=3$)				1		1			1	6
Neoadjuvant ($n=7$)		1	1	1	2	1	2			5
Recurrence (measurable) ($n=5$)					2	1		1	1	4
Group B										
Postoperative high risk ($n=24$)	3		10	5	1	5				3
Secondary postoperative high risk ($n=1$)						1				4

Data are *n*.

Table 4
Non-hematological toxicity.

	Grade 1	Grade 2	Grade 3
Hypersensitivity			2
Ventricular arrhythmia		1	
Peripheral neuropathy	9		
Nausea/vomiting	7	4	
Alopecia	6	18	
Liver dysfunction	3		
Taste disturbance	1		

Data are *n*.

completion of chemotherapy. The means (± SEM) of QOL scores in each Group A and Group B were 66.1 (±6.4), 81.5 (±3.5) before chemotherapy, 74.0 (±4.7), 82.4 (±3.3) after one cycle of chemotherapy, 82.1 (±4.3), 85.2 (±4.9) after 3 cycles of chemotherapy and 82.9 (±4.6), 84.0 (±3.0) after the completion of chemotherapy, respectively. Fig. 1 summarizes the baseline and change in QOL scores during therapy. In Group A, QOL scores were significantly improved after 3 cycles of chemotherapy ($p=0.037$), and after the completion of chemotherapy ($p=0.045$). In general, upward trend values parallel early and sustained clinical response. However, Group B, QOL scores did not change during therapy. These results support our observation that the regimen was well tolerated with little impact on global QOL.

Discussion

The primary objective of this study was to describe the feasibility of administering a dose-dense and dose-intense paclitaxel combination with every 3-week carboplatin in women with endometrial cancer. We defined feasibility as the likelihood to receive at least 3 intended cycles of therapy with acceptable toxicity and within 2-week treatment-delay [11]. The eligibility criteria were broad and included women with primary disease harboring high-risk post-operative local–regional factors implicating a need for systemic therapy, women with advanced stage disease felt unamenable to primary extirpation, women with subtotally resected metastatic disease, and women with recurrent disease. In this mixed population, 78% of patients received at least first 3 cycles of therapy with acceptable toxicity and within 2-week treatment-delay. Despite this observation, 17 patients (43%) ultimately required a delay in treatment (median 8 days) with prolonged exposure. We recognize the lack of prior exposure to, or concomitant use of abdomino-pelvic radiation in our patients may overstate treatment feasibility, particularly in these populations of patients. In light of this we recommend caution in making generalized conclusions of safety.

We also observed significant clinical activity with overall response rate in measurable disease patients of 86.7% (13/15). While interest in dose-dense paclitaxel and carboplatin for endometrial cancer patients is high due to it manageable side-effect profile, this report confirms the tolerability observed in a limited number of previous reported trials in endometrial cancer patients [13–15]. One of the most trouble side-effect of paclitaxel is neuropathy. Actually, the present incidence of peripheral neuropathy was 22.5%, but that did not exceed grade 1. Then the hematological toxicity was moderate and controllable. These favorable profiles are familiar to patients; it may reflect the fact that the median treatment was 4 cycles and no patients received radiation previously. In addition, QOL measures confirm the tolerability and activity of this regimen in women who participated in this aspect of the study. In Group A (measurable disease patients), QOL scores were significantly improved after 3 cycles of chemotherapy ($p=0.037$), and after the completion of chemotherapy ($p=0.045$) compared with baseline before chemotherapy. We suspect that overall status was improved by tumor reduction or disappearance, particularly in light of the high overall response rate (86.7%) and acceptable toxicity profile. Significant improvements in QOL were not found in patients receiving postoperative adjuvant chemotherapy (Group B). However, QOL scores did not fall during chemotherapy in this cohort. On the other hand, these QOL results are analyzed by the data of only 18 patients obtained additional consent, and it is necessary to treat carefully whether these results represent other 22 cases.

Several cytotoxic agents have shown promise in endometrial cancer. Response rates above 20% in previously reported single-agent phase II studies include doxorubicin (37%) [16], epirubicin (26%) [17], cisplatin (20%) [18], carboplatin (30%) [19] and paclitaxel (37%) [20]. In general, combination strategies have produced higher response rates, and in some cases better PFS and OS, but at the expense of higher toxicity. For instance, GOG-107 compared doxorubicin to doxorubicin plus cisplatin (AP) in patients with measurable, advanced stage or recurrent endometrial cancer. In this study, response rate and PFS for the combination was superior (42% vs 25%, $p=0.004$; 5.7 months vs 3.8 mos, $p=0.014$); however, no difference in OS was observed and AP was associated with higher degree and more frequent hematological and non-hematological toxicity [21]. Similarly, GOG 177, comparing TAP (paclitaxel, doxorubicin, cisplatin, G-CSF) to AP demonstrated higher objective response (57% vs 34%; $p<0.01$), PFS (8.3 vs 5.3 months; $p<0.01$), and, for the first time OS (15.3 vs 12.3 months; $p=0.037$); however neurologic toxicity was substantially worse in the beginning after just two cycles of therapy [22].

