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

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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/m², followed by weekly (C) AUC 2 on day 1, 8, and 15 of a 28-day cycle 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.

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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
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 setting, 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/m², followed by carboplatin AUC2 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 ≤2, adequate bone marrow reserve (WBC count \( \geq 3.5 \times 10^9/L \), ANC count \( \geq 1.5 \times 10^9/L \), platelets \( \geq 100 \times 10^9/L \) and hemoglobin \( \geq 10 \text{ g/dL} \)), adequate renal function (measured creatinine clearance \( \geq 60 \text{ mL/min} \)) and adequate liver function (transaminases less than 2 × 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/m² 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.
Assessment of toxicity
Toxicity grading was based on the common terminology criteria for adverse event (NCI-CTC, version 3.0) [16].

Primary and secondary endpoints
The primary endpoints of the study were overall response and toxicity. Secondary end points were the progression-free survival and overall survival.

Statistical analysis
Thirty-two patients were recruited in the study between December 2007 and January 2011. Patients were followed up until December 2013. At the time of analysis, the median follow-up duration was 14 months (95% CI; 13.3–14.7 months).

Overall survival (OS) rates were calculated from the start of dose-dense weekly paclitaxel (T) and carboplatin (C) to the time of the last follow-up visit or death using the Kaplan–Meier method [17] with SPSS [Statistical package] (version 12.0).

Progression-free survival was the time elapsed from the date of initiation of dose-dense weekly T and C to the date of first evidence of disease progression or death in the absence of disease progression. The Kaplan–Meier method [17] is used for estimating survival and log rank for comparison of curves. Mean and standard deviation were estimates of quantitative data. The 95% confidence intervals (95% CIs) were calculated with the exact method. Fisher exact test was used for qualitative data and Kruskal–Wallis test was used for comparing quantitative data for more than 2 groups. All P values were two-tailed; a value of ≤0.05 was considered significant.

Results
Patient characteristics
Thirty-two patients were enrolled in the study. The baseline demographic and clinical characteristics of all enrolled patients are listed in Table 1. The mean age was 57.1 years (range; 35–77 years). Stage III and IV constitute 78.1% of all of the patients at initial presentation prior to any treatment and 26 patients (81.2%) had serous pathological subtype. Grade III tumor represented more than half (19 patients, 59.4%). Most of the patients had ECOG performance status score ≥1 (71.9%).

Treatment administration
A total of 174 cycles were administrated with a median number of 5.4 cycles (range 3–6). No dose reduction was recorded and only 2 patients had dose delay for one week.

Activity of both drugs (patient response to those drugs)
The overall response rate (including complete response and partial response) was 62.5% (20/32). For the platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients the overall response rate was 44.4% (4/9), 60.0% (6/10) and 76.9% (10/13), respectively, and one (11.1%), 2 (20.0%) and 5 (38.5%) patients, respectively, had complete response (CR, confirmed by PET-study). Stable disease (SD) was recorded in 2 (22.2%), 2 (20.0%), and 2 (15.3%) patients of platinum-resistant, intermediate platinum-sensitive and platinum sensitive patients, respectively, while progressive disease (PD) was recorded in 3 (33.3%), 2 (20.0%), and 1 (7.7%) patients of platinum-resistant, intermediate platinum sensitive and platinum sensitive patients, respectively (Table 2). Six patients reported to progress on study protocol.

Survival
All our patients were followed up regularly as mentioned previously in patients and methods, with no one having lost follow up in this study. The median follow up duration was 14 months (95% CI; 13.3–14.7 months).

Median progression free survival (PFS) was 9.1 months (95% CI 8.1–10.1) (Fig. 1). Median PFS was 6.1, 9.1 and 12.2 months, for platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients, respectively (P < 0.001), (Fig. 2).

Twenty four patients died during the observation period. Median overall survival (OS) was 14 months ± SE 0.35 (range; 4.1–38.5 months), with its 95% CI 13.3–14.7 (Fig. 3). Median OS was 9.2, 15.2 and 19.2 months for platinum-resistant, intermediate platinum-sensitive and sensitive platinum-patients, respectively (P < 0.001), (Fig. 4).

