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Original article

Phase II clinical trials of cisplatin-then-paclitaxel and paclitaxel-then-cisplatin in patients with previously untreated advanced epithelial ovarian cancer

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Summary

Purpose: To examine the activity and safety of two sequentially scheduled chemotherapy regimens comprising four cycles of paclitaxel (pctx) 200 mg/m^2/3 hours then four cycles of cisplatin (cisDDP) 100 mg/m^2, and *vice versa*, in patients with previously untreated advanced ovarian cancer.

Patients and methods: Between January 1994 and February 1996, we recruited 30 patients to the pctx-then-cisDDP regimen and 29 to cisDDP-then-pctx, in parallel phase II trials.

Results: Both regimens were predictably active with responses seen in 22 of 30 patients (OR 74%; CR 27%, PR 47%) treated with pctx-then-cisDDP, as against 13 of 21 patients (OR 62%; CR 38%, PR 24%) treated with cisDDP-then-pctx. The OR rate to four cycles of pctx (induction) was 43%, with 27% disease progression; the OR to four cycles of cisDDP (induction) was 57%, with 5% progression. However, progression rates across both induction and consolidation phases were 16% (pctx-then-cisDDP) and 29% (cisDDP-then-pctx). Both regimens were unacceptably neurotoxic, 11 patients suffering grade 3 sensory neurotoxicity (5 on pctx-then-cisDDP, 6 on cisDDP-then-pctx) and 20 having grade 3 deafness (9 on pctx-then-cisDDP, 11 on cisDDP-then-pctx).

Conclusion: The activity of these sequential regimens justifies their further development using the less neurotoxic platinum analogue carboplatin, perhaps combining paclitaxel with other platinum non-cross resistant drugs.

Key words: cisplatin, ovarian cancer, paclitaxel, sequential chemotherapy

Introduction

In May 1993, the Gynaecologic Oncology Group (GOG) presented interim results of the GOG111 study, a randomised phase III trial, demonstrating that the substitution of paclitaxel for cyclophosphamide in combination with cisplatin improved the median progression-free survival of patients with sub-optimally debulked stage IIIc–IV ovarian cancer by four months [1]. At the time, these interim data were widely interpreted as disappointing, given the optimism previously engendered by paclitaxel's reported activity of 30% in heavily pre-treated patients in early phase II trials [2]. They prompted us to consider whether the sequential exhibition of cisplatin and paclitaxel might be superior to their conventional simultaneous combination.

Probabilistic models of tumour cell heterogeneity and lineage infidelity, developed in the late 1970's by Goldie and Coldman, relate the spontaneous development of drug resistant cell clones to the number of actively dividing tumour cells present and their mutation rate [3]. These predict that regimens combining non-cross-resistant cytotoxic drugs would retard the evolution of drug resistant clones, and minimise the risk of treatment failure [4]. Unfortunately, phase III clinical trials in both small-cell lung cancer and advanced breast cancer have failed to substantiate this hypothesis [5, 6].

Norton and Day have attributed this failure to the unexpectedly stringent implications of some assumptions made by Goldie and Coldman, in particular that the available non-cross resistant cytotoxics were equipotent in their individual log cell kill [7]. Computer models, which corrected for this real-life asymmetry, predicted that improved overall therapeutic effect might be obtained by exhibiting the worse drug (that with lower log cell kill) first, until the tumour was cytoreduced to the point where the spontaneous evolution of forms resistant to the better drug was diminishingly improbable.

Prospective clinical trials testing this hypothesis have not, to our knowledge, been undertaken. These appear difficult to frame as we have no direct knowledge of how to quantify log cell kill *in vivo:* Response rate seems an imperfect surrogate. Furthermore, the limitations of the Norton–Day modification itself are all too clear: not only are differences in cytotoxic log cell kill a frequent occurrence, but so is incomplete and asymmetric non-cross

resistance. Each of these eventualities may have potentially confounding implications for the design of sequential regimens.