The GOG is comparing TAP to paclitaxel and carboplatin (every 21 days, bolus infusion) in this same cohort of patients (GOG 209). The latter regimen has been evaluated by others and been found to have promising clinical activity. Hidaka and colleagues compared patients receiving cisplatin, adriamycin and cyclophosphamide to paclitaxel and carboplatin [23]. They demonstrated in this small retrospective study a response rate of 78%, which favorably compared

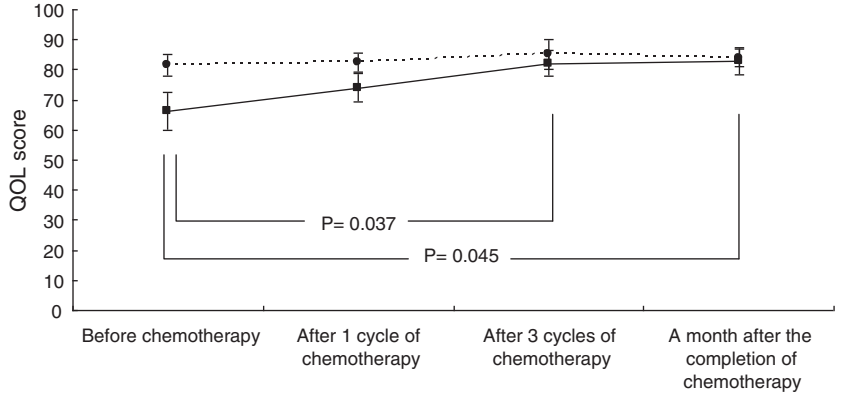

Fig. 1. Quality of life (QOL) scores obtained at baseline (pretreatment) and 3 subsequent timepoints. The solid line represents mean score (± SEM) of patients in Group A; the dashed line, similar for Group B patients.

with their previous standard, but with a better toxicity profile. Similarly, Sovak and colleagues reported on the efficacy of paclitaxel and carboplatin administered adjuvantly to 48 optimally cytoreduced stages III and IV endometrial cancer patients [24]. Overall, 90% of the patients received 6 planned cycles of therapy every 3 to 4 weeks. At a median follow-up of 20 months, 29 had recurred giving a median progression-free interval of 13 months and a median overall survival of 47 months. The investigators concluded the regimen was active and well tolerated and should be studied further.

A few previous reports of weekly paclitaxel and carboplatin have recently been reported for patients with endometrial cancer [13–15]. Secord and colleagues treated 13 advanced or recurrent endometrial cancer patients with paclitaxel (80 mg/m^2) and carboplatin (AUC 2) on days 1, 8 and 15 of each 28-day cycle [13]. They observed 62% overall response rate and low incidence of grade 3 or 4 hematologic toxicity (21% neutropenia, 7% thrombocytopenia). They concluded this regimen had antitumor activity with acceptable toxicity. Tabata and colleagues treated 14 ovarian cancer patients and 11 endometrial cancer patients with venous thrombosis [14]. They used paclitaxel (80 mg/m^2) and carboplatin (AUC 2) on days 1, 8 and 15 of each 21-day cycle. They observed grade 3 or 4 neutropenia and peripheral neuropathy in 26% and 4%, respectively. They concluded this regimen was a reasonable treatment option for gynecologic cancer patients with venous thrombosis. Vandenput and colleagues treated 42 advanced or recurrent endometrial cancer patients [15]. Their regimen was paclitaxel (90 mg/m^2) and carboplatin (AUC 4) on days 1 and 8 of each 21-day cycle. Overall response rate was 71% (20/28) in chemotherapy-naïve patients. This regimen, marked by a higher treatment day dose of paclitaxel, but with a lower dose intensity (60 mg/m^2/week), frequently required dose and administration modifications due to grade 3 or 4 hematologic toxicities. All our trial regimens compare favorably with these reports, both in efficacy and toxicity.

There has been renewed interest in dose-dense and dose-intense chemotherapy strategies in gynecologic malignancies following the recent report of weekly paclitaxel and bolus carboplatin in ovarian cancer patients. In this randomized phase III clinical study of previously untreated primary stages II–IV ovarian cancer patients, Katsumata and colleagues demonstrated an improved progression free survival and overall survival relative to conventional paclitaxel (180 mg/m^2) and carboplatin (AUC = 6) [25]. Their experimental regimen (weekly paclitaxel 80 mg/m^2 and carboplatin AUC = 6 every 3 weeks, 21-day schedule) was resemble that used in the current study. Although confirmatory larger trials are needed, this regimen appears promising for endometrial cancer.

Finally, emerging data from biologically targeted therapy may provide an additional avenue of drug development in this disease. Indeed, Aghajanian and colleagues [26] recently reported that bevacizumab had single agent activity (response rate of 15.1%) in recurrent or persistent endometrial cancer patients. Similarly, several agents targeting the PI3K-AKT-mTOR pathway are relevant in this disease and actively being investigated. Combinatorial approaches of dose-dense/dose-intense chemotherapeutic backbones with anti-angiogenic agents have entered the clinical domain in ovarian cancer and, it may be anticipated the strategy to be of great interest in endometrial cancer as well.

Conclusion

A regimen of triweekly carboplatin and weekly paclitaxel appears to be an active and feasible regimen for endometrial cancer, which can be delivered with acceptable patient compliance. The efficacy of this regimen should be confirmed by further study.

Conflict of interest statement
None of the authors has a potential conflict of interest relevant to the material presented in this article.

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