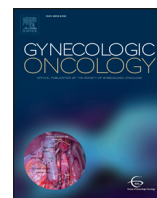




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Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: A study in 108 patients by the Belgian Gynaecological Oncology Group

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HIGHLIGHTS

- A prospective study examines the addition of prophylactic G-CSF (filgrastim) to a weekly paclitaxel/carboplatin regimen in patients with gynecologic cancers.
- Treatment is effective with acceptable toxicity in patients with platinum-resistant or platinum-refractory ovarian, advanced or recurrent endometrial and cervical carcinoma.
- The incidence of grade 3–4 neutropenia is lower compared with earlier studies without routine use of prophylactic G-CSF.

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ABSTRACT

Objective. To investigate the addition of prophylactic G-CSF to each weekly paclitaxel/carboplatin course in patients with recurrent platinum-resistant ovarian (OC), or recurrent or advanced endometrial (EC) or cervical carcinoma (CC).

Methods. 108 patients were enrolled i.e. 36 in each cohort. Eighteen courses of paclitaxel (60 mg/m²) and carboplatin (AUC 2.7) were administered weekly. G-CSF (filgrastim) was given to all patients on day 5 (and if needed on day 6).

Results. For patients with OC, 91% had platinum-resistant and 9% platinum-refractory disease. Median number of prior chemotherapy lines was 3 for OC, 1 for EC, and 1 for CC. Grade 3–4 neutropenia was observed in 34% of patients (95% CI: 26%–44%, $P < 0.0001$) (OC 29%, EC 36%, CC 38%). This is lower compared to historical data in all cohorts (84%). Confirmed sepsis was observed in 5%, grade 3–4 thrombocytopenia in 41%, grade 2–3 peripheral neuropathy in 17% of patients. In 71% of patients dose was delayed. Dose reduction was necessary for carboplatin in 47% and paclitaxel in 18% of patients. ORR was 51% (OC 48%, EC 45%, CC 58%). Median (95% CI) PFS and OS was 7.1 (5.1–8.1) and 12.7 (10.2–16.3) months, respectively (OC 7 and 13, EC 6 and 19, CC 6 and 14).

Conclusion. Weekly paclitaxel/carboplatin with G-CSF is an effective treatment with acceptable toxicity in patients with platinum-resistant or platinum-refractory OC, advanced or recurrent EC and CC. The incidence of

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grade 3–4 neutropenia is lower with the addition of weekly G-CSF compared with earlier studies without routine use of prophylactic G-CSF.

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1. Introduction

Three-weekly paclitaxel/carboplatin is considered the standard first-line chemotherapy for patients with ovarian cancer [1]. The addition of a third cytotoxic drug to three-weekly paclitaxel/carboplatin did not improve PFS or OS in first line [2]. Only recent results showed that adding the vascular endothelial growth factor (VEGF) inhibitor bevacizumab improved median PFS with 1.5–3.8 months [3,4]. Another approach to increase antitumor activity and prolong survival is by increasing the dose per cycle or by reducing the time-interval between dose administrations. This has been termed dose-dense therapy [5]. The use of weekly paclitaxel in combination with three-weekly carboplatin has been recently shown to be superior as first-line therapy in a randomized phase III study of the Japanese Gynecologic Oncology Group (JGOG) [6,7]. Three other multicenter randomized phase III studies investigating paclitaxel/carboplatin regimen as first-line treatment for ovarian cancer in European patients have been recently published [8,9]. Van der Burg et al. could not find a benefit in terms of ORR, PFS or OS for a weekly dose-dense paclitaxel/cis or carboplatin regimen nor for extended chemotherapy [8]. The survival results correspond to those of the MITO-7 study [9]. Neurotoxicity was increased while the weekly regimen in the MITO-7 study was associated with fewer toxic effects and better quality of life [9]. A third study was recently reported by the Gynecologic Oncology Group (GOG262) [10] and showed that dose dense paclitaxel with 3-weekly carboplatin did not improve progression-free survival in first-line therapy of ovarian cancer. However, in a stratified analysis, weekly dose dense paclitaxel was associated with a 4 month improvement in PFS compared to every 3 week treatment in those who opted not to receive bevacizumab (unpublished results). Several studies have shown the promising activity of dose-dense or weekly paclitaxel/carboplatin in recurrent, even platinum-resistant ovarian carcinoma [11–15], endometrial carcinoma [16,17] and cervical cancer [18]. The majority of the dose-dense regimens have been associated with a high rate of dose reductions, grade 3–4 neutropenia and neutropenic fever. The dosages used per week in the Leuven weekly dose regimen (paclitaxel 60 mg/m², carboplatin area under the plasma concentration-time curve (AUC) 2.7) are higher than the most studies using dose-dense paclitaxel/carboplatin in ovarian cancer. However they were also associated with neutropenia. In this study we investigated the use of prophylactic G-CSF (filgrastim) on day 5 (and if needed on day 6) of each weekly paclitaxel/carboplatin course in patients with recurrent platinum-resistant ovarian, or advanced or recurrent endometrial or cervical carcinoma.