However, several studies have been published which have empirically evaluated sequentially scheduled cytotoxic regimens. Perhaps the most influential has been the Milan Group's demonstration of the superiority of a sequential regimen of doxorubin-then-CMF over an alternating regimen of identical duration and dose intensity in the adjuvant therapy of higher risk node positive early stage breast cancer [8, 9]. Two other trials in small-cell lung cancer and node positive breast cancer point to the sequential addition of non-cross-resistant drugs being advantageous [10, 11]. Well-documented relationships between pharmacokinetic parameters and response or survival data are all too rare in clinical oncology, and its intriguing that one of the first should be recorded within the second phase of a sequential regimen [12].

Further prospective studies of sequentially scheduled non-cross resistant regimens therefore appear justified. However, any attempt to apply the Norton-Day principles to the rational development of a sequential regimen of paclitaxel and cisplatin for ovarian carcinoma, for example, requires *a priori* knowledge of these drugs' relative potency and respective patterns of non-cross resistance, specifically their extent and symmetry. Whilst the literature contained ample data concerning both the activity of first-line cisplatin in epithelial ovarian cancer [13] and response rates to paclitaxel salvage after early relapse [2], at the time of initiation, there was a dearth of information about the activity of first-line paclitaxel, and the extent to which immediate crossover to second-line cisplatin might salvage those patients unresponsive to first-line paciltaxel. We therefore carried out a study of paclitaxel-then-cisplatin (pctx-then-cisDDP) in women with measurable ovarian cancer. Simultaneously, we undertook a second study of cisplatin-then-paclitaxel (cisDDP-then-pctx) in women with non-measurable tumour (but poor prognosis by virtue of diffuse peritoneal seedlings), initially as a pilot to look for preliminary evidence of any sequence-specific toxicological effects, and subsequently in patients with measurable disease to further examine patterns of sequential activity.

Patients and methods

Patient selection

These prospective studies were initiated in January 1994. Entry criteria included a histologically confirmed diagnosis of advanced epithelial ovarian cancer, adequate marrow reserve (WBC $\geqslant 3$, platelets $\geqslant 100{,}000$), renal function (Cr-labelled EDTA clearance $\geqslant 45$ mls/min), and bilirubin $\leqslant 30$ μmol/l. All patients were sub-optimally debulked (> 2 cm) or left with diffuse small volume peritoneal seedlings. Patients with unstable angina, uncontrolled heart failure, chronic neurological conditions, previous malignancy (other than adequately treated squamous or basal cell carcinoma, or *in situ* carcinoma of uterine cervix), previous treatment with cytotoxic drugs or radiotherapy, or coexistent medical or psychiatric conditions likely to preclude compliance with the requirements of the study were excluded. Ethics committee approval was obtained for each site. All patients provided written informed consent in accordance with institutional guidelines.

Treatment program

Patients with measurable disease were assigned to receive four cycles of pctx 200 mg/m^2/3 hours followed by four cycles of cisDDP 100 mg/m^2. Patients without measurable disease, but with diffuse peritoneal seedling disease documented at laparotomy, were allocated treatment with four cycles of cisDDP 100 mg/m^2, followed by four cycles of pctx 200 mg/m^2. Patients with evidence of clinical disease progression after their first two cycles of treatment were crossed over immediately. Drugs were administered according to institutional protocols, with saline diuresis and 5-HT3 antagoinst-based anti-emetic regimens.

A three-week dose interval was maintained throughout, conditional to an absolute neutrophil count $\geqslant 2 \times 10^9$/l, or platelets $\geqslant 100 \times 10^9$/l on day 22. Renal function was monitored during the cisplatin phase of treatment using the Cockcroft calculation and carboplatin substituted (Calvert formula, AUC 7 [14]) if the calculated clearance fell to < 50 ml/min. Carboplatin was also substituted for cisplatin in the event of grade 2 neuropathy. Recombinant growth factors were not used.

Response and toxicity criteria

Therapeutic effects were gauged using standard UICC criteria, in relation to baseline clinical assessment, CT imaging and chest X-rays, repeated after four and eight cycles of chemotherapy. Thus, objective responses (OR) were documented as partial response (PR) rate and complete response (CR) rate measured across first-line (induction) treatment and for all treatment (both induction and consolidation phases). CA125 measurements were made before each chemotherapy cycle and three weeks after completion.

