Escalating doses of paclitaxel and epirubicin in combination with cisplatin in advanced ovarian epithelial carcinoma: a phase I–II study

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Our objective was to identify a new active three-drug combination regimen consisting of paclitaxel (PTX), epirubicin (EPI) and cisplatin as first-line line chemotherapy for advanced ovarian carcinoma. A phase I study was carried out to evaluate the dose-limiting toxicity (DLT) and the maximally tolerated dose (MTD) of PXT and EPI in combination with a fixed dose of cisplatin every 4 weeks. Side-effects were recorded according to the NCI Common Toxicity Criteria. Patients were treated in cohorts of three with fixed-dose cisplatin 80 mg/m^2 and EPI 80→100 mg/m^2 and PXT 100→160 mg/m^2 until DLT was reached. Once MTD was identified, a single-step phase II study was therefore carried out to test the clinical activity and panel of toxicity of such regimen. Objective responses were recorded according to the WHO criteria. Time to progression and overall survival (OS) were secondary endpoints. The DLT was myelosuppression and, in more detail, febrile neutropenia, which occurred at the fifth dose level (PTX 140 mg/m^2, EPI 100 mg/m^2 and cisplatin 80 mg/m^2) in two out of three patients. Other side-effects were grade 3 mucositis in two out of three patients and grade 3 anemia in one case. The combination of cisplatin 80 mg/m^2 plus EPI 80 mg/m^2 and PCT 140 mg/m^2 every 4 weeks was considered as the MTD. In the phase II study a complete response was observed in six patients (33%) and a partial response in nine cases (50%) for an overall response rate of 83% [95% confidence limits (CL) 59–96%]. Median time to progression of patients with measurable disease was 16.4 months. Median OS was not reached after a follow-up of 42 months. This study demonstrated that PTX and EPI can be safely administered in combination with cisplatin to fit patients with advanced epithelial ovarian carcinoma. The three-drug regimen of cisplatin 80 mg/m^2, EPI 80 mg/m^2 and PTX 140 mg/m^2 every 4 weeks is very active, at least in terms of objective response rate. This level of activity overlaps with the 95% CL of the activity of cisplatin alone; however, it does encourage future trials of the combination. *Anti-Cancer Drugs* 14:359–364 © 2003 Lippincott Williams & Wilkins.

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Introduction

Despite considerable advances achieved in the management of advanced epithelial ovarian carcinoma (AEOC) in the last decade, clinical results of systemic chemotherapy in terms of overall survival (OS) are still unsatisfactory [1–4].

The combination regimen of cisplatin 75 mg/m^2 and paclitaxel (PTX) 135 mg/m^2 over 24-h infusion has been widely employed as front-line chemotherapy on the basis of the results reported by the Gynecologic Oncology Group (GOG) showing a survival advantage of this regimen over the 'standard' combination of cisplatin and cyclophosphamide [5]. Further studies have shown that shorter infusion of PTX at 175 mg/m^2 plus cisplatin yields clinical results overlapping those reported by the GOG, although at the cost of greater neurotoxicity [6]. Some studies have tested the possibility of substituting cisplatin by carboplatin, and final results have suggested similar clinical activity of PTX plus cisplatin and PTX plus carboplatin [1,2,7,8]. Because of these observations, to date the regimen of PTX plus a platinum analog is considered as the reference treatment for AEOC by most oncologists [2,3,9,10] and the basis regimen to develop new active multidrug combinations [11,12].

Although anthracycline drugs are very active in AEOC, to date the role of anthracyclines in the management of

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AEOC is still not fully understood [13–16]. Indeed three large meta-analyses [17–19] have pointed out the positive impact on survival of anthracycline/cisplatin-based regimens when compared to cisplatin-based therapy without anthracyclines. Among various anthracyclines, epirubicin (EPI) has shown the most favorable toxicity profile with good antineoplastic activity also in AEOC [20]. The relative lack of cross-resistance of anthracycline drugs with taxanes and platinum compounds makes EPI a good partner for PTX and cisplatin in designing an aggressive three-drug regimen, which should allow adequate actually delivered dose intensity, however [21].

