Phase I study of carboplatin, doxorubicin and weekly paclitaxel in patients with advanced ovarian carcinoma

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Background: Doxorubicin is an active compound in epithelial ovarian cancer (EOC), but adding it to carboplatin–paclitaxel causes toxicity. Toxicity can be reduced by weekly administration. We examined the tolerability of weekly paclitaxel in combination with carboplatin and doxorubicin.

Patients and methods: Chemotherapy naïve patients with EOC were treated with doxorubicin (50 mg/m² day 1), carboplatin (AUC 6 day 1) and paclitaxel (days 1, 8, 15, 21), 28-day cycle. Three patients were treated at each paclitaxel dose level, starting at 60, 75 and 90 mg/m²/week. If more than two patients in a cohort experienced dose-limiting toxicity (DLT) three more patients were treated at the dose level below.

Results: Twelve patients with advanced EOC received a median of six cycles (range 2–6) of the three-drug combination. DLT occurred at dose level 3: prolonged grade 4 febrile neutropenia, 1 patient; grade 3 peripheral neuropathy, 1 patient. All six patients treated at dose level 2 experienced short-lived grade 4 neutropenia, which led to dose modifications resulting in an actual delivered dose of paclitaxel of 64 mg/m²/week. Eight out of 12 patients had measurable disease on CT scan: four obtained a partial remission; three had stable disease.

Conclusions: The combination of carboplatin, doxorubicin and paclitaxel in patients with EOC is active and its main toxicity is myelosuppression. Dose intensity of paclitaxel can be maintained in a three-drug combination through weekly administration (65 mg/m²).

Key words: carboplatin, doxorubicin, ovarian carcinoma, weekly paclitaxel

Introduction

The majority of patients presenting with epithelial ovarian cancer (EOC) have advanced disease and standard management requires both surgery and chemotherapy. The currently accepted gold standard treatment for these patients is optimal surgical debulking followed by chemotherapy with the combination of a platinum drug and paclitaxel [1–4].

In the pretaxane era, two meta-analyses [5, 6] showed that the addition of an anthracycline to a platinum-based regimen resulted in a survival benefit for patients with EOC. In contrast, a subsequent randomised trial failed to demonstrate any survival difference between treatment with single-agent carboplatin and a combination of cisplatin, doxorubicin and cyclophosphamide [7]. Nevertheless, a number of groups, including our own [8–12], examined the feasibility of combining platinum drugs with anthracyclines and paclitaxel in a conventional 3- to 4-week schedule. However, myelotoxicity was found to be a major concern even with granulocyte colony-stimulating factor (G-CSF) support.

In order to minimise toxicity, paclitaxel can be given weekly instead of 3-weekly [13, 14]; this results in a higher dose intensity of the drug [15]. Two non-randomised trials [16, 17] have suggested that the activity of paclitaxel in EOC is dose-dependent, and a randomised trial [15] has shown reduced toxicity with weekly scheduling without any detriment to efficacy.

We have therefore examined the tolerability of increasing doses of weekly paclitaxel in combination with carboplatin and doxorubicin as first-line treatment for advanced ovarian carcinoma in order to combine these three drugs with less myelotoxicity.

Patients and methods

Patients

Patients naïve to chemotherapy with histologically confirmed advanced (stage IC–IV) epithelial carcinoma of the ovary or fallopian tube, primary peritoneal carcinoma or patients with intra-abdominal carcinoma of unknown origin thought to originate in the genital tract were eligible for this study. Other inclusion criteria were: good performance status, World Health Organization (WHO) grade 0–2; measurable or evaluable disease; life expectancy ≥3 months; age 18–70 years; normal cardiac ejection fraction, as estimated by a baseline MUGA (multigated acquisition) scan; neutrophil count ≥1.5 × 10⁹/l; platelet count ≥100 × 10⁹/l; haemoglobin ≥10 g/dl; glomerular filtration rate (GFR; measured by ⁵¹Cr-EDTA or creatinine clearance) ≥60 ml/min; and
total bilirubin and transaminases <2 × upper limit of normal range (ULN), <3 × ULN in the presence of liver metastasis.

Exclusion criteria were: previous pelvic irradiation (limited prior radiotherapy, for example a single fraction for bone pain, was allowed); borderline histology; central or peripheral neuropathy, common toxicity criteria (CTC) grade ≥2; undrained ascites; bowel obstruction; significant comorbidities; history of a second malignancy, unless disease-free for ≥3 years; cerebral metastases; allergy to any study medication or to cremophor-containing drugs; and pregnancy or lactation. The protocol was approved by the local protocol review and research ethics committees and written informed consent was obtained from all participating patients.