Toxicity was graded according using CTC common toxicity criteria. For each patient, the worst grade suffered during or immediately after treatment was recorded. Audiograms were undertaken before and after treatment to record ototoxicity. The ECOG scale was used to record performance status (PS).

Statistical methods

The primary endpoints of the pctx-then-cisDDP study were conventional UICC response rates, across first phase of treatment (after four cycles) and overall, at completion (after eight cycles); secondary endpoints were serological response rates (recorded as time to remission and percentage change in CA125), toxicity, progression-free survival and overall survival.

The original primary endpoints of the cisDDP-then-pctx study were toxicological with secondary endpoints serological response rates, progression-free survival, overall survival and UICC response rates (for those patients with measurable disease latterly included).

Survival was calculated from date of entry to trial until date of death, or until date last seen, if alive. Progression-free survival (PFS) was defined as the time from entry until progression if clinically progressed, until date of death if died with no recorded progression or until date last seen, if alive and have not progressed. Survival curves were constructed using the method of Kaplan and Meier [15].

The median percentage change in CA125 levels across each phase of treatment was calculated for each patient and compared using a Wilcoxon rank sum test. Potential difficulties in formulating CA125 (serological) response were addressed by recording serological remission if CA125 levels reached the normal value of 30 U/ml. Time to remission was calculated from the date start treatment until date of serological remission, or until the date finished treatment for those not in remission. All analyses were carried out using SAS statistical software (SAS Institute, SAS Circle, Cary, North Carolina, USA).

Table 1. Patient characteristics on entry.

	Chemotherapy sequence		
	pctx-cisDDP	cisDDP-pctx	
	n (%)	*n* (%)	*n* (%)
Number for analysis	30 (all)	29 (all)	21 (meas)
Age (years)			
Median	59	53	55
Range	31–73	23–70	23–70
Stage			
Ic (relapsed)	0 (0)	2 (7)	2 (10)
IIb	0 (0)	1 (3)	0 (0)
IIIa	1 (3)	0 (0)	0 (0)
IIIb	1 (3)	2(7)	0 (0)
IIIc	14 (47)	20 (69)	15 (71)
IV	14 (47)	4 (14)	4 (19)
Histology			
Serous	16 (53)	19 (66)	13 (62)
Endometroid	5 (17)	4 (14)	3 (14)
Clear cell	2 (7)	0 (0)	0 (0)
Undifferentiated	5 (17)	4 (14)	4 (19)
Mixed epithelial	2 (7)	1 (3)	0 (0)
Transitional	0 (0)	1 (3)	1 (5)
Tumour grade			
Well	5 (17)	0 (0)	0 (0)
Moderate	7 (23)	18 (62)	12 (57)
Poor	16 (53)	11 (38)	9 (43)
Not known	2 (7)	0 (0)	0 (0)
ECOG performance status			
0	7 (23)	9 (31)	4 (19)
1	17 (57)	9 (31)	8 (38)
2	6 (20)	3 (10)	2 (9)
3 & 4	0 (0)	6 (21)	6 (29)
Not known	0 (0)	2 (7)	1 (5)
Measurable			
Evaluable	1 (3)	0 (0)	
Measurable	29 (97)	21 (72)	
Non-measurable	0 (0)	8 (28)	
Serum albumin (g/l)			
Median	38	39	39
Range	27–46	28–49	28–45

Results

Between January and December 1994, 31 patients were enrolled on the pctx-then-cisDDP trial. However, over the same period, just eight patients were registered on the cisDDP-then-pctx trial. Therefore, the entry criteria were changed to include only patients with measurable disease and the cisDDP-then-pctx trial subsequently recruited a further 21 patients on this basis. One patient allocated pctx-then-cisDDP was subsequently excluded from all analyses after histology review indicated a diagnosis of colorectal carcinoma.