2. Patients and methods

2.1. Patient eligibility

In this prospective study 108 patients were needed to detect a 15% reduction in the occurrence of grade 3–4 neutropenia ($\alpha:0.05$; $\beta:0.95$) compared with the historical incidence of 84% by using prophylactic filgrastim on day 5 of each of the 18 weeks [11,16]. The patients were equally recruited over all cohorts i.e. 36 for OC, EC and CC. Eligibility criteria included > 18 years of age, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , adequate bone marrow function, represented by an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, hemoglobin ≥ 9 g/dL (5.6 mmol/L) and platelets $\geq 100 \times 10^9/L$. They were required to exhibit adequate renal function, in accordance with a calculated creatinine clearance (Cockcroft) ≥ 30 mL/min. Moreover, participants had to demonstrate an adequate hepatic function, as evidenced

by total bilirubin concentrations $\leq 1.5 \times$ the upper normal limit and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ the upper normal limit. The first cohort included patients with histologically confirmed diagnosis of invasive epithelial ovarian, fallopian tube, or peritoneal carcinoma. Patients with at least one earlier platinum treatment could be included in this cohort but they had to be platinum-refractory or platinum-resistant. Patients experiencing progression within 28 days after the last dose of platinum were defined as platinum-refractory. Patients experiencing progression within 6 months after the last dose of platinum were defined as platinum-resistant. Earlier weekly or dose-dense regimens with paclitaxel and carboplatin were not allowed in this cohort while consolidation after the last platinum dose with non-platinum containing chemotherapy or molecular targeted drugs was allowed. Disease should be measurable by Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria [19] or serum cancer antigen 125 (CA125) measurements of progression using the Gynecological Cancer Intergroup (GCIG) criteria [20,21].

Patients with recurrent or advanced endometrial cancer could be included in the endometrial cancer cohort. Patients with recurrent or advanced cervical carcinoma could be included in the cervical cancer cohort. Earlier platinum therapy was allowed in these 2 last cohorts but earlier weekly or dose-dense regimens with paclitaxel and carboplatin were not allowed. Disease should be measurable by RECIST version 1.1 criteria. All patients must sign an informed consent prior to performance of study specific procedures or assessments, and must be willing to comply with treatment and follow-up.

Baseline computed tomography/magnetic resonance imaging (CT/MRI) of the abdomen and pelvis (and if applicable CT thorax) was carried out within 4 weeks prior to enrolment. Blood samples for evaluation of hemoglobin, white blood cells, neutrophils and thrombocytes were taken prior to the start of therapy, before each treatment and within 4 weeks after the last treatment. Blood samples for the evaluation of biochemistry including CA125, total bilirubin, AST, ALT, Gamma GT, creatinine clearance (calculated according to Cockcroft) were taken prior to the start of therapy, after every three cycles and within 4 weeks after the last treatment.