Based on the above-reported rationale, we carried out a phase I–II study to evaluate the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), safety and clinical efficacy of a three-drug regimen consisting of PTX, EPI and cisplatin in a series of fit patients with chemotherapy-naive AEOC.

Materials and methods

Study design and treatment plan

The trial included a open label phase I study carried out at three institutions in which patients were assigned to a dosage level in cohorts of three with the aim of identifying DLT and MTD of PTX and EPI in combination with fixed-dose cisplatin on a 4-week schedule in a series of previously untreated patients with AEOC. Once the recommended doses were identified, further patients were enrolled into the phase II study in order to assess clinical efficacy and the panel of toxicity of the three-drug combination regimen

DTL was defined during the first three cycles of chemotherapy for each cohort of three patients as follows: any grade 3–4 non-hematological toxicity with the exception of alopecia, grade 3–4 febrile leukopenia or absolute neutrophil count $\geq$ 500 cells/ml for more than 5 days, grade 3–4 thrombocytopenia or any persistent grade ≤ 2 side-effect that caused treatment delay of 1 week in two out of three patients enrolled at a single dose level since delay of recycling could cause a significant reduction in planned dose intensity. MTD was the treatment dose below the level at which DLT was recorded in at least two of three patients. Once the MTD was reached, the recommended dose of PTX and EPI in combination with cisplatin for phase II study was established.

The treatment schedule included: cisplatin 80 mg/m^2 diluted in 500 cm^3 of normal saline given as a 1-h infusion with a standard pre- and post-hydration protocol with electrolyte supplements and forced diuresis with 250 ml of 18% mannitol on day 2, plus EPI 80–100 mg/m^2 diluted in 100 ml of normal saline given as an i.v. bolus on day 2. PTX was given on day 1 at the starting dose of 80 mg/m^2 diluted in 500 ml of normal saline given over 3 h employing a polyethyl infusion set and standard pre-medication therapy for the first group of three patients. Therefore PTX dosage was escalated in the absence of unacceptable toxicity or achievement of DLT to 100, 120, 140 and 160 mg/m^2 for subsequent groups of three patients until the DLT and MTD were reached.

Anti-emetic therapy, i.e. tropisetron 5 mg i.v., was standardized for all patients to avoid bias in gastrointestinal toxicity recording due to differences in anti-emetic therapy. Prophylactic administration of granulocyte colony stimulating factor (G-CSF) was not programmed, but investigators could use G-CSF in case of febrile neutropenia. Interim blood cell counts were obtained at day 1 and 8 of each cycle, and in case of severe myelosuppression the counts were made every 2 days in order to closely monitor the kinetic of leukopenia and/or thrombocytopenia.

Chemotherapy was continued until progressive disease or unacceptable toxicity ensued. Side-effects were closely monitored and recorded according to the NCI Common Toxicity Criteria. In case of severe grade 3–4 toxicity, including febrile neutropenia, dose reduction was done. PTX and/or EPI dosages were reduced by 20 and 10 mg/m^2 for subsequent cycles, respectively. Cardiotoxicity was closely monitored by ECG and echocardiography before every cycle of chemotherapy.

Eligibility criteria

Before entry into the study, all patients had to fulfill the following eligibility criteria: written informed consent; histologically proven diagnosis of advanced, stage III–IV ovarian epithelial carcinoma; age 18–65 years; ECOG performance status 0–1; life expectancy of at least 3 months; adequate bone marrow function [white blood cells $\leq$ 4000/mm^3, platelets (PTL) $\leq$ 120 000/mm^3, hemoglobim $\leq$ 9 g%]; adequate liver (serum bilirubin $\geq$ 1.2 mg%, serum transaminases $< 2 \times$ the normal value) and renal functions (serum creatinine $\geq$ 1.2 mg%, BUN $\geq$ 50 mg%); normal cardiac function as evaluated by ECG and echocardiography; no signs of CNS metastases; and absence of severe, uncontrolled metabolic, respiratory, cardiovascular or neurological diseases. Other prerequisites necessary for eligibility included: absence of second malignancy with the exception of adequately managed *in situ* uterine carcinoma or cutaneous basal cell carcinoma; and geographical accessibility to the oncological centers in order to guarantee correct follow-up. Patients had not to have previously received chemotherapy and/or radiotherapy for any reason. The presence of bidimensionally measurable disease according to WHO criteria was not a necessary prerequisite due to the phase I nature of the first part of the study. On the other hand,

measurable disease was mandatory for patients enrolled in the phase II part of the study.