Patient characteristics

The pre-treatment characteristics of the 59 eligible patients enrolled on both trials are recorded in Table 1. The median age of those treated with pctx-then-cisDDP was 59 years; all had an ECOG performance status 0–2. Sixteen (53%) patients had serous morphology and two (7%) had clear-cell tumours; sixteen (53%) patients had poorly differentiated tumours; fourteen (47%) had stage IIIc tumours and fourteen (47%) stage IV.

The median age for those treated with cisDDP-then-pctx was 53 years; 6 (21%) had a performance status of 3 or 4 at the outset. Nineteen (66%) patients had serous morphology, but none had clear-cell morphology; eleven (38%) patients had poorly differentiated tumours; twenty (69%) had stage IIIc tumours and four (14%) stage IV. Characteristics of the 21 patients with measurable disease treated on the modified protocol with cisDDP-then-pctx are shown separately in Table 1.

Table 2. Chemotherapy delivered.

	Number of cycles	Chemotherapy sequence	
		pctx-cisDDP *n* (%)	cisDDP-pctx *n* (%)
Paclitaxel	0	0 (0)	3 (10)
	1	1 (3)	0 (0)
	2	1 (3)	4 (14)
	3	4 (14)	1 (4)
	4	24 (80)	21 (72)
Cisplatin	0	5 (16)	0 (0)
	1	3 (10)	4 (14)
	2	2 (7)	4 (14)
	3	2 (7)	5 (17)
	4	17 (57)	16 (55)
	5	1 (3)	0 (0)
Carboplatin	0	16 (54)	18 (62)
	1	4 (13)	4 (14)
	2	4 (13)	3 (10)
	3	2 (7)	3 (10)
	4	3 (10)	1 (4)
	5	1 (3)	0 (0)

Chemotherapy delivered

Details of the chemotherapy received are shown in Table 2. A similar proportion of patients completed four cycles of pctx in either trial (80% pctx-then-cisDDP, 72% cisDDP-then-pctx). The main reason for not completing pctx treatment for patients allocated pctx-then-cisDDP was disease progression, and neuropathy for those allocated cisDDP-then-pctx (Table 3).

Similar numbers of patients completed at least four cycles of cisDDP in both trials (60% pctx-then-cisDDP, 55% cisDDP-then-pctx) and a similar proportion required carboplatin substitution (46% pctx-then-cisDDP, 38% cisDDP-then-pctx) (Table 2). The main reason for this in both trials was hearing loss (Table 3).

Therapeutic activity

Responses were evaluated for 30 patients treated with pctx-then-cisDDP and 21 patients with cisDDP-then-pctx. Following response assessment after the first four cycles, a similar proportion of patients in each trial

Table 3 Reasons for not completing the full course of treatment.

	Chemotherapy sequence	
	pctx-cisDDP	cisDDP-pctx
Reasons for not completing four cycles of pctx		
Anaphylactic shock	0	1
Neuropathy	0	4
Withdrew consent	0	2
Progression	4	0
Early death	2	1
Reasons for not completing four cycles of cisDDP		
Allergic reaction & hearing loss	1	0
Diarrhoea	1	0
Haematemesis	0	1
Hearing loss	4	8
Neuropathy	2	0
Vomiting	1	2
Withdrew consent	0	1
Progression	1	0
Early death	2	1

experienced both CR (pctx-then-cisDDP 10%, cisDDP-then-pctx 9%) and stable responses (pctx-then-cisDDP 30%, cisDDP-then-pctx 33%). However, there were ostensible differences in PR (pctx-then-cisDDP 33%, cisDDP-then-pctx 48%) and progression rates (pctx-then-cisDDP 27%, cisDDP-then-pctx 5%).

The OR across both phases of treatment for pctx-then-cisDDP was 74% (CR 27%, PR 47%), stable disease (SD) 10%, and progression 16%. For cisDDP-then-pctx, OR was 62% (CR 38%, PR 24%), SD 9% and progression 29%.