2.2. Treatment plan and dose medication

Patients received on day 1 of each 7-day cycle, with a maximum of 18 cycles, intravenous paclitaxel at a dose of 60 mg/m² and carboplatin at an AUC of 2.7 with dose calculated according to the Cockcroft formula. The regimen was given on an outpatient basis. Premedication with oral antihistamines (10 mg of cetirizine hydrochloride) and oral steroids (10 mg of dexamethasone) and H₂ antagonist (or equivalent) was given 12 h and 3 h prior to paclitaxel infusion. Paclitaxel (60 mg/m²) was given as a 1 hour intravenous infusion in 250 mL NaCl 0.9% followed by carboplatin, dissolved in 500 ml glucose 5% (adjusted to NaCl 0.9% when needed) was given intravenously over 60 min following the administration of paclitaxel. Filgrastim (Neupogen®) 30 Mio U (0.600 mg/mL) was given to all patients on day 5 of each course in patients weighing less than 60 kg and filgrastim (Neupogen®), 48 Mio 0.5 mL (0.960 mg/mL) to patients of 60 kg or more. The courses were repeated 18 times weekly, except for course 10, which was given 2 weeks after course 9. Imaging (CT) was performed during week 10. The mean dosage per week, taking reductions and delays into account, was for paclitaxel 52 mg/m² and for carboplatin 2.3 AUC.

Dose adjustments and delayed administration were based on bone marrow toxicity. The full dose of carboplatin and paclitaxel was given without delay when on day 8 the absolute neutrophil count (ANC)

was $0.5 \times 10^9/L$ or more and the platelet count was $50 \times 10^9/L$ or more. When ANC was lower than $0.5 \times 10^9/L$ on day 8 without a history of fever, the dose was delayed until ANC was $0.5 \times 10^9/L$ or more and paclitaxel and carboplatin are given in the same dose with filgrastim on days 5 and 6. When ANC was lower than $0.5 \times 10^9/L$ on day 8 without a history of fever but with former course with filgrastim on days 5 and 6, the dose was delayed until ANC was $0.5 \times 10^9/L$ or more. Then a reduced dose of paclitaxel 40 mg/m^2 and carboplatin AUC 2.0 was given with filgrastim on days 5 and 6. Chemotherapy was not re-escalated. When there was a history of neutropenic fever during the study (STEP A), also a reduced dose of paclitaxel 40 mg/m^2 and carboplatin AUC 2.0 was given together with filgrastim on days 5 and 6. When there was a history of neutropenic fever during the study after STEP A, the study is terminated. When platelet count was lower than $50 \times 10^9/L$ (STEP B) on day 8 and the number of neutrophils was sufficient, the dose was delayed until platelet count was $50 \times 10^9/L$ or more and paclitaxel 60 mg/m^2 and carboplatin AUC 2.0 were administered. The study was terminated when the patient was not recovered after 21 days. The study was also stopped when a patient experienced peripheral neuropathy grade 3. Erythropoietin and intravenous iron therapy was started according to the discretion of the investigator.

2.3. Assessment of response, progression-free and overall survival

Tumor response to therapy was evaluated with clinical examination, on imaging (CT/MRI abdomen and pelvis (and if applicable CT thorax)) and by CA125. Response evaluation was assessed according to the Evaluation Criteria In Solid Tumors (RECIST) criteria [19] and Gynecological Cancer Intergroup (GICG) criteria [20,21]. Scans for response assessment to therapy were evaluated at visit 10, at the end of treatment and every 3 months until progression thereafter.

At the end of treatment, the rates of Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD) were calculated. The response rate (CR + PR) was presented with a 95% confidence interval (95% CI). If response was confirmed by a following assessment of response while on the regimen or in the follow-up period, the term “confirmed” was added to the obtained result. 1-year and 5-year PFS and OS rates were calculated and survival curves were generated using the Kaplan–Meier methodology. All analyses are complete case analyses and were performed using SAS software version 9.3 (SAS Institute Inc, Cary, NC, USA). PFS was defined as the time between the start of treatment and assessment of PD or death. Patients without any of both events were censored at the date of the last scan. OS was defined as the time between the start of treatment and death. Patients alive were censored at the last follow-up date. Follow-up procedures consisting of general and gynecological examination were performed every 3 months in the first 2 years after termination of treatment and every 6 months in year 3 to 5.

2.4. Assessment of toxicity

Toxicity grading was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). For the entire patient population and per cohort, the proportion of patients with grade 3–4 neutropenia was calculated and a 95% CI was constructed based on Wilson's method. The occurrence of grade 3–4 neutropenia during weekly paclitaxel/carboplatin without prophylactic G-CSF for the treatment of ovarian, endometrial and cervical cancer has been reported in previous studies to be 84% [11, 16]. If the upper 95% CI limit is lower than 84%, we can conclude that the occurrence of grade 3–4 neutropenia is lower compared to historical data. The binomial test was used for comparing proportions to historical data.

