Cancer Chemother Pharmacol (2001) 48: 255–258
DOI 10.1007/s002800000271

CLINICAL TRIAL REPORT

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Cisplatin and escalating doses of paclitaxel and epirubicin in advanced ovarian cancer. A phase I study

Received: 12 October 2000 / Accepted: 2 January 2001 / Published online: 30 June 2001

Abstract *Purpose*: The combination of paclitaxel and cisplatin is considered the standard regimen for advanced ovarian cancer (AOC). A meta-analysis has shown that the incorporation of anthracyclines into first-line chemotherapy might improve long-term survival by 7–10%. We designed a phase I–II study in patients with AOC using a combination of a fixed dose of cisplatin with paclitaxel and epirubicin both given at escalating doses every 3 weeks. The objectives of this study were to determine both the maximum tolerated dose (MTD) and the antitumor activity of this combination. *Methods*: Six different dose levels were planned. The starting doses were cisplatin 75 mg/m^2, paclitaxel 140 mg/m^2, and epirubicin 50 mg/m^2. The doses of paclitaxel were escalated in 20-mg/m^2 increments, alternating with 20-mg/m^2 increments of epirubicin. Ten patients with AOC entered the phase I study. Three patients each were enrolled at level I and level II and four patients at level III, and at each level, 15 courses were administered. Patients received a median of five courses. *Results*: Nonhematological toxicity was generally mild, except for grade 3 mucositis in one course at levels II and III, and grade 3 vomiting in one course at levels I and III. Hematological toxicities were grade 3–4 neutropenia in 60%, 47% and 60% of courses at levels I, II and III, respectively, and grade 3 anemia in one course at level III. At level III two of four patients developed a dose-limiting toxicity which was grade 4 neutropenia lasting more than 1 week. *Conclusions*: The MTD was reached at level II with cisplatin 75 mg/m^2, paclitaxel 160 mg/m^2, and epirubicin 50 mg/m^2. The phase II part of the study is currently ongoing.

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Keywords Ovarian cancer · Taxol · Epirubicin · Advanced ovarian cancer

Introduction

Randomized trials have proven the superiority of platinum-based combinations over single-agent cisplatin and over non-cisplatin-containing regimens for advanced ovarian cancer (AOC) [1]. Platinum-based chemotherapy produces an improvement in median survival of 12 months as compared to alkylating agent therapy. However, the long-term results of platinum-containing regimens, with fewer than 20% of patients alive and disease-free after 7–10 years from the diagnosis, point to the need for new drugs and treatment modalities for AOC [10].

Taxanes are an important new class of anticancer agents that exert their cytotoxic effect by promoting the assembly of microtubules [15]. On the basis of data from phase I and II studies [14], the Gynecologic Oncology Group has performed a prospective randomized comparison of standard treatment with cyclophosphamide plus cisplatin versus cisplatin plus paclitaxel (24-h infusion) in previously untreated patients with AOC (FIGO stages III and IV with suboptimal disease) [9]. Patients randomized to paclitaxel combination had a higher response rate (73% vs 60%, $P=0.01$), an improvement in surgically defined complete response (26% vs 19%, $P=0.08$), a longer disease-free survival (18 vs 13 months), and a 12–14 month prolongation of median survival time. Because of these encouraging results, the Gynecologic Oncology Group has accepted paclitaxel and cisplatin as the standard regimen for patients with AOC suboptimally debulked.

Piccart et al. carried out a confirmatory phase III trial in which patients were randomized to paclitaxel (as a 3-h infusion) and cisplatin versus cyclophosphamide and cisplatin. The paclitaxel arm showed a significant advantage in overall clinical response rate (59% vs 45%, $P=0.01$), in progression-free survival (median of

15.5 months vs 11.5 months, $P = 0.0005$) and in overall survival (median of 35.6 months vs 25.8 months, $P = 0.0016$) [13].

A meta-analysis has shown a statistically significant survival benefit ($P = 0.02$) and a significant advantage in frequency of negative second-look laparotomy for the PAC (cisplatin, doxorubicin and cyclophosphamide) regimen versus the CP (cisplatin, and cyclophosphamide) regimen. However, because the dose intensity of the three-drug combination was greater than that of the two-drug combination in three of the trials, it remains unresolved to what extent the benefit of PAC is due to the greater dose-intensity and to what extent to the doxorubicin itself [11]. On the other hand, two trials have found no evidence of a difference between a three-drug combination including anthracyclines (epirubicin, cyclophosphamide and cisplatin or carboplatin) and carboplatin as a single agent in terms of progression-free and overall survival [7, 16].

