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Full Length Article

Weekly dose-dense paclitaxel and carboplatin in recurrent ovarian carcinoma: A phase II trial

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KEYWORDS

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Abstract *Purpose:* The aim of this study was to investigate efficacy and toxicity of the dose-dense weekly paclitaxel (T) and carboplatin (C) in the management of platinum-resistant/sensitive recurrent epithelial ovarian cancer (EOC) previously treated with 3 weekly paclitaxel/carboplatin.
Methods: Thirty two patients with recurrent EOC who had received 3 weekly TC before were enrolled. Nine patients relapsed within 6 months (platinum-resistant), 13 patients relapsed after 12 months (platinum-sensitive) and in 10 patients recurrence occurred between 6 and 12 months (intermediate platinum-sensitive). Weekly (T) at a dose of 80 mg/m^2, followed by weekly (C) AUC 2 on day 1, 8, and 15 of a 28-day cycle for 6 planned cycles were administrated. End-points were overall response rate (ORR), progression free survival (PFS), overall survival (OS) and toxicity.
Results: The ORR was 62.5%. For the platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients the ORR was 44.4% (4/9), 60% (6/10) and 76.9% (10/13), respectively, and 1 (11.1%), 2 (20%) and 5 (38.46%) patients, respectively had CR. PFS was 9.1 months (6.13, 9.1 and 12.17 months, for the 3 groups, respectively) ($P < 0.001$). OS was 14 months (9.17, 15.2, and 19.23 months, for the 3 groups, respectively) ($P < 0.001$). Treatment-related adverse events were manageable with only 1 patient (3.1%) suffering from grade 4 neutropenia. Grade 3 hematological and non-hematological toxicities were neutropenia in 8 (25%), and peripheral neuropathy in 4 (12.5%) patients, respectively.
Conclusion: Weekly TC is active and well-tolerated in platinum-resistant and platinum-sensitive patients with recurrent EOC previously treated with TC given every 3 weeks.

Introduction

Among gynecologic malignancies, ovarian cancer is the most deadly [1]. Aggressive cytoreductive surgery, followed by combination of taxane and carboplatin chemotherapy is the standard of care for EOC with relatively high response rates to first-line platinum-based therapies [2]. Unfortunately, the majority present with advanced stage disease (75% stage III & IV). Of these, 70–80% will recur and require second-line

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palliative chemotherapy in an effort to maintain quality of life and slow progression of disease [1,3,4].

Platinum progression free interval (PFI) was defined as the interval between the last platinum-chemotherapy and progressive disease (PD). Platinum-resistant disease was defined as progression or recurrence within 6 months, while platinum-sensitivity was defined as recurrence greater than 12 months, while disease recurrence between 6 and 12 months was defined as intermediate platinum-sensitive disease [5].

Optimization of pharmacokinetics via manipulation of the dosing schedule of platinum and taxane has been suggested as a method of improving response rates in both platinum-sensitive and platinum resistant disease [1]. Weekly dosing exposes a higher number of cancer cells to cytotoxic treatment during a critical phase in the cell cycle [6]. The high response rate and the lack of cardiotoxicity suggest that this regimen should be considered for future adjuvant therapy [7]. In addition, the use of weekly paclitaxel may have additional anti-angiogenic effects when used in a fractionated schedule [8].

Dose-dense weekly paclitaxel plus carboplatin improved survival compared with the conventional regimen and represents an active treatment option in women with advanced epithelial ovarian cancer [9]. The noteworthy results stem from the Japanese Gynecologic Oncology Group (JGOG) trial 3016 which was a large, prospective randomized trial that compared dose-dense weekly paclitaxel plus carboplatin versus the conventional dosing schedule for those two drugs in the adjuvant sitting, established a significant benefit for both median overall survival (Median overall survival has not yet been reached in the dose-dense treatment group, and OS at 5 years was higher in the dose-dense treatment group than the conventional treatment group (58.6% vs. 51.0%, HR 0.79, 95% CI, 0.63–0.99; $P = 0.0448$)) and median progression-free survival (28.2 months vs 17.5 months $P = 0.0037$) for the dose-dense treatment group versus the conventional treatment group, respectively [10].

This entity of platinum-resistant ovarian cancer represents a different clinical scenario. Several chemotherapeutic agents such as topotecan, gemcitabine, liposomal doxorubicin, paclitaxel and etoposide have been used in the treatment of platinum resistant disease with unexciting disappointed response rates in the range of 6–15% [11,12]. There is increasing evidence suggesting that the use of extended dose-dense chemotherapy results in response rates of 40–60% in this otherwise the poor prognosis group [13,14].

This study was a phase II study to assess the efficacy and tolerability of weekly paclitaxel at a dose of 80 mg/m^2, followed by carboplatin AUC 2 on day 1, 8, and 15 of a 28-day cycle for six planned cycles in female patients with recurrent EOC who had received 3 weekly paclitaxel carboplatin before.

Patients and methods

Patient eligibility criteria

Between December 2007 and January 2011, 32 female patients with recurrent epithelial ovarian cancer (EOC) previously treated with 3 weekly paclitaxel carboplatin in the Clinical Oncology Department, Tanta University Hospital were enrolled. Patients fulfilled the following criteria: age between 18 and 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leqslant 2$, adequate bone marrow reserve (WBC count $\geqslant 3.5 \times 10^9$/L, ANC count $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, and hemoglobin $\geqslant 10$ g/dL), adequate renal function (measured creatinine clearance $\geqslant 60$ mL/min) and adequate liver function (transaminases less than $2 \times$ upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Progressive disease was defined according to modified WHO criteria [15]. The new appearance of disease related pleural effusion or ascites was also considered as progressive disease.

Patients suffering from secondary malignancy or concurrent serious, uncontrolled medical illness (e.g. persistent immune-compromised states, uncontrolled infection, severe peripheral neuropathy, and clinically significant cardiac disease) were excluded from this study.

Design of the study

This study is a prospective single-arm phase II single institution study. The Ethics Committee in the Faculty of Medicine, Tanta University, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

Treatment plan and dose medication

Weekly paclitaxel at a dose of 80 mg/m^2 was delivered as an intravenous infusion over 60 min (in 500 mL of 5% glucose solution), followed by carboplatin AUC2 (dissolved in 250 mL 0.9% saline) as an intravenous infusion over 30 min on day 1, 8, and 15 of a 28-day cycle for six planned cycles. Chemotherapy was discontinued in case of disease progression or major toxicities. Cycles were administered on an outpatient basis. Adequate antiemetic, antacid, antihistaminic and corticosteroid therapy were provided for all patients.

Adequate hematological and within normal range organ functions were insured prior to each cycle. Adverse events were monitored throughout the study. A complete resolution of hematologic and non-hematologic toxicity was required except for alopecia and fatigue. If toxicities did not resolve, then a 1-week delay was allowed. 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.

Patient assessment

Assessment of clinical benefit

A tumor response assessment was performed after every three cycles of treatment. Pre- and on-treatment monitoring consisted of medical history, physical and gynecological examination, trans-vaginal ultrasound (TVU), CT-scan of the chest, abdomen and pelvis, and CA125 measurement. Criteria of complete response, partial response, stable disease and progressive disease were based on the standard definitions according to modified WHO criteria [15] with the overall response rate, including complete response and partial response. An increase in CA125 levels not associated with radiologic or clinical evidence of tumor progression was not used as the sole indicator of progressive disease.