2.5. Primary and secondary endpoints

The primary endpoint of the study was the occurrence of grade 3–4 neutropenia. The incidence resulting from this study was compared with historical data. The secondary endpoints of the study were the occurrence of grade 3–4 neutropenia per cohort, other toxicities, dose reductions and delays, PFS, ORR and OS.

2.6. Study conduct

This study was performed according to the ENGOT model C [22].

3. Results

3.1. Patients' characteristics

In this prospective phase II study 108 patients with histologically confirmed recurrent ovarian, endometrial and cervical cancer (each cohort 36 patients) were enrolled at 12 Belgian and Luxemburg Gynecological Oncology Group (BGOG) centers between February 20, 2012 and March 14, 2013. Six patients were excluded from the analyses due to a lack of data or scarce data resulting in 102 patients eligible for toxicity and survival evaluation. Baseline characteristics of the patients included for analyses are listed in Table 1. The median age of the evaluable patients was 61 years (range 51–70 years). The median number of prior chemotherapy lines was 3 for ovarian, 1 for endometrial and 1 for cervical cancer. The majority of patients had ECOG performance score 1 or 2 (63.7%). In total, 32 patients (31.4%) had serous histological subtype, 20 patients (19.6%) had adenocarcinoma and another 20 patients (19.6%) had squamous histological subtype. For patients with ovarian cancer, 91.4% had platinum-resistant disease and 8.6% had platinum-refractory disease.

3.2. Toxicity

In 71% of the patients, there was a delay of at least one treatment with a median delay of 2 weeks (63% for OC, 70% for EC, and 79% for CC). Dose reduction was necessary for carboplatin in 47% and for paclitaxel in 18% of patients (mean dose/week taking reductions and delays into account, respectively AUC 2.3 and 52 mg/m^2). The main reason for dose delay and carboplatin dose reduction was thrombocytopenia (46% and 68%, respectively). The incidence of grade 3–4 neutropenia is presented in Table 2. The proportion of patients with grade 3–4 neutropenia in the entire patient population was 34% (95% CI: 26%–44%, $P < 0.0001$). Binomial tests show that this is lower compared to historical data in all cohorts (84%). Grade 4 neutropenia occurred in 15% of patients. The incidence of grade 3–4 neutropenia per cohort was for OC 29%, EC 36% and CC 38%. The incidence of other relevant toxicities displayed by grade 3–4 neutropenia is presented in Table 3. The most frequent grade 3–4 hematological side effect was anemia in 40 patients (39%). Mild anemia (grades 1–2) was present in 47 patients (46%). The incidence of sepsis, confirmed with positive hemoculture was 5%. Grade 3–4 thrombocytopenia occurred in 41% and 13% of patients experienced grade 4 thrombocytopenia. The incidence of grade 2–3 peripheral neuropathy was 17%. One patient (1%) experienced an episode of grade 4 neutropenic fever without sepsis. No grade 3–4 alopecia was reported.

Information on blood transfusion is available on 98 patients. Ten patients (10.2%) required platelet transfusion (OC 3%, EC 9%, CC 19%) and 70 (71%) patients required a red blood cell transfusion (OC 64%, EC 70%, CC 81%). Erythropoietin was administered in 24.5% of patients (OC 27%, EC 9%, CC 38%). Fatigue, nausea, vomiting and diarrhea were the most frequent non-hematological side effects. Fatigue was the most frequent grade 3–4 non-hematological side effect recorded in 13 patients (13%). None of the patients experienced grade 3–4 nausea and vomiting and 5 patients (5%) developed grade 3–4 diarrhea. Peripheral neuropathy grade 4 was not observed. Eight patients developed allergic reactions

Table 1
Patient characteristics.