Further data have confirmed that the addition of doxorubicin significantly improves survival (hazards ratio 0.85, CI 95%, $P = 0.003$), and the size of this benefit is comparable to that with platinum [2]. The use of epirubicin in platinum-based combination regimens (PEC) as first-line therapy leads to better tolerability in terms of hematological and cardiological toxicity when compared with PAC and CP regimens, but no statistically significant survival difference has been found between PAC and PEC [6]. Epirubicin in association chemotherapy produces an overall response rate of 58–82% [3, 4, 8].

On the basis of these data, we designed a phase I–II study in patients with AOC, using a combination of a fixed dose of cisplatin plus paclitaxel and epirubicin, both given at escalating doses. The objective of the phase I study was to establish the maximum tolerated dose (MTD) of this regimen and of the subsequent phase II study was to evaluate its activity.

Materials and methods

Eligibility criteria included stage III or IV ovarian cancer, no previous chemotherapy or radiotherapy, ECOG performance status (PS) of 2 or less, age above 18 years and below 70 years, and adequate hematological, renal, hepatic, cardiac, and neurological functions. Informed consent was required from all patients.

The starting doses of the drugs were cisplatin 75 mg/m^2, paclitaxel 140 mg/m^2 as a 3-h infusion and epirubicin 50 mg/m^2. Cycles were repeated every 3 weeks. Epirubicin was administered as an intravenous (i.v.) bolus immediately followed by paclitaxel, diluted in 500 ml 5% dextrose or normal saline solution. Cisplatin was given after paclitaxel; it was administered after an i.v. infusion of 5% dextrose in 1/2-normal saline plus 10 mEq/l KCl at a rate of 1 l/h for 2 h. Furosemide 40 mg i.v. was given at the start of the infusion. Doses of paclitaxel were escalated in 20-mg/m^2 increments, alternating with 20-mg/m^2 increments of epirubicin (Table 1).

To prevent paclitaxel-associated hypersensitivity reactions, standard premedication with prednisone 125 mg given orally 12 and 6 h before paclitaxel and orphenadrine 40 mg intramuscularly plus ranitidine 50 mg i.v. 30 min prior to paclitaxel was given to all patients. To prevent emesis, the association of dexamethasone 8 mg plus antiserotoninergic drugs (ondansetron 8 mg, granisetron 3 mg or tropisetron 5 mg) were administered i.v. just before cisplatin and dexamethasone 8 mg i.v. and metoclopramide 40 mg orally were given 24 and 48 h after the start of chemotherapy.

At least three patients were treated at each dose level. Dose-limiting toxicities (DLT) were evaluated according to standard World Health Organization (WHO) criteria and are defined as follows: grade 4 (ANC $< 0.5\times10^9$/l) neutropenia lasting more than 7 days, or ANC $< 0.1\times10^9$/l lasting more than 3 days, grade 4 thrombocytopenia requiring platelet transfusions lasting more than 1 week, any episode of febrile neutropenia, peripheral neuropathy greater than grade 2, or any WHO grade 4 nonhematological toxicity, except for alopecia and nausea and vomiting. If no DLT was encountered, the dose was escalated for the next cohort. If one of three patients developed a DLT, three additional patients were enrolled at the same dose level. If no DLT was seen in the second group of three patients, the next dose level was opened. If in the first group of three patients the incidence of DLT was equal to or greater than two of three patients, the MTD was considered to have been reached. The MTD was defined as the dose level immediately below the DLT. For each level, the first treated patient was followed for 3 weeks before the following patients were allowed to enter the study.

In the planned phase II trial, all patients will be treated at the MTD.

Results

Ten patients with AOC entered the study. Seven patients had FIGO stage III disease (one optimally and six suboptimally debulked), and three patients stage IV. Histology included serous (six patients), mucinous (two patients), endometrioid (one patient) and undifferentiated (one patient). The median age was 57.5 years (range 50–68 years), and median ECOG PS was 1 (range 0–1). Six dose levels of escalating epirubicin and paclitaxel, combined with a fixed dose of cisplatin were foreseen. Paclitaxel and epirubicin were escalated in alternating dose levels. Three patients were enrolled at both level I and level II and four patients at level III, and 15 courses were administered at each level, for a total of 45. Patients received a median of five courses (range one to eight).