Toxicity

The number of patients suffering severe neurotoxicity was similar in each trial. In the pctx-then-cisDDP trial, five patients suffered grade 3 sensory neurotoxicity, nine had grade 3 hearing loss and one had grade 3 motor deficiency. In comparison in the cisDDP-then-pctx trial, 6 patients suffered grade 3 sensory neurotoxicity, 11 had grade 3 hearing loss and 2 had grade 3–4 motor deficiency. There were no patients with a PS of 3 or 4 at registration amongst those allocated pctx-then-cisDDP but this increased to 13% during treatment. For patients allocated cisDDP-then-pctx, 21% were PS 3–4 at the outset, rising to 28% at worst. Overall expected rates of grade 3 and 4 emetic (29%) and GI (5%) toxicity were encountered. The incidence of grade 3 fever was 3% in the pctx-then-cisDDP trial and incidence of proven infection 14% in cisDDP-then-pctx. Thirty percent of those receiving pctx-then-cisDDP required hospital admission at some time during treatment, compared with 48% of those allocated cisDDP-then-pctx. The incidence of treatment delay was very similar in both studies (54% overall). With pctx first, 6 patients encountered delays for day 22 neutropenia; 1 for neutropenic sepsis; 1 for non-neutropenic infection; and 10 for miscellaneous reasons, e.g., administrative reasons. Amongst those receiving cisDDP first, seven patients were delayed for day 22 neutropenia; two for thrombocytopenia; one for both neutropenia and thrombocytopenia; one for neutropenic sepsis; one for non-neutropenic infection; and two others, miscellaneous. All thrombocytopenia and neutropenia causing delays on day 22 were either grade 2 or 3.

Survival data

The median length of follow-up for the 3 surviving patients who received pctx-then-cisDDP was 48 months and 45 months for the 9 remaining alive on cisDDP-then-pctx. The median survival of patients receiving pctx-then-cisDDP was 25 months (95% confidence interval (CI): 18–29 months) and 30 months for those having cisDDP-then-pctx (95% CI: 17–42 months).

Clinical progression-free survival was similar for both trials. One patient remains alive without progression on pctx-then-cisDDP and five patients on cisDDP-then-pctx. The median progression-free survival was 10 months (95% CI: 8–15 months) for patients allocated to pctx-then-cisDDP and 12 months (95% CI: 9–13 months) for those receiving cisDDP-then-pctx.

Tumour marker data

The median CA125 levels at baseline were comparable (384 U/ml pctx-then-cisDDP, 399 U/ml cisDDP-then-pctx). The median reduction in CA125 was significantly greater across the first phase for patients given cisDDP-then-pctx (92%) than for those receiving pctx-then-cisDDP (54%) ($z = 2.97$, $P = 0.003$). However, the median reduction in CA125 across the second phase was larger for patients allocated to pctx-then-cisDDP (60%) than for those receiving cisDDP-then-pctx (29%) ($z = -2.26$, $P = 0.02$). The overall reduction in CA125 was comparable (pctx-then-cisDDP 90%, cisDDP-then-pctx 94%, $z = 0.75$, $P = 0.45$).

Seven patients who had CA125 levels below 30 U/ml throughout were excluded from this analysis (1 pctx-then-cisDDP, 6 cisDDP-then-pctx). Thirteen (45%) patients receiving pctx-then-cisDDP and fourteen (61%) patients given cisDDP-then-pctx were in remission according to their CA125 measurements. Median time to remission was seven months for those receiving pctx-then-cisDDP and five months for those patients given cisDDP-then-pctx.

Discussion

The major cause of treatment failure in patients with ovarian cancer is platinum resistance [16]. We undertook these pilot trials as a prelude to larger studies to examine whether initial treatment with paclitaxel might minimize this problem, by reducing the number of platinum resistant cell clones. We were most interested to

define the activity of paclitaxel first line, thence to explore the applicability of the 'worst drug first rule' [7, 17]. In particular, were the response rates to paclitaxel induction worse, we wished to investigate the effectiveness of cisplatin in salvaging those with paclitaxel-resistant disease. To expedite this, we initially sought to offer all patients with measurable disease ptx-then-cisDDP.