Variable	Diagnosis age median (IQR)	Prior lines median (IQR)	ECOG 0 n/N (%)	ECOG 1–2 n/N (%)	Main histological subtype at initial diagnosis
Ovary	63.0 (54.9–71.3)	3.0 (2.0–4.0)	7/35 (20%)	28/35 (80%)	Serous 65.7%
Endometrium	66.5 (62.1–75.6)	1.0 (0.0–2.0)	11/33 (33.3%)	22/33 (66.6%)	Endometrioid 39.4%
Cervix	49.3 (44.5–56.9)	1.0 (0.0–1.0)	19/34 (55.9%)	15/34 (44.1%)	Squamous 55.9%
Total	60.9 (51.3–70.4)	1.0 (0.0–3.0)	37/102 (36.3%)	65/102 (63.7%)	Serous 31.4%

to carboplatin and an adjusted infusion scheme was given in the following courses without any problems [23].

3.3. Assessment of response, progression-free and overall survival

The weekly paclitaxel/carboplatin regimen was used in 27%, 27%, 18%, 16% and 13% as first, second, third, fourth, and fifth chemotherapy lines or higher, respectively. Nine patients (9%) were excluded for the response analysis because the overall response was not evaluable resulting in 93 evaluable patients. ORR according to RECIST criteria was 51%. Four (4%) and 43 (46%) patients achieved CR and PR, respectively. Twenty-nine (31%) patients had SD and 17 (18%) patients developed PD on treatment. The observed rates of CR, PR (confirmed/unconfirmed) were as follows: 3 (3%) CR confirmed, 23 (25%) PR confirmed, 1 (1%) CR unconfirmed and 20 (22%) PR unconfirmed. The ORR for the group with ovarian cancer, endometrial cancer and cervical cancer was 48.4%, 44.8% and 57.6%, respectively. The confirmed RR for the group with OC, EC and CC was 29.0%, 20.7% and 33.3%, respectively.

For the total study population, median PFS was 7.1 (95% CI 5.1–8.1) and OS was 12.7 months (95% CI 10.2–16.3). At study closure, 21% patients were still alive without disease progression and 58% were deceased. ORR, median PFS and OS per cohort and number of chemotherapy lines are shown in Table 4. Median PFS and OS per cohort are presented in Figs. 1 and 2.

4. Discussion

Neutropenia and anemia were the most frequent bone marrow related side effects with the weekly paclitaxel/carboplatin regimen. As primary endpoint of this study we used the incidence of grade 3–4 neutropenia in comparison with historical controls. Although this adverse event does not always affect the patients clinically, we used this endpoint as a surrogate of the clinically more important incidence of neutropenic fever. The current study showed that the use of prophylactic G-CSF resulted in less grade 3–4 neutropenia, but no reduction of neutropenic fever was observed.

In the present study, the toxicity profile of the weekly paclitaxel/carboplatin regimen (60 mg/m², AUC 2.7) in combination with prophylactic G-CSF was acceptable with 35 of 102 (34%) patients with gynecological cancers suffering from grade 3–4 neutropenia. This was lower than it is in other studies investigating a paclitaxel/carboplatin regimen without the routine use of G-CSF not only in ovarian cancer (67%) [11, 12] but also in endometrial cancer (90%) [16] and cervical cancer (95%) [18].

First, we focus on recent studies investigating paclitaxel/carboplatin regimens in recurrent ovarian cancer and including platinum-resistant patients. Cadron et al. (2013) investigated the same weekly paclitaxel/

carboplatin regimen (60 mg/m²/AUC 2.7) as in our study for 18 cycles in 63 heavily pretreated patients with recurrent ovarian cancer. Forty-three patients were platinum-resistant. RR for platinum-resistant patients was 37% which was lower than the RR for the OC group (48%) in our study. Median PFS and OS for the platinum-resistant group were comparable with the median PFS (6 vs. 7.5 months) and OS (9 vs. 12.7) for the OC group in our study. The incidence of grade 3–4 neutropenia and neutropenic fever was 67% and 6% of patients, respectively. The frequency of these toxicities in our study was lower i.e. 34% and 1%. The grade 3–4 neutropenia in the OC group was 29%. The authors showed grade 3–4 anemia and grade 3–4 thrombocytopenia in 40% and 35% of patients, respectively which is comparable in our study i.e. 39% and 41%. None of the patients experienced grade 3–4 peripheral sensory neuropathy while it was observed in 3% of patients in our study. In the study of Cadron et al. prophylactic G-CSF was given in only 22% of patients after an episode of persistent neutropenia [12].