Table 2 summarizes the more severe toxic effects that occurred, according to WHO criteria. Nonhematological toxicity was generally mild. A grade 2 mucositis was observed in one course at level II (6.6%) and a grade 3 mucositis in one course at levels II (6.6%) and III (6.6%). A grade 2 vomiting was observed in three courses at level II (20%) and a grade 3 vomiting was observed in one course at level I (6.6%) and in another one course

Table 1 Planned dose-intensification levels (courses repeated every 3 weeks)

Level	Cisplatin (mg/m^2)	Paclitaxel (mg/m^2)	Epirubicin (mg/m^2)	No. of patients
I	75	140	50	3
II	75	160	50	3
III	75	160	70	4

Table 2 Grades 3 and 4 toxicity per course

Level	Leukopenia		Neutropenia		Thrombocytopenia		Anemia		Nausea/vomiting		Mucositis		Neurotoxicity/myalgia	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
I	6/15 (40%)	–	5/15 (33.3%)	4/15 (26.6%)	–	–	–	–	1/15 (6.6%)	–	–	–	–	–
II	4/15 (26.6%)	1/15 (6.6%)	6/15 (40%)	1/15 (6.6%)	–	–	–	–	–	–	1/15 (6.6%)	–	–	–
III	4/15 (26.6%)	3/15 (20%)	1/15 (6.6%)	8/15[a] (53.3%)	–	–	1/15 (6.6%)	–	1/15 (6.6%)	–	1/15 (6.6%)	–	3/15 (20%)	–

[a]DLT in 2/15 courses

at level III (6.6%). A grade 2 peripheral neuropathy was observed in one patient at level II after the first cycle and a grade 3 peripheral neuropathy in one patient at level III after the third cycle. Complete alopecia was seen in all patients.

As regards the hematological toxicity, at level I a grade 3 and a grade 4 neutropenia were observed in 5 of 15 (33.3%) and 4 of 15 courses (26.6%), respectively. At level II, a grade 3 neutropenia occurred in 6 of 15 courses (40%) and a grade 4 in one cycle only (6.6%). At level III in 8 of 15 courses (53.3%) a grade 4 neutropenia was observed. At this level, two patients showed a grade 4 neutropenia lasting more than 1 week, so that two out of four patients developed a DLT. Only at level III was a grade 3 anemia seen in 1 of 15 courses (6.6%). No cases of thrombocytopenia were recorded. According to the DLT definition above, The MTD was identified as level II.

Of note, out of nine patients evaluable for response (one patient refused treatment after the first cycle at level II), two had a complete clinical response, one at level I pathologically confirmed and one at level II. Four patients achieved a partial response (one at level I, one at level II and two at level III), one stable disease and two progressive disease.

Discussion

Few studies on the combination of paclitaxel, epirubicin and platinum compounds have been reported to date. The same combination described in the present study, with higher doses of the drugs with granulocyte-colony stimulating factor (G-CSF) support, has been tested in a phase I trial in which a fixed dose of cisplatin (100 mg/m^2) was combined with escalating doses of epirubicin and paclitaxel. At the time of writing, the study is still ongoing and the current doses are epirubicin 110 mg/m^2 and paclitaxel 195 mg/m^2; the MTD has not yet been reached [5]. Only one phase II trial has been reported, in which the same combination, with a lower paclitaxel dose (135 mg/m^2), was supported with G-CSF [12]. Our experience was the first to test this combination without hematopoietic growth factors.

In the present study, cisplatin 75 mg/m^2 combined with paclitaxel 160 mg/m^2 and epirubicin 50 mg/m^2 given every 3 weeks, are the recommended doses for phase II trials in AOC. We used a low anthracycline dose; only with hematopoietic growth factor support could a higher dosage of this drug be reached, and this would be an expensive and less-safe regimen. The tolerability of this regimen is attractive and the preliminary results on the dactivity of this regimen are promising and should be confirmed in the phase II part of the study that is currently ongoing.

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