Toxicity
In our study the toxicity profile of this regimen was well tolerated with only one (3.1%) and 8 (25.0%) patients suffering from grade 4 and grade 3 neutropenia, respectively. Grade 3 anemia occurred in 2 patients (6.3%), and 2 patients (6.3%) experienced grade 3 thrombocytopenia.

Peripheral neuropathy was the most frequent grade 3 non-hematological side effects recorded in 4 (12.5%) patients in our study (Table 3).

Discussion
Most of the patients with advanced epithelial ovarian cancer (EOC) will ultimately recur and require second-line palliative chemotherapy [18–20]. Second-line palliative chemotherapy demonstrated advantages over best supportive care for recurrent EOC patients, in an effort to maintain an acceptable quality of life, control symptoms, and prolonging survival if possible [21–26]

van der Burg et al. [5] reported that the RR in published series on non-platinum paclitaxel regimen was 16% for pegylated liposomal doxorubicin (PLD), 13% for topotecan in platinum resistant patients. Sharma et al. [14] reported that several chemotherapeutic agents such as topotecan, gemcitabine, liposomal doxorubicin and etoposide have been used in the treatment of platinum-resistant disease with unexciting response rates in the range of 10–15% in this patient group. Kumar et al. [26], in a review article reported that the best response rates in platinum-resistant patients have been in the 10–20% range.
We used weekly paclitaxel at a dose of 80 mg/m², followed by carboplatin AUC 2 on day 1, 8, and 15 of a 28-day cycle for six planned cycles, unless discontinuation due to severe toxicity or disease progression, more than 75% of our patients received 6 cycles, and this treatment schedule and doses were selected based on previous studies [5,14]. This treatment schedule appeared to have good clinical efficacy (62.5% overall response rate).

Sharma et al. [14] reported an overall response rate of 60% for patients who received carboplatin AUC 3 and paclitaxel 70 mg m² on day 1, 8, and 15 q 4 weekly for six planned cycles in recurrent EOC patients. This is also consistent with previous published studies by van der Burg et al. [5] and Cadron et al. [27] who reported a response rate of 62%, and 66%, respectively.

The use of extended dose-dense chemotherapy for the platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients in our study results in an overall response rate of 44.4% (4/9), 60% (6/10) and 76.9% (10/13), respectively. van der Burg et al. [5] reported response rate of

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**Table 1** Demographic characteristics of the 32 patients with platinum-resistant/sensitive recurrent EOC previously treated with 3 weekly paclitaxel/carboplatin at baseline.

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<th>%</th>
<th>N = 13</th>
<th>%</th>
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<td>6</td>
<td>46.1</td>
<td>19</td>
<td>59.4</td>
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**Table 2** Tumor response to dose-dense weekly paclitaxel and carboplatin in the management of the 32 patients with platinum-resistant/sensitive recurrent EOC.

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<th>Response</th>
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<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
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<td>20.0</td>
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**Figure 1** Kaplan–Meier curve of progression-free survival. Median progression-free survival time was 9.1 months.
of platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients, respectively. Cadron et al. [27] reported response rate of 38%, 73% and 80% after the weekly paclitaxel/carboplatin therapy for the platinum-resistant, intermediate platinum-sensitive and platinum-sensitive patients, respectively. In our study, the median progression free survival (PFS) was 9.1 months (6.1, 9.1 and 12.2 months, for platinum-resistant, intermediate platinum-sensitive and sensitive platinum-patients, respectively). Cadron et al. [27] reported a comparable median progression free survival (PFS) of 9 months (6.8, 10.5 and 12.8 months, for platinum-resistant, intermediate platinum-sensitive and sensitive platinum-patients, respectively). However, the median PFS in our study was better than those reported in other trials which reported PFS of 5–8 months [13,28,29], and was lower than those reported in van der Burg et al. [5] study, in which the median PFS was 8.0, 11.0 and 13.0 months for platinum-resistant, intermediate platinum-sensitive and sensitive platinum-patients, respectively.