**Treatment**

Doxorubicin and carboplatin were given at a fixed dose on day 1 of each 28-day cycle: doxorubicin 50 mg/m² was given by a slow i.v. bolus injection; and carboplatin was dosed according to the GFR measured by 51Cr-EDTA clearance using the Calvert formula to an area under the curve (AUC) of 6 and administered i.v. as a 1-h infusion in 500 ml of 5% dextrose.

Paclitaxel was administered weekly in a planned dose escalation scheme starting with a dose of 60 mg/m²/week (level 1), increasing with each successive cohort to 75 mg/m²/week (level 2) and then to 90 mg/m²/week (level 3). There were no intrapatient dose escalations.

Patients were premedicated with dexamethasone 20 mg p.o. (at −12 h and −6 h), chlorpheniramine 10 mg i.v. and cimetidine 200 mg i.v. (both at −30 min). Paclitaxel was administered as a 1-h infusion in 5% dextrose, at a concentration not exceeding 1.2 mg/ml. Chemotherapy drugs were given in the following order: doxorubicin, carboplatin, paclitaxel. These drugs were given in this order to try to separate the administration of doxorubicin and paclitaxel as much as would be practicable in the context of a regimen that could be administered in a single day. This separation was felt to be advisable because of the reported interaction between the two drugs in relation to cardiotoxicity.

Intravenous granisetron, oral dexamethasone (prior to chemotherapy and for three consecutive days) and metoclopramide were administered as antiemetic prophylaxis. G-CSF at a dose of 300 µg/day by s.c. injection was given to patients during periods of neutropenia when neutrophil count was <0.5 × 10⁹/l.

**Tumour and toxicity assessment**

WHO response criteria for objective responses were used comparing computed tomography (CT) scans at baseline with follow-up scans after the second, fourth and sixth chemotherapy cycles. If progressive disease was documented, treatment was stopped. Otherwise patients were planned to receive six complete chemotherapy cycles.

Toxicity was graded according to the CTC. Dose-limiting toxicity (DLT) was defined as the occurrence of any of the following: grade 4 neutropenia or thrombocytopenia lasting >7 days; grade 3–4 non-haematological toxicity (except nausea, vomiting or alopecia); and any toxic death.

**Dose modification**

Three patients were included at each dose level and if a DLT occurred in one patient the number of patients in this cohort was expanded to six. If two or more patients experienced DLT at the same dose level, the cohort at this level was closed and three more patients were included at the dose level below, which then was considered to be the maximum tolerated dose (MTD).

A 25% dose reduction of doxorubicin was made if the neutrophil nadir was <0.5 × 10⁹/l for ≥7 days or if the platelet nadir was <50 × 10⁹/l for ≥7 days. If this same haematological toxicity occurred again, then the paclitaxel dose was also reduced by 25%. Treatment was delayed for 1 week if on day 1 the neutrophil count was <1.5 × 10⁹/l or the platelet count was <100 × 10⁹/l, therapy then resumed but with a 25% reduction in doxorubicin dose. Treatment was stopped if non-haematological toxicities of grade ≥2 occurred. Carboplatin and paclitaxel were reduced 25% for grade 2 neurological toxicity; carboplatin was reduced to AUC 5 or 4 for GFR impaired to <60 ml/min or <50 ml/min, respectively; and doxorubicin was reduced by 25% for grade 2 mucositis with vesiculation and/or ulcers. If a symptomatic cardiac arrhythmia or an atrioventricular block greater than first degree was noticed, treatment was stopped.

**Results**

Twelve women with histologically confirmed EOC were included in the study (Table 1). Their median age was 53 years (range 41–72). One patient had FIGO (International Federation of Gynecology and Obstetrics) stage IC disease, seven patients had stage IIIC disease and four patients had stage IV disease. All patients had abdominal surgery prior to entering the study; in six patients macroscopic residual disease after surgery was ≥2 cm in diameter and eight patients had measurable disease on CT scanning post-surgery.

Three patients were treated at the starting dose level of paclitaxel 60 mg/m²/week, six patients at 75 mg/m²/week and three patients at 90 mg/m²/week. A total of 66 cycles were administered and the median number of cycles per patients was six (range 2–6).