Staging

Pre-treatment disease evaluation included: medical history and physical examination, chest X-ray, abdominal sonograms, hemocromocytometric parameters, serum chemistry tests, Ca125, cardiac evaluation with ECG and echocardiography, and computed tomography or magnetic resonance imaging of the involved areas. These procedures were employed for restaging as needed.

Objective response and survival

Patients were evaluated for objective response after 3 cycles of chemotherapy. Objective responses were analyzed according to the WHO criteria [22]. Briefly, complete response (CR) was defined as the complete disappearance of all signs and symptoms of tumor for a minimum of 4 consecutive weeks; partial response (PR) was defined as a $\leq 50\%$ reduction in the sum of the largest perpendicular diameters of all measurable lesions for at least 4 weeks without the appearance of any new metastases; stable disease (SD) as a $< 50\%$ decrease or $\geq 25\%$ increase in the size of tumor lesions; and progressive disease (PD) as a $> 25\%$ increase in the size of tumor deposits and/or the appearance of any new metastases. Time to progression (TTP) was calculated starting from the first day of treatment until progressive disease was recorded. Overall survival (OS) was calculated for the first day of chemotherapy until death or was censored on the date of last documented follow-up.

Statistics

At entry, all eligible patients were centrally registered at the coordinating centre and clinical data were centrally monitored at the Division of Medical Oncology, La Maddalena Clinic for Cancer, Palermo, Italy. The phase II study was designed as a single-step trial. Objective responses were reported as relative rates with 95% confidence limits (95% CL). Univariate analysis of duration of objective responses and survival data according to the Kaplan–Meier product-limit analysis was carried out. Calculation of dose intensity (DI) was carried out as previously described [21] and the Wilcoxon rank-sum test was employed for evaluation of differences in delivered DI.

Results

Patient population

Table 1 depicts the main clinical and demographic characteristics of enrolled patients. In the phase I study 22 patients with AEOC were enrolled at seven different dose levels. This group of patients had a median age of 54 years (range 38–65) with a median ECOG performance status of 0 (range 0–1). Most patients (82%) had a serous cystoadenocarcinoma and 45% of patients had histological grade 3. Seventy-seven percent of patients had received previous surgery with optimal debulking in 13% of cases and suboptimal debulking in 64%. Five patients were previously untreated because the reference surgeon preferred a pre-operatory chemotherapeutic approach. No patient had previous chemotherapy or radiation therapy.

Table 1 Clinical and demographic characteristics of patients

	Phase I study [*n* (%)]	Phase II study [*n* (%)]
Number of enrolled patients	22 (100)	20 (100)
Median age [years (range)]	54 (38–65)	56 (33–64)
Performance status		
ECOG 0	16 (73)	14 (70)
ECOG 1	8 (27)	6 (30)
Stage (FIGO)		
III	10 (46)	8 (40)
IV	12 (54)	12 (60)
Previous therapy		
none	5 (23)	4 (20)
surgery	17 (77)	16 (80)
optimal	3 (13)	2 (10)
suboptimal	14 (64)	14 (70)
Histology		
serous	8 (82)	15 (75)
endometrioid	2 (9)	2 (10)
undifferentiated	2 (9)	2 (10)
mucinous	0	1 (5)
Grade		
1	0	1 (5)
2	12 (55)	9 (45)
3	10 (45)	10 (50)

Table 1 also shows patients enrolled in the phase II part of the trial. Globally, 20 eligible patients were enrolled into the phase II study with a median age of 56 years (range 33–64) and a median performance status 0 according to the ECOG scale. Histologically, 75% of patients had serous cystoadenocarcinoma. Most patients (80%) had received surgery, with optimal debulking in 10% of cases and suboptimal in 70% of cases.