In our study, the median overall survival (OS) of 14 months (9.2, 15.2 and 19.2 months, for platinum-resistant, intermediate platinum-sensitive and sensitive platinum-patients, respectively). Cadron et al. [27] reported a median overall survival of 9 months (6.8, 10.5 and 12.8 months, for platinum-resistant, intermediate platinum-sensitive and sensitive platinum-patients, respectively). However, the median OS in our study was better than those reported in other trials which reported OS of 10–11 months [13,28,29], and was lower than those reported in van der Burg et al. [5] study, in which the median OS was 15.0, 28.0 and 26.0 months for platinum-resistant, intermediate platinum-sensitive and sensitive platinum-patients, respectively.

Toxicity is an important consideration for patients with recurrent disease for whom chemotherapy is palliative. In our study the toxicity profile of this regimen was well tolerated, with only one (3.1%) and 8 (25.0%) patients suffering from grade 4 and 3 neutropenia, respectively. Grade 3 anemia occurred in 2 patients (6.3%), and 2 patients (6.3%) experienced grade 3 thrombocytopenia. The frequency of these toxicities was somewhat nearly similar to those reported by
Sharma et al. [14] and lower than those reported by van der Burg et al. study [5]. Sharma et al. [14] administered weekly paclitaxel at 70 mg/m² and carboplatin at AUC 3 on day 1, 8, and 15 every 4 weeks in patients with recurrent ovarian cancer, and prior treatment with a platinum-agent regimen recorded that the most common hematological adverse events were grade 3/4 neutropenia in 30.0%, grade 3 anemia in one (5.0%) patient and no grade 3 thrombocytopenia. van der Burg et al. [5] reported ≥ 3 grade neutropenia and thrombocytopenia in 40.0% and 8.0% of patients, respectively in the weekly phase. The addition of G-CSF to avoid neutropenia and maintain dose intensity, and decrease the incidence of dose delay was considered in the subsequent cycles.

Interestingly, peripheral neuropathy which was the most frequent grade 3 non-hematological side effects did not represent a high incidence rate, only reported in 4 (12.5%) patients in our study, despite the majority of patients having had prior treatment with a taxane. Sharma et al. [14] recorded grade 3 neuropathy in 3 (14%) patients.

So, one hour infusion of paclitaxel in weekly schedule is associated with less neurotoxicity and decrease in dose per injection of paclitaxel (weekly schedule) also was associated with a decrease in myelosuppression.

Conclusion

Prospective randomized clinical trial incorporating targeted agents and newer forms of paclitaxel (Abraxane) aimed at decreasing toxicity, increasing efficacy, improving ease of administration, and to show if it can reverse acquired clinical platinum resistance patients if demanded. However limited resources are an obstacle to be used frequently for recurrent EOC patients in our country.

The area of recurrent ovarian carcinoma is a hot topic with ongoing trials evolving and confirming the role of anti-angiogenic and PARP inhibitor drugs with dose dense taxol carboplatin and in order to detect predictive biomarkers to identify patients most likely to benefit and personalized treatment to each patient.

From our study, we conclude that, extended dose-dense carboplatin/paclitaxel regimen with ‘3 weeks on, 1 week off’ affords the opportunity to treat effectively and safely with minimal toxicity in heavily pretreated EOC patients. This finding is of importance as platinum resistance ultimately becomes the dominant problem for most patients with ovarian cancer. However final conclusions about the superiority of our regimen for platinum resistant disease needed prospective randomized studies with larger numbers of patients to be analyzed.

Conflict of interest

The authors have no conflict of interest to declare.

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[16] National Cancer Institute, US. NCI common terminology criteria for adverse events v3.0 (CTCAE v3.0) [online]. <http://ctep.cancer.gov/protocoldevelopment/>


