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Combining platinum, paclitaxel and anthracycline in patients with advanced gynaecological malignancy

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Abstract

Two meta-analyses have suggested that the addition of an anthracycline to platinum-based chemotherapy may improve survival in advanced ovarian cancer, and two randomised trials have demonstrated superiority of paclitaxel over cyclophosphamide in platinum combinations. A combination of platinum, anthracycline and paclitaxel would, therefore, be a reasonable experimental arm of any future randomised trial in patients with epithelial ovarian carcinoma (EOC). Patients who required chemotherapy for EOC but were ineligible for standard trials or had other gynaecological tumours that required similar platinum-based chemotherapy were considered for this pilot. The platinum/anthracycline/paclitaxel regimen (G-CAT) was given 3-weekly and consisted of doxorubicin 50 mg/m^2 or epirubicin 60 mg/m^2 intravenously (i.v.) bolus, paclitaxel 175 mg/m^2 (i.v.) over 3 h and either cisplatin 75 mg/m^2 (i.v.) or carboplatin AUC 6, with granulocyte colony-stimulating factor (G-CSF) at the neutrophil nadir. Different combinations were used in order to determine the least toxic regimen. Toxicity and response were assessed according to CTC and WHO criteria, respectively. 26 patients entered the study, 13 with EOC and 13 with other gynaecological cancers (peritoneal, fallopian tube, mixed Mullerian). Median age was 49 years (range: 27–67). 8 patients received carboplatin/doxorubicin/paclitaxel, 8 cisplatin/doxorubicin/paclitaxel and 10 carboplatin/epirubicin/paclitaxel. A total of 135 cycles of chemotherapy were delivered, with a median of 6 cycles per patient (range: 2–6). 54 (40%) cycles required G-CSF support and 17 (65%) patients required at least one dose reduction. All patients experienced grade 4 neutropenia and 13 (50%) patients developed grade 3–4 thrombocytopenia (12 of whom had received carboplatin). There were 4 (15%) patients with grade 3/4 infections but no septic deaths. Non-haematological toxicities were manageable, lethargy occurred in 75% of cisplatin-treated patients. Grade 1/2 cardiotoxicity, as assessed pre- and post-treatment by left ventricular ejection fraction, was observed in 6/13 (46%) patients who had received doxorubicin and 2/7 (29%) epirubicin-treated patients. No clinically detectable cardiac toxicity was encountered. The response rate in 25 evaluable patients was 76% (12 CR, 7 PR). Dose intensity was highest in the carboplatin/epirubicin/paclitaxel combination. G-CAT shows high activity and can be administered safely, but only very fit patients are suitable for this regimen as it is associated with considerable toxicity. Carboplatin/epirubicin/paclitaxel was the best tolerated regimen overall.

Keywords: Platinum; Anthracycline; Paclitaxel; Ovarian cancer

1. Introduction

Epithelial ovarian cancer (EOC) is the commonest gynaecological cancer and it presents as advanced disease in the majority of patients. The overall prognosis remains poor despite high response rates with combination therapy. Standard treatment involves platinum-based regimens with carboplatin and cisplatin appearing to be equally effective [1,2]. Meta-analyses suggest that platinum-based combination therapy results in a survival benefit when compared with single-agent platinum treatment [1,3]. The cytotoxic agents most frequently combined with platinum in the past were the alkylating agents, the anthracyclines and in recent years paclitaxel. Paclitaxel is the most developed of a number of promising new cytotoxics, with response rates in relapsed disease ranging from 19 to 47% [4–7]. Objective responses have been reported in patients who have demonstrably platinum-resistant disease i.e. progression during platinum therapy, and the response rate in this group of patients in one study was 21% [8].

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The Gynaecologic Oncology Group (GOG) trial 111 compared paclitaxel plus cisplatin against cyclophosphamide plus cisplatin as initial treatment for patients with advanced ovarian cancer [9]. A significant survival benefit was demonstrated for the paclitaxel plus cisplatin arm, and this regimen is now standard therapy in the USA and many other countries. A confirmatory study performed by an Intergroup (EORTC-NCI-NOCOVA-Scottish Intergroup) confirmed the benefit of the cisplatin–paclitaxel combination over cisplatin–cyclophosphamide in terms of response, progression-free and overall survival [10]. The combination of a platinum drug and paclitaxel is now standard therapy for patients with EOC. The role of anthracyclines in combination regimens has in the past been called into question despite the suggestion from the Ovarian Cancer Meta-Analysis project that the addition of doxorubicin to platinum-based chemotherapy might confer a survival benefit [11]. This possibility has been supported by the results of a more recent meta-analysis involving data from the Advanced Ovarian Cancer Trialists Group and the Ovarian Cancer Meta-analysis Project [12]. There is therefore a sound clinical rationale for including an anthracycline in a new combination regimen, and since platinum, paclitaxel and anthracyclines are amongst the most active single agents in epithelial ovarian cancer it is reasonable to combine these drugs. Furthermore, the *in vitro* evidence of synergy between paclitaxel and doxorubicin provides a preclinical justification for combining these two agents [13]. We have, therefore, proposed a study to investigate the feasibility of combining paclitaxel with one agent from each of the other two groups of drugs. We also examined the relative merits of utilising cisplatin or carboplatin as the platinum compound and doxorubicin or epirubicin as the anthracycline.