Dose escalation

Analysis of dose escalation of PTX and EPI in subsequent cohorts of patients is shown in Table 2. One patient was lost to follow-up before the second administration of chemotherapy; therefore, a total of 21 patients was included into the dose-escalation trial. All patients received a fixed dose of cisplatin 80 mg/m^2.

The first group of three patients was treated with PTX 80 mg/m^2 and EPI 80 mg/m^2 (Level 1), and did not show any severe side-effects with the exception of grade 3 alopecia and one case of grade 3 neutropenia. Therefore, the PTX dosage was escalated to 100 mg/m^2 with EPI 80 mg/m^2 (Level 2) for a subsequent cohort of three patients. At this dose level two patients had grade 3 neutropenia and one patient had grade 2 anemia. No other significant side-effects were recorded. At Level 3,

Table 2 Dose escalation of PTX and EPI in combination with fixed-dose cisplatin

Level (patients)	Cisplatin/EPI/PTX dose (mg/m^2)	Toxicity (NCI)	Planned DI (mg/m^2/week)	Delivered DI (mg/m^2/week)	Objective response (WHO criteria)
1 (3 pts)	80/80/80	G3 neutropenia 1 pt	PTX 20	19.6 (98%)	PR
		G3 alopecia 3 pts	EPI 20	19.6 (98%)	PR
		G1 PTL 1 pt	cisplatin 20	19.6 (98%)	PR
		G1 anemia 1 pt			
2 (3 pts)	80/80/100	G3 neutropenia 2 pts	PTX 25	24.2 (97%)	CR
		G2 anemia 1 pt	EPI 20	19.4 (97%)	PR
		G1 PTL 1 pt	cisplatin 20	19.4 (97%)	SD
		G3 alopecia 3 pts			
3 (3 pts)	80/80/120	G3 neutropenia 3 pts	PTX 30	29.0 (97%)	PR
		G1 PTL 1 pt	EPI 20	19.2 (96%)	SD
		G1 anemia 1 pt	cisplatin 20	19.6 (98%)	not evaluated
		G2 stomatitis 2 pts			
4 (3 pts)	80/100/120	G2 anemia 2 pts	PTX 30	26.1 (87%)	PR
		G2 PTL 2 pts	EPI 25	19.1 (76%)	not evaluated
		G3 neutropenia 2 pts	cisplatin 20	18.3 (91%)	CR
		G4 neutropenia 1 pt			
5 (3 pts)	80/100/140	G4 neutropenia with fever 2 pts	PTX 35	29.5 (84%)	PD
			EPI 25	18.0 (72%)	PR
		G3 neutropenia 1 pt	cisplatin 20	17.2 (86%)	CR
		G3 stomatitis 2 pts			
		G2 anemia 1 pt			
		G3 anemia 1 pt			
6 (3 pts)	80/80/140	G4 neutropenia 1 pt	PTX 35	31.0 (89%)	CR
		G3 neutropenia 2 pts	EPI 20	19.6 (98%)	PR
		G2 anemia 1 pt	cisplatin 20	19.6 (98%)	PR
		G1 PTL 2 pts			
		G3 stomatitis 1 pt			
7 (3 pts)	80/80/160	G4 neutropenia with fever 2 pts	PTX 40	24.7 (62%)	PR
		G3 neutropenia 1 pt	EPI 20	14.1 (70%)	PR
		G3 stomatitis 2 pts	cisplatin 20	18.0 (90%)	PR
		G2 anemia 2 pts			
		G2 PTL 2 pts			

G=grade, pt=patient.

