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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/m^2) 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.

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/m^2, 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 (α:0.05; β: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) ≥ 1.5×10^9/L, hemoglobin ≥ 9 g/dL (5.6 mmol/L) and platelets ≥ 100×10^9/L. They were required to exhibit adequate renal function, in accordance with a calculated creatinine clearance (Cockroft) ≥ 30 mL/min. Moreover, participants had to demonstrate an adequate hepatic function, as evidenced by total bilirubin concentrations ≤ 1.5 × the upper normal limit and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × 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 Cockroft) 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/m^2 and carboplatin at an AUC of 2.7 with dose calculated according to the Cockroft 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/m^2) 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/m^2 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)