The dose and schedule for each agent were derived from published data. Trials of combinations of paclitaxel with carboplatin, at high-dose with or without peripheral blood stem cell support, suggest that at doses of 250 mg/m^2 of paclitaxel and an AUC 10 for carboplatin, neuropathy and emesis are not significant [14]. A high-dose study combining doxorubicin, paclitaxel and cyclophosphamide has been reported using 250 mg/m^2 paclitaxel and 90 mg/m^2 doxorubicin with granulocyte colony-stimulating factor (G-CSF) support in which grade 3 haematological toxicity occurred in less than 10% of patients [15]. Granulocytopenia is dose limiting when paclitaxel is given at a dose of 135 mg/m^2 over 24 h together with carboplatin AUC 7.5 but other toxicities are mild and myelosuppression can be substantially reduced if G-CSF support is given [16]. In view of this information G-CSF was included in our regimen, although only at the neutrophil nadir. The anthracycline was in all cases delivered prior to the paclitaxel since the reverse sequence appears to increase toxicity, at least in patients with breast cancer [17]. Studies with single-agent paclitaxel have shown that toxicity is less with a 3-h infusion compared with a 24-h infusion and schedule appears to be more important than dose within the range studied [5].

The objectives of this feasibility study were to determine the toxicity profiles of three different platinum/anthracycline/paclitaxel combinations in patients with advanced gynaecological malignancy with particular emphasis on cardiac toxicity, and to investigate their therapeutic activity.

2. Patients and methods

Patients with histologically confirmed, chemonaïve stage Ic-IV EOC or with advanced stage intra-abdominal malignancy whose treatment is similar to that of EOC (e.g. peritoneal carcinoma, fallopian tube carcinoma, intra-abdominal carcinoma of probable genital tract origin) were considered for this study. Patients with EOC who enter this study were ineligible for first-line chemotherapy trials, owing to, for example, a prior or concurrent malignancy.

The treatment regimens were administered at the following doses in the sequence indicated: doxorubicin 50 mg/m^2 or epirubicin 60 mg/m^2 intravenous (i.v.) bolus, paclitaxel 175 mg/m^2 i.v. over 3 h, carboplatin AUC 6 or cisplatin 75 mg/m^2 i.v. over 1 h. Standard premedication was given prior to paclitaxel administration and similarly standard hydration with normal saline containing potassium and magnesium was utilised pre- and postdelivery of cisplatin. Treatment was delivered on a 3-weekly cycle. G-CSF 300 μg/day was commenced subcutaneously if the neutrophil count fell below 0.5×10^9/l and continued until it recovered to above this level in keeping with unit policy at the time. Antiemetic prophylaxis consisted of i.v. ondansetron prechemotherapy and oral dexamethasone and metoclopramide for 3 days afterwards.

Pretreatment assessment consisted of full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT), serum calcium, serum CA 125, ^{51}[Cr] EDTA clearance, electrocardiogram, radionuclide MUGA scan for left ventricular ejection fraction, chest X-ray and computerised tomography (CT) of the abdomen and pelvis. The FBC, U&E, LFTs and CA 125 were repeated prior to each course of therapy or 4 weeks after the last course of treatment. Patients were also assessed at these time points for subjective toxicities according to the NCI common toxicity criteria [18]. In addition, FBCs were repeated on day 10 after each cycle, ^{51}[Cr] EDTA clearance was repeated after cycles 3 and 6 and MUGA scans 4 weeks after the last treatment.

Dose reductions were instituted as follows: grade 4 neutropenia or thrombocytopenia for greater than 7 days, paclitaxel reduced by 25% and if further grade 4

toxicity occurred on a subsequent cycle, the anthracycline was reduced by 25% (carboplatin doses were not reduced as it was felt to be important to maintain the dose intensity of the platinum in the regimen); grade 2–4 mucositis, paclitaxel reduced by 25%, and if further grade 2–4 toxicity occurred on a subsequent cycle, the anthracycline was reduced by 25%; grade 1 neuropathy, paclitaxel and cisplatin reduced by 25%, grade 2 neuropathy, paclitaxel and cisplatin reduced by 50%, grade 3–4 neuropathy, patient withdrawn from study.