Four studies including platinum-resistant patients with recurrent ovarian cancer investigated a paclitaxel/carboplatin regimen and used a different regimen than in our study [11,13–15]. Cadron et al. administered paclitaxel/carboplatin (90 mg/m² and AUC 4) on days 1 and 8, every 3 weeks for 6 cycles. Nine patients were platinum-resistant. For platinum-resistant patients, RR was 38%, median PFS and OS was 6.8 and 8 months, respectively. The incidence of grade 3–4 neutropenia was 94%. Neutropenic fever was observed in 5 patients. Of these patients, 3 received antibiotics and G-CSF. G-CSF was preventively prescribed in 41% of patients. Seven patients experienced grade 3 and one patient grade 4 thrombocytopenia [11]. Sharma et al. investigated 20 platinum-resistant/refractory patients receiving paclitaxel/carboplatin (70 mg/m² and AUC 3) on days 1, 8, and 15, q 4 weekly for 6 planned cycles. RR was 60%. Median PFS and OS were 7.9 and 13.3 months, respectively. Six patients (29%) experienced grade 3 neutropenia and one patient experienced grade 4 neutropenia. No grade 3–4 thrombocytopenia was reported. One patient experienced grade 3 anemia. They dose delayed patients rather than to administer G-CSF. Only three patients received G-CSF (14%) [13]. Van der Burg et al. administered six cycles weekly paclitaxel/carboplatin followed by six 3-weekly cycles in platinum-resistant (43 patients) and platinum-sensitive patients (n = 65) who were previously treated with 3-weekly paclitaxel/carboplatin. For platinum-resistant patients, RR was 58%, median PFS and OS was 8 and 15 months, respectively. Grade 3–4 toxicity included: thrombocytopenia 8%, neutropenia 30%, and neutropenic fever 0.5% [14]. Shawky et al. investigated weekly paclitaxel/carboplatin (80 mg/m², AUC 2), on days 1, 8 and 15 of a 28-day cycle for six planned cycles in platinum-resistant and platinum-sensitive patients previously treated with 3 weekly paclitaxel/carboplatin. For platinum-resistant patients (9

Table 3
Incidence of other toxicities displayed by grade.

Event	Grade 1		Grade 2		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
Anemia	4	3.9	43	42.2	36	35.3	4	3.9
Neutropenia	7	6.9	17	16.7	20	19.6	15	14.7
Febrile neutropenia	0	0.0	0	0.0	0	0.0	1	1.0
Thrombocytopenia	10	9.8	12	11.8	29	28.4	13	12.7
Peripheral neuropathy	22	21.5	14	13.7	3	2.9	0	0.0
Sepsis unconfirmed	–	–	–	–	–	–	8	7.8
Sepsis confirmed	–	–	–	–	–	–	5	4.9

Table 2
Incidence of grade 3–4 neutropenia.

Neutropenia grade 3–4	n/N	Incidence (95% CI)	P-value*
Ovary	10/35	29% (16–45%)	<0.0001
Endometrium	12/33	36% (22–53%)	<0.0001
Cervix	13/24	38% (24–55%)	<0.0001
Total	35/102	34% (26–44%)	<0.0001

* P-value for a comparison with historical data (84%) using a Binomial test; the occurrence of grade 3–4 neutropenia is lower than 84% in all cohorts.

Table 4
Overall response rate, progression free survival and overall survival.

	N (evaluable)	ORR	Median PFS (95% CI) months	Median OS (95% CI) months
Ovarium (PR/R)	31	48%	7 (6–8)	13 (8–19)
Prior lines: 1–2	11	73%	7 (3–8)	13 (4–undefined)
3–9	20	35%	8 (2–9)	11 (8–19)
Endometrium	29	45%	6 (4–9)	19 (8–undefined)
Prior lines: 0	11	73%	8 (2–undefined)	Undefined
1–4	17	29%	5 (3–9)	12 (6–undefined)
Cervix	33	58%	6 (4–10)	14 (10–16)
Prior lines: 0	13	77%	6 (3–10)	16 (8–undefined)
1–2	16	44%	6 (3–12)	12 (8–19)
Total		51%	7 (5–8)	13 (10–15)

of 32) the RR was 44.4% (4/9), median PFS and OS were 6.1 and 9.2, respectively. The incidence of grade 3–4 neutropenia was 28%. Grade 3 toxicities included: anemia 6%, thrombocytopenia 6%, and peripheral neuropathy 12%. No prophylactic use of G-CSF was recommended and in case of grade 3–4 neutropenia therapeutic and prophylactic use of G-CSF was allowed [15].