The data presented here show a response rate for first-line paclitaxel of 43% (10% CR, 33% PR), comparable with the 42% recorded in GOG 132 which employed the same dose, albeit with a 24-hour infusion [18]. In our study, consolidation of paclitaxel-pretreated patients with cisplatin increased their overall response rate from 43% to 74%, reflecting an improvement in CR rate from 10% to 27% and PR rate of 33% to 47%. Note that an initial progression rate of 27% across paclitaxel induction is reduced to an overall progression rate of just 16% by cisplatin consolidation. There is therefore no striking evidence that exhibiting paclitaxel first prejudices outcome. Prompt cisplatin salvage seems effective.

At the outset, response endpoints in the cisplatin-then-paclitaxel sequence were of secondary interest only, as we anticipated that paclitaxel consolidation would provide only modest improvement over and above the response achieve by an initial four cycles of cisplatin. This prejudice reflected the modest activity of paclitaxel in platinum refractory disease [19,20] in relation to that originally reported [21].

The response rate to cisplatin induction in our study was just 57% (9% CR, 48% PR), against 67% recorded in GOG 132, for the same dose. Patient mix and small numbers apart, it should be stressed that the response rates recorded here were measured after just four cycles of treatment compared with the six cycles employed in GOG 132. As anticipated, we observed only a marginal improvement in OR from 57% to 62%, consequent to second-line paclitaxel, following cisplatin induction. However, we were interested to observe a simultaneous improvement in CR rate from 9% to 38% (with a commensurate reduction in PR rate from 48% to 24%). However, the overall progression rate of patients treated with cisDDP-then-pctx was 29%.

To the authors' knowledge, these are the first trials to address sequential schedules of paclitaxel and cisplatin in epithelial ovarian cancer. This 'dose dense' approach is of increasing interest. Several arms of the imminent GOG 182 trial (previously 172R) will adopt a sequential couplet design, although with platinum in both phases. The results of at least one previous sequential study prompt caution in deferring initial platinum and also, in its carboplatin control arm, provide evidence for the influence of platinum cycle number on complete remission rate [22].

The other significance of these sequential trials lies in the extent to which they may help interpret other studies whose results may have been confounded by 'crossover' ahead of progression [18]. Such events inevitably provoke considerable debate, because of the relatively modest degrees of non-cross resistance documented for such salvage agents in conventional phase II studies [23, 24]. Were our observation that sequential paclitaxel increased CR rate, at the expense of partial responses, to reflect the generality of the case, we might have a ready explanation for why such salvage treatments might even impact on survival.

The unfortunately severe neurotoxicity seen in both studies was surprising and discouraged their continuation. We could discern no definite sequence of administration-specific differences in toxicity. A total cisplatin dose of 400 mg/m^2 over 12 weeks was chosen, mindful of the Scottish experience using cisplatin 100 mg/m^2, which showed that neurotoxicity limited the median deliverable cumulative dose to 500 mg/m^2 [25]. In our study, this was followed, or preceded, by four cycles of paclitaxel 200 mg/m^2, providing a total dose of 800 mg/m^2 paclitaxel over a further 12 weeks, in a 'dose-dense' design. By reference to GOG 111 [1, 26], the total dose of cisplatin achieved in our study was slightly less (400 mg/m^2, as against 450 mg/m^2) and the total paclitaxel dose was near identical (800 mg/m^2, as against 810 mg/m^2), although administered over 3 hours, rather than 24 hours.

In keeping with contemporary practice, the further development of sequential protocols for use in epithelial ovarian cancer will necessarily employ carboplatin, a less neurotoxic platinum analogue, with similar activity [30, 31]. The use of other platinum non-cross-resistant agents in combination with paclitaxel, such as gemcitabine [32] may also be advantageous in this setting, and studies using this approach are already in progress, exhibiting carboplatin first. However, our overall response data suggests that there are no convincing safety reasons against exhibiting platinum second and the possibility remains that this might be advantageous. A randomised controlled trial would be required to resolve this issue. Either way, interest in a sequential approach to scheduling non cross resistant drugs for ovarian cancer has increased since the presentation of preliminary data from the ICON-3 trial, which suggest that carboplatin and paclitaxel, conventionally combined, may have only very modest superiority over carboplatin alone [33].

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