Tumour responses were assessed according to standard UICC criteria by clinical examination and CT scans after cycles 2, 4, 6: complete response (CR), disappearance of all documented tumour manifestations for a minimum of 4 weeks; partial response (PR), decrease of 50% or greater in total tumour load of the lesions that have been measured to determine the effect of therapy, for a minimum of 4 weeks; stable disease (SD), smaller than 50% decrease and 25% increase, respectively, in the size of lesion(s) with appearance of no new lesions; progressive disease (PD), increase of 25% or greater in the size of one or more measurable lesions or appearance of new lesions.

The duration of CR was measured from the date the complete response was first recorded until the date of documented disease progression. Time to tumour progression (TTP) was calculated from the date of the first treatment cycle until disease progression. TTP was recorded in patients with partial responses as well as those with stable disease. Dose intensity was calculated per drug per course taking the doses from course one as 100%.

Fully informed written consent was obtained from all patients prior to study entry in accordance with the guidelines issued by The Royal Marsden NHS Trust Research Ethics Committee.

3. Results

26 patients were entered into this study between March 1995 and October 1996. 13 patients had EOC, 6 patients had intra-abdominal carcinomatosis of unknown origin, 4 patients were thought to have primary peritoneal carcinoma, 2 patients had carcinoma of the fallopian tube and 1 patient had carcinosarcoma. The majority of the patients, 22/26 (85%) had bulk disease at presentation. One patient (4%) was stage Ic, 2 (8%) stage IV and the remainder (88%, $n=23$) stage IIIc. The first 8 patients received carboplatin/doxorubicin/paclitaxel (Regimen 1), the next 8 patients were treated with cisplatin/doxorubicin/paclitaxel (Regimen 2) and in the last cohort of 10 patients the treatment consisted of carboplatin/epirubicin/paclitaxel (Regimen 3). The median age of patients was 49 years (range: 27–67). The median number of cycles per patient was 6 (range: 2–6) with a total of 135 cycles of chemotherapy being administered (Table 1).

All patients were evaluated for toxicity. The major toxicity encountered in this study was myelosuppression and Table 2 shows the overall and day 21 maximum haematological toxicity per patient. All patients had transient grade 4 neutropenia and 13 patients (50%) grade 3–4 thrombocytopenia, but recovery by day 21 was normally observed and did not vary significantly between regimens. The incidence of grade 3–4 thrombocytopenia was significantly greater in those patients who received carboplatin compared with cisplatin (67% ($n=12$) versus 12% ($n=1$), $P=0.015$). 4 patients (15%) developed grade 3/4 infections but there were no deaths related to sepsis from this treatment. 2 patients died of progressive disease after only two and three courses, respectively.

Non-haematological toxicities were manageable and are shown in Table 3. A toxicity of particular note was that of severe lethargy (ungraded, assessed by a fall in performance status compared with the pretreatment level) which occurred in 9 patients (35%); its incidence was significantly more frequent in cisplatin-treated patients (75%, $n=6$) than in those receiving carboplatin (17%, $n=3$, $P=0.003$). Cardiotoxicity as assessed by MUGA scan is shown in Table 4; 6/13 (46%) patients receiving doxorubicin and 2/7 (29%) of patients receiving epirubicin developed grade 1–2 cardiotoxicity but this difference was not statistically significant. Full cardiotoxicity data are not available for all patients as

Table 1
Patient characteristics, delivery of chemotherapy and response[a]

		n (%)
Patients	Total treated	26 (100)
Age (years)	Median (range)	49 (27–67)
Primary site	Ovary	13 (50)
	Peritoneum	4 (15)
	Fallopian tube	2 (8)
	Carcinosarcoma	1 (4)
	Unknown	6 (23)
Regimen	Carboplatin/doxorubicin/paclitaxel (R1)	8 (31)
	Cisplatin/doxorubicin/paclitaxel (R2)	8 (31)
	Carboplatin/epirubicin/paclitaxel (R3)	10 (38)
Cycles delivered	Total	135 (100)
Cycles with G-CSF		54 (40)
Cycles/patient	Median (range)	6 (2–6)
Dose reductions	Number of patients	17 (65)
Response	CR	12 (48)
	PR	7 (28)
	NC	2 (8)
	PD	3 (12)
	NE	1 (4)

[a] R, regimen; NE, not evaluable; NC, no change; CR, complete responder; PR, partial responder; PD, progressive disease.

Table 2
Haematological toxicity, worst grade per patient ($n=26$)

CTC grade	0	1	2	3	4
a-overall					
Leucopenia	0	0	5	6	15
Neutropenia	0	0	0	0	26
Anaemia	0	8	9	9	0
Thrombocytopenia	4	6	3	5	8
b-Day 21					
Leucopenia	9	7	6	4	0
Neutropenia	16	2	5	3	0
Anaemia	3	11	12	0	0
Thrombocytopenia	18	1	2	3	2

some stopped treatment before a second assessment due to progression of disease or other unacceptable toxicities. There were no episodes of clinically detectable cardiac dysfunction.