Second, two studies investigated a three-weekly dose-dense [16] and a weekly [17] paclitaxel/carboplatin regimen in patients with primary advanced or recurrent endometrial cancer. Both dose regimens seem effective, however, with a considerable hematologic toxicity. Patients in the three-weekly dose dense study were divided into 2 groups: chemotherapy-naïve group (group 1; n = 28) and a group with previous chemotherapy (group 2; n = 14). Grade 3–4 neutropenia was observed in 11 of 14 patients in group 2 (79%). Only 2 patients (14%) in group 2 received G-CSF [16]. Patients in the weekly paclitaxel/carboplatin regimen were also divided into 2 groups: chemotherapy-naïve group (group 1; n = 16) and a group with previous chemotherapy (group 2; n = 13). Grade 3–4 neutropenia was observed in 87% and 92% of the patients in groups 1 and 2, respectively. Only 7% of the patients in this study received G-CSF [17].

Third, weekly dosing was also evaluated earlier in a study comparing the same paclitaxel/carboplatin regimen as in our study with a dose-dense regimen in recurrent or primary cervical cancer [18]. RR was 55% for chemotherapy-naïve patients. As second or more line therapy, the RR was 29% for the weekly regimen [18]. The RR for the cervical

cancer group that received one or two prior chemotherapy lines in our study was 44%. Median PFS was not yet reached and median OS was 10 months. Although grade 3 and 4 neutropenia was observed during the weekly regimen in 52% and 43% of patients, respectively, none of them experienced an episode of neutropenic fever. Grade 3 and 4 thrombocytopenia was registered during the weekly regimen in 48% and 10% of patients. None experienced grade 3–4 peripheral neuropathy. None of the patients received prophylactic G-CSF with the weekly dose regimen [18].

Although no study has demonstrated, the addition of G-CSF may also be important to preclude dose reductions and decrease the incidence of dose delays. Dose reductions were needed in the earlier retrospective studies in ovarian [12], endometrial [17] and cervical cancer [18] in 24%, 42% and 12% of the patients respectively, and delays in 62%, 43% and 75% respectively. In the current study reduction of carboplatin was needed in 47% and of paclitaxel in 18% of the patients, not unexpectedly mainly due to thrombocytopenia. Hence the addition of G-CSF did not result in a decrease of dose reductions compared with earlier studies not using routine G-CSF. However, in the current study the mean weekly dosages delivered were quite comparable with the intended dose density (52 mg/m² vs 60 mg/m² for paclitaxel and AUC 2.3 vs 2.7 for carboplatin).

A limitation of the previously mentioned studies was their small study group and non-randomized study design. Moreover, because of the differences in dose-intensities for both paclitaxel and carboplatin in these studies, the different proportions of platinum-resistant patients, the different gynecological cancers, no routine use of prophylactic G-CSF and the lack of direct comparison, it is hard to draw firm conclusions.

The use of weekly carboplatin in combination with weekly paclitaxel as used in the current study has recently been questioned based on the disappointing results with weekly carboplatin in monotherapy [24] and the excellent results with paclitaxel weekly with or without bevacizumab [25] in platinum resistant ovarian cancer. However, both the current study and earlier studies showed interesting response rates in platinum-resistant ovarian cancer and recurrent endometrial or cervical carcinoma with the combination of weekly carboplatin and weekly paclitaxel [5,11–18]. In the current study only 3 out of 35 patients with platinum-resistant ovarian cancer presented with platinum-refractory disease. In one of these 3 patients we observed a partial response. In order to establish the role of weekly carboplatin in combination with weekly

