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Long-term results of weekly paclitaxel carboplatin induction therapy: An effective and well-tolerated treatment in patients with platinum-resistant ovarian cancer

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Abstract ***Background:*** Weekly paclitaxel/cisplatin is effective in platinum-resistant epithelial ovarian cancer (EOC). To reduce toxicity, paclitaxel/cisplatin was replaced by paclitaxel/carboplatin.

Patients and methods: Patients with progressive EOC after prior 3-weekly paclitaxel/carboplatin were treated with six cycles weekly paclitaxel 90 mg/m^2 and carboplatin area under the curve (AUC) 4 mg/ml/min, followed by six cycles 3-weekly paclitaxel/carboplatin. Endpoints were progression free survival (PFS), overall survival (OS), response rate (RR) and toxicity.

Results: Median progression free interval after last platinum was 9 (0–81) months in 108 patients; 43 were platinum-resistant, of whom 13 started weekly paclitaxel/carboplatin <6 months after progression. During 633 weekly cycles grade 3/4 toxicity included; thrombocytopenia 8%, neutropenia 30%, febrile neutropenia 0.5%. Non-haematologic toxicity was low. Treatment was delayed in 16%, and dose reduced in 2% of cycles. RR was 58% for platinum-resistant and 76% for platinum-sensitive patients, median PFS were 8 (range 1–21) and 13 (1–46) months, median OS 15 (1–69) and 26 (4–93) months, respectively. The 13 platinum-resistant patients with a platinum-therapy free interval <6 months had a significant shorter PFS (4 versus 10 months, $p = 0.035$) and OS (9 versus 15 months, $p = 0.002$).

Conclusion: Six cycles weekly paclitaxel/carboplatin followed by six 3-weekly cycles is well-tolerated and highly active in platinum-resistant and platinum-sensitive patients.

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1. Introduction

Platinum combination therapy is the most effective treatment in both primary and recurrent epithelial ovarian cancer (EOC).[1–4] In relapsing patients the benefit of chemotherapy relates to platinum progression free interval (platinum-PFI). In platinum-sensitive (platinum-PFI >6 months) patients, platinum combination chemotherapy yields response rates (RR) of 47–65% with a median progression free survival (PFS) of 8–13 months and median overall survival (OS) of 18–29 months.[2–4] In platinum-resistant disease (platinum-PFI ⩽6 months) the RR to single-agent platinum is only 10%,[5] to non-platinum therapy 7–35% with a median PFS of 2–4 and OS of 6–12 months, respectively.[6–10] Dose-dense regimens with weekly cisplatin in combination with etoposide, topotecan or paclitaxel showed RR of 46–63%, PFS of 5–8 months and OS of 10–11 months.[11–13] Since recurrent disease is rarely curable, symptom control, maintaining quality of life, reducing adverse events (AE) and prolonging PFS and OS are of paramount importance. When first-line treatment 3-weekly paclitaxel/carboplatin was shown to be equally effective, but less toxic than 3-weekly paclitaxel/cisplatin,[14] we performed a phase I study that showed that weekly paclitaxel 90 mg/m^2 could safely be combined with carboplatin area under the curve (AUC) 4.[15] In the current study, we explored the activity and toxicity of six cycles weekly paclitaxel/carboplatin induction therapy followed by six cycles 3-weekly paclitaxel/carboplatin in recurrent EOC.

2. Patients and methods

2.1. Patient selection

Patients with progressive EOC and prior treatment with paclitaxel and carboplatin were treated according to the standardised treatment protocol for weekly paclitaxel/carboplatin, regardless the number of prior therapies. Progressive disease (PD) was confirmed by spiral computed tomography (CT-scan), trans-vaginal ultrasound (TVU), and/or gynaecological and physical examination. Eligibility criteria were WHO performance status ⩽2, at least one measurable lesion, creatinine clearance calculated by Cockcroft-Gault ⩾50 ml/min, bilirubin <20 μmol/L, serum transaminases <60 U/L, white blood cell count (WBC) ⩾3.0 × 10^9/L and platelets ⩾100 × 10^9/L. All patients gave informed consent. This study was conducted in agreement with the Helsinki declaration of 1996.

2.2. Treatment regimen

Treatment according to standardised treatment protocol consisted of six weekly induction cycles paclitaxel 90 mg/m^2 and carboplatin AUC 4, both administered by one-hour infusion on days 1, 8, 15, 29, 36, and 43. Patients with clinical benefit (stable disease (SD), partial response (PR) and complete response (CR)) continued treatment with six 3-weekly maintenance cycles paclitaxel 175 mg/m^2 in 3-hour infusion, and carboplatin AUC 6 in 1-hour infusion. Standard premedication was given according to local protocol (supplement 1).

2.3. Dose modifications

If on days 8, 15, 36, and 43 WBC were <1.0 × 10^9/L and/or platelets <50 × 10^9/L and if day 29 of the weekly or day 1 of the 3-weekly cycles WBC were <3.0 × 10^9/L and/or platelets <100 × 10^9/L treatment was delayed by one week until recovery. In case of febrile neutropenia or grade 4 neutropenia on 2 successive weekly counts paclitaxel/carboplatin was reduced by 20%, in case of thrombocytopenia grade 4 carboplatin was reduced by 10%. Red blood cell transfusion was administered at symptomatic anaemia and/or erythropoietin was started if haemoglobin was <6.2 mmol/L. In case of a hypersensitivity reaction, paclitaxel or carboplatin infusion was interrupted immediately and 2 mg clemastine was administered intravenously. After recovery, infusion was restarted with a prolonged infusion rate; starting with an infusion rate of 15 ml/h during 15 min, followed by 84 ml/h during 15 min. If no reaction occurred, infusion was continued at the normal infusion rate. The same schedule was used for all subsequent cycles, together with extra dexamethasone premedication.

2.4. Treatment monitoring and toxicity scoring

Pre- and on-treatment monitoring consisted of medical history, physical and gynaecological examination, CT-scan of thorax, abdomen and pelvis, TVU and CA125 measurement. Before each cycle, and during follow-up, AE were scored according to the Common Toxicity Criteria of the National Cancer Institute (CTC version 2.0).[16] Routine blood tests included CA125, haematology, electrolytes, kidney and liver function tests. Response was evaluated according to the response evaluation criteria in solid tumours (RECIST)[17] after six weekly, and three and six 3-weekly cycles of paclitaxel/carboplatin. During follow-up patients were checked bimonthly the first, three-monthly the second, four-monthly the third and fourth, six-monthly the fifth year and thereafter once a year. This included physical and gynaecological examination ± TVU, and blood tests including CA125. A CT-scan was only performed in case of clinical signs or symptoms of progression.

2.5. Statistical methods

Analyses were conducted according to the intention-to-treat-principle. Platinum-PFI was defined as the