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>53</td>
</tr>
<tr>
<td>Range</td>
<td>42–72</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
</tr>
<tr>
<td>Residual disease after surgery</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>6</td>
</tr>
<tr>
<td>≥2 cm</td>
<td>6</td>
</tr>
<tr>
<td>Measurable disease on CT scan</td>
<td>8</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>8</td>
</tr>
<tr>
<td>Mucinous</td>
<td>2</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>1</td>
</tr>
<tr>
<td>Transitional cell</td>
<td>1</td>
</tr>
<tr>
<td>Histopathological grade</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>1</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6</td>
</tr>
<tr>
<td>Not graded</td>
<td>1</td>
</tr>
</tbody>
</table>

FIGO, International Federation of Gynecology and Obstetrics; CT, computed tomography.
Six cycles. First, a 43-year-old patient treated at the 90 mg/m^2/week dose level had to stop chemotherapy after five cycles because of grade 3 peripheral neuropathy (a DLT), which prompted dose reduction in three patients [grade 2 in four patients (33%)]. Stomatitis was the DLT in most previously published trials [9, 10, 12, 18, 19]. Several groups have investigated the addition of an anthracycline to platinum–paclitaxel combinations but the toxicity of such three-drug combinations can be a problem [8–12, 18, 19].

In a randomised trial [15], chemotherapy-induced myelotoxicity and neurotoxicity in patients with EOC was significantly reduced without any detriment to efficacy when paclitaxel was administered weekly instead of 3-weekly. Furthermore, in vitro cancer models have demonstrated that paclitaxel can have antiangiogenic effects and these are thought to be more pronounced with weekly scheduling [20]. Remarkably, a recently published phase II trial showed responses to weekly paclitaxel in EOC patients refractory to 3-weekly paclitaxel–platinum [21].

In this phase I study, paclitaxel was administered weekly in order to reduce toxicity whilst maintaining dose intensity. DLTs, occurring at paclitaxel 90 mg/m^2/week, consisted of prolonged febrile neutropenia and grade 3 peripheral neuropathy. Myelotoxicity was the DLT in most previously published trials [9, 10, 12, 18, 22] for the combination of platinum–taxane–anthracycline, and it appears from our current study that weekly administration of paclitaxel does not result in less myelosuppression. All our patients experienced short-lived grade 4 neutropenia at the MTD.

An alternative strategy to reduce treatment-related neutropenia has been to use cisplatin rather than carboplatin. However, the combination of 3-weekly cisplatin (75 mg/m^2), paclitaxel (135 mg/m^2) and doxorubicin has not been recommended because it caused renal DLT and thrombocytopenia at a doxorubicin dose level of only 40 mg/m^2 every 21 days in one trial [8].

Non-haematological DLT in our current study was peripheral neuropathy which occurred at a frequency of 8% (one patient) and 33% (four patients) with grade 3 and 2 severity, respectively; this is consistent with other phase I studies using weekly paclitaxel as a single agent [14] or a three-drug combination of platinum–doxorubicin–paclitaxel [22].

Dose-limiting toxicity occurred at dose level 3 (paclitaxel 90 mg/m^2/week) and consisted of prolonged (>7 days) grade 4 febrile neutropenia in one patient and grade 3 peripheral neuropathy in a second patient. Thus, three more patients were treated at the lower dose (level 2, 75 mg/m^2/week), which was then considered to be the MTD.

Grade 3/4 neutropenia was observed in all patients and grade 3/4 thrombocytopenia in nine out of 12 patients (Table 2). 50% of patients required at least one hospital admission with short (<7 days) episodes of febrile neutropenia. Haematological toxicity did not cause a treatment termination in any patient, but led to dose modifications in six patients. The actual delivered dose intensity was 49 mg/m^2/cycle (12 mg/m^2/week) for doxorubicin, AUC 5.8/cycle (AUC 1.4/week) for carboplatin and 65 mg/m^2/week for paclitaxel. In the cohorts intended to be treated with 60, 75 and 90 mg/m^2/week of paclitaxel, the actual delivered doses were 54, 64 and 77 mg/m^2/week, respectively.

There were no grade 4 non-haematological toxicities. Fatigue was common, with grade 3 fatigue reported in two patients (17%) and grade 2 in five patients (42%). Other frequent toxicities were peripheral neuropathy, manifesting as paraesthesia [grade 3 in one patient (8%), grade 2 in four patients (33%)], stomatitis [grade 2 in four patients (33%)] and nail changes (not graded). Peripheral neuropathy led to a dose reduction in three patients (two at level 2, one at level 3). In the four patients who underwent a post-treatment MUGA scan, the ejection fractions remained normal and no evidence of congestive heart failure was found.