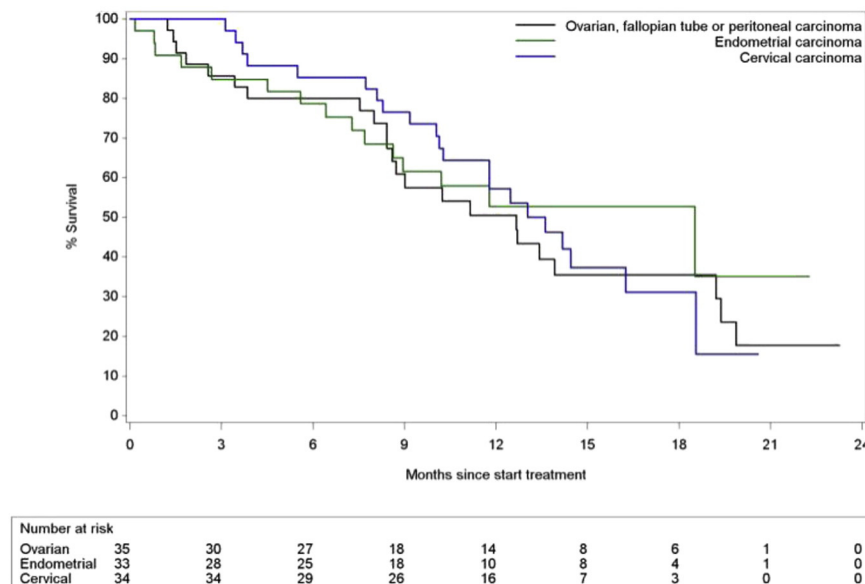


Fig. 1. Median progression-free survival (95% CI) per cohort.

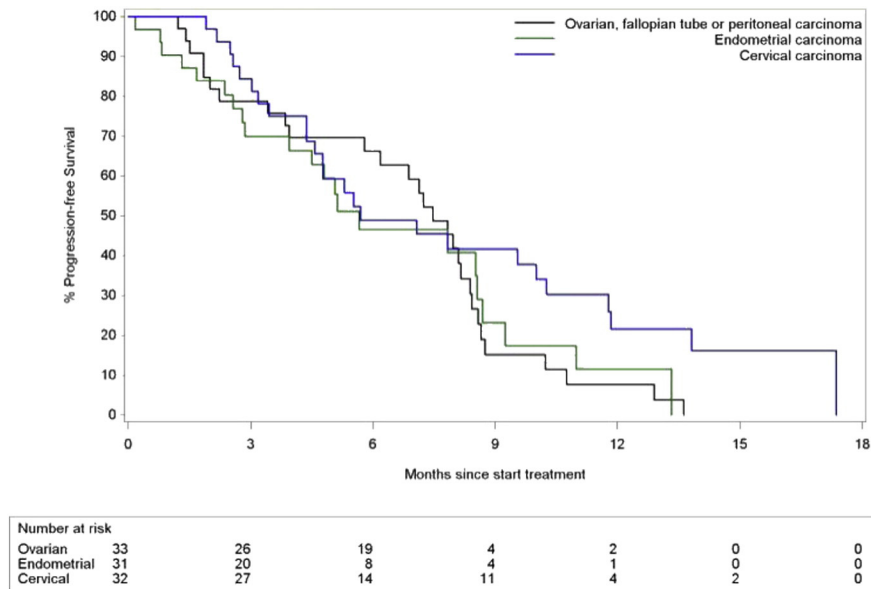


Fig. 2. Median overall survival (95% CI) per cohort.

carboplatin in platinum-resistant ovarian cancer, a phase III randomized trial comparing this regimen versus weekly paclitaxel alone versus 3-weekly carboplatin and weekly paclitaxel would be needed to establish the value of these 3 regimens.

In conclusion, weekly paclitaxel/carboplatin with G-CSF is feasible with an acceptable toxicity in patients with platinum-resistant or platinum-refractory ovarian cancer, advanced or recurrent endometrial cancer and cervical cancer. The incidence of grade 3–4 neutropenia is lower with the addition of weekly G-CSF compared with earlier studies without the routine use of prophylactic G-CSF. However, the study showed a limited effect on the incidence of febrile neutropenia making the routine use of G-CSF with this regimen questionable. In addition, the incidence of dose reductions or delays (in this series mainly due to thrombocytopenia) was not better compared with our historical data.

Conflict of interest statement

There are no conflicts of interest.

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