17 patients (65%) patients required at least one dose reduction and 19 (73%) patients received G-CSF for 54 cycles. Generally it was possible to maintain dose intensity across time especially for the platinum drug and anthracycline. Regimen 3 was delivered at a marginally higher dose intensity than regimen 2, The dose intensity of regimen 1 was significantly lower than either of the other two regimens.

One patient was not evaluable for response as there was no measurable disease. The response rate in the remaining 25 evaluable patients was 76% (12 complete remissions, 7 partial remissions, 95% confidence interval (CI): 61–93%). One patient showed no change in their disease and 3 patients progressed on treatment. The median follow-up in this study is 36 months, the median failure-free survival is 16 months and the mean overall survival is 33 months. Currently 11 patients are still alive at 17, 31, 33, 34, 35, 36, 36, 42, 45, 46 and 47 months, respectively.

4. Discussion

Anthracyclines, platinums and taxanes are the three most active groups of compounds in patients with advanced EOC. We have been able to combine drugs from each group in a patient population for whom ovarian cancer-type therapies are commonly utilised. This strategy has produced a very high rate of complete remission ($n=12/25$, 48%) but was attended by significant toxicity. Clinically relevant dose escalation is thus unlikely to be feasible. In addition, it is apparent that only fit patients are likely to tolerate this combination regimen at the doses we delivered. The dose-limiting toxicity was myelosuppression as anticipated, with all patients developing grade 4 neutropenia although only 4 patients developed a serious infection and there were no septic deaths. It is worth emphasising that taking a blood count at the neutrophil nadir (i.e. day 10) the recorded haematological toxicity was exaggerated, as shown by recovery of patient blood counts at day 21 (Table 2b). Growth factor support was given to patients only when indicated and it remains to be assessed whether or not the prophylactic use of G-CSF would reduce the overall toxicity of platinum/anthracycline/paclitaxel combinations and allow for their delivery to a wider patient population.

Table 3
Non-haematological toxicity, worst grade per patient ($n=24$)

CTC grade	0	1	2	3	4
Nausea	3	10	7	4	0
Vomiting	10	3	6	5	0
Mucositiss	9	8	6	1	0
Diarrhoea	9	6	8	1	0
Constipation	6	14	3	1	0
Neuropathy	7	13	3	1	0
Alopecia	0	2	22	0	0
Infection	8	8	4	4	0

Table 4
Cardiac toxicity as assessed by MUGA scan pre-and post-treatment ($n=20$)

Grade	Doxorubicin	Epirubicin
0 (< 5% fall)	7 pts[a]	5 pts
1 (5–20% fall)	3 pts	2 pts
2 (> 20% fall)	3 pts	0 pts
Total (n)	13 pts	7 pts

[a] pts, patients.

We have shown differences in toxicity between analogues within the same group of compounds. For instance, thrombocytopenia was significantly less marked with cisplatin compared with carboplatin but its use increased lethargy and nausea. Neither of these two toxicities are life threatening but they can affect patient compliance and 2 patients refused to complete the intended six courses because of disabling fatigue. Neurotoxicity was not a problem in this study, even in the patients who received cisplatin. Studies have shown that the cardiotoxicity of doxorubicin and paclitaxel is schedule dependent, probably as a consequence of the prolongation of the half-life of anthracyclines by the cremaphor vehicle of paclitaxel [19–21]. There are indications from our data that epirubicin is less cardiotoxic than doxorubicin within the context of our regimens but this difference failed to reach statistical significance, possibly a result of the relatively small numbers of patients involved. The clinical significance of this finding is also uncertain since no patients developed clinically apparent cardiac dysfunction. Dose intensity was highest with the carboplatin/epirubicin/paclitaxel regimen and this is mirrored by the lower toxicity seen with this combination.

The overall response rate (76%) was very encouraging but difficult to interpret in this series due to the mixed nature of the patient population. However, this high CR rate was not translated into a particularly favourable relapse-free survival (median: 16 months). The latter may reflect the poor prognosis of some of the tumours which were not of ovarian origin, rather than any deficiency in the regimens. Three other groups have reported results of similar combinations in gynaecological malignancies [22–25]. All report high activity and acceptable toxicity, providing further evidence of the feasibility of such regimens and justification for continued investigation into their development.

Paclitaxel and carboplatin can be safely combined with doxorubicin or epirubicin and the combination of carboplatin/epirubicin/paclitaxel is now being assessed as first-line treatment by the AGO in a randomised study. Our data suggest that there is less lethargy and nausea with carboplatin and because of the other well known advantages of carboplatin over cisplatin, we recommend carboplatin as the platinum compound of choice in combination regimens that include anthracycline, paclitaxel and platinum.

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