Three patients stopped treatment before completing the planned six cycles. First, a 43-year-old patient treated at the 90 mg/m^2/week dose level had to stop chemotherapy after five cycles because of grade 3 peripheral neuropathy (a DLT), which progressed even after a 25% dose reduction of paclitaxel during the fourth cycle. Secondly, a 53-year-old patient (at the dose level of 75 mg/m^2/week) who had had a nephrectomy in her youth for unknown reasons, developed urinary sepsis with impairment of renal function while neutrophil counts were normal and stopped treatment after five cycles had been given. Thirdly, on day 12 of the second cycle a 52-year-old patient with stage IIIC disease presented with neutropenic sepsis and progressive disease. Intensive care treatment including mechanical ventilation allowed her to recover from sepsis but she died 2 months later of progressive disease.

Eight out of 12 patients had measurable disease on CT scan: four obtained a partial remission; four had stable disease; and one patient progressed on treatment (Table 3). The median time to progression for all patients entering this study was 15.5 months [95% confidence interval (CI) 12.5–18] and the median survival was 35.2 months (95% CI 26.7–43.7).

### Table 2. Haematological toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Paclitaxel dose level (mg/m²/week)</th>
<th>60 (n = 3)</th>
<th>75 (n = 6)</th>
<th>90 (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>1</td>
<td>2</td>
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</tr>
<tr>
<td>Grade 4</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grade 3</td>
<td>1</td>
<td>3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>2</td>
<td>2</td>
<td>1</td>
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</table>

### Table 3. Objective response in eight patients with measurable disease

<table>
<thead>
<tr>
<th>Response</th>
<th>Paclitaxel dose level (mg/m²/week)</th>
<th>60 (n = 2)</th>
<th>75 (n = 3)</th>
<th>90 (n = 3)</th>
<th>All patients (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Partial remission</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td></td>
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</tbody>
</table>
We have found that the MTD of paclitaxel in this combination therapy was 75 mg/m²/week (level 2). However, the actual dose delivered at level 2 was only 64 mg/m²/week, since all six patients experienced at least one episode of grade 4 neutropenia that required dose reduction or delay. Thus, we were able to maintain the standard paclitaxel dose intensity commonly used for the platinum–paclitaxel combination, whilst adding an anthracycline. In contrast, the dose intensity of anthracycline in our study seems low (12.5 mg/m²/week) when compared with the doses used by other groups: 25 mg/m²/week in the on-going phase III intergroup trial performed by NSGO–EORTC–NCIC [11]; and 20 mg/m²/week in the recently completed phase III trial by AGO–GINECO [12]. It is worth noting however, that the latter two studies use epirubicin for which cumulative cardiotoxicity occurs at considerably higher dose levels than for doxorubicin which was used here. For three-drug combinations including doxorubicin in EOC, comparable doses have been used by others [22].

A reduction in toxicity, one of the rationales for using weekly paclitaxel in this schedule, was not achieved. If the observation that weekly paclitaxel is more effective in EOC than three-weekly paclitaxel [21] is confirmed in future studies, our schedule merits further investigation. Paclitaxel and doxorubicin are both eliminated by biliary excretion mediated via P-glycoproteins, and this can result in an increase in the plasma concentration of doxorubicin and its metabolite doxorubicinol [23], which is thought to be responsible for cardiotoxicity, when both drugs are administered concurrently. This pharmacokinetic interference is dose-dependent [23] and in our weekly paclitaxel schedule the paclitaxel dose administered on the same day as doxorubicin is significantly lower than in the previously described 21-day schedules. This may reduce cardiotoxicity, and in our study no patient developed heart failure.

There are numerous different histological subtypes of EOC but generally they tend to be treated by the same first-line chemotherapy, i.e. carboplatin–paclitaxel. In some patients with endometrioid histology there can be doubt about the origin of the primary, if for instance there are tumour deposits in both the ovary and the endometrium. These patients might benefit from the addition of doxorubicin to a carboplatin–paclitaxel regimen, because randomised data suggest that a platinum–doxorubicin combination is superior to single-agent platinum in patients with endometrial cancer [24]. There are no randomised controlled trials supporting the use of carboplatin–paclitaxel in endometrial cancer, although phase II data suggest that paclitaxel is active [25].

In summary, the combination of carboplatin, doxorubicin and paclitaxel in patients with EOC is active and its main toxicity is myelosuppression. No cardiotoxicity was observed; grade 2 or 3 fatigue and neurotoxicity occurred in 57% and 41%, respectively. Weekly administration of paclitaxel allows the delivery of a three-drug combination whilst maintaining dose intensity with equivalent toxicity. A weekly paclitaxel dose of 65 mg/m² is recommended for phase II trials of this three-drug combination.

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