PTX was increased to 120 mg/m^2 with fixed EPI 80 mg/m^2. In this cohort grade 3 neutropenia was recorded in three patients with two cases of grade 2 stomatitis. At the next dose level (Level 4), EPI was escalated to 100 mg/m^2 with PTX fixed at 120 mg/m^2. Two patients had grade 3 neutropenia and one had grade 4 neutropenia, and two patients had grade 2 thrombocytopenia. At the next step (Level 5), patients received PTX 140 mg/m^2 and EPI 100 mg/m^2: grade 4 febrile neutropenia and grade 3 stomatitis were observed in two out of three patients, grade 2 anemia in two cases and grade 3 anemia in one patient. Subsequent patients were entered at the Level 6 dose and treated with PTX 140 mg/m^2 plus EPI 80 mg/m^2. Two patients suffered from grade 3 neutropenia and one patient from grade 4 non-febrile neutropenia. Grade 2 anemia was recorded in two cases. The last cohort of patients (Level 7) received PTX 160 mg/m^2 plus EPI 80 mg/m^2. Grade 4 febrile neutropenia was observed in two out of three patients, grade 2 thrombocytopenia in two cases, and grade 2 anemia in two patients. Therefore, DTL was represented by myelosuppression and, in more detail, by febrile neutropenia. DLT was reached at the dose of PTX 140 mg/m^2 plus EPI 100 mg/m^2 (Level 5) and PTX 160 mg/m^2 plus EPI 80 mg/m^2 (Level 7).

In the first three steps lack of severe toxicity resulted in no significant alteration of programmed DI: in these patients delivered DI was above 90% of the programmed one. In Levels 4, 5 and 7 the actually delivered DI of EPI fell to 70–76% due to hematological toxicity, while in Level 6 EPI DI was maintained over 90%. Actually delivered DI of PTX was reduced below 90% in Levels 4, 5 and 7, while in Level 7 it remained over 90%.

Table 3 Objective response

	Phase I study (%)	Phase II study (%)	Pooled data (%)
ORR	75	83	79
CR	25	33	29
PR	50	50	50
SD	12	11	12
PD	12	6	9

Sites of disease: peritoneum/abdomen ($n=20$ patients), liver ($n=2$ patients), pleura ($n=2$ patients) and node ($n=5$ patients).

The combination of cisplatin 80 mg/m^2 plus EPI 80 mg/m^2 and PTX 140 mg/m^2 was considered as the MTD.

Objective response and survival

Type and rates of objective response calculated according to an intent-to-treat analysis are shown in Table 3. Although evaluation of objective responses was not the main aim of the dose-finding part of the study, 16 patients were evaluable for objective response. Six patients (26%) were not evaluable for objective response:

three suboptimally debulked patients without radiologically measurable disease and three patients with optimal debulking were not submitted to second-look laparotomy because evaluation of disease was not part of the phase I study. Among evaluable patients, a major objective response was seen in 12 cases for a 75% overall response rate (95% CL 48–93%) with four clinico-radiological CRs (25%; 95% CL 7–52%) and eight PRs (50%; 25–75%). Two patients had SD. Progression was recorded in two cases.

In the phase II study, all but two patients were evaluable for objective response. Two patients with optimally debulked disease refused second-look laparotomy accordingly to the trial rules. A CR was observed in six out of 18 patients (33%; 13–59%), a PR was observed in nine patients (50%; 95% CL 26–74%) for an objective response rate (ORR) of 83% (95% CL 59–96%). There were also two patients with SD (11%) and one with PD (6%).

When pooled data of the phase I and II studies were analyzed, a CR was seen in 10 out 34 evaluable patients (29%; 95% CL 15–47%) and a PR in 50% of cases (95% CL 32–68%) for an overall response rate of 79% (95% CL 62–91%).

Median TTP of patients with measurable disease was 16.4 months (range 6.0–37.2 +). Median OS of patients with measurable disease was not reached after a 42-month follow-up.

Toxicity

No toxic deaths were observed. Patients received a total of 118 cycles of chemotherapy with a mean of 5.9 cycles/patient.

With regard to hematological toxicity, the incidence of severe grade 3–4 neutropenia was 55% with six episodes of febrile neutropenia and three cases of grade 3–4 thrombocytopenia. Hospitalization was required in six cases (30%). Grade 1–2 neutropenia and thrombocytopenia was reported in 42 and 32% of cases, respectively. Grade 2 anemia was present in five patients (25%).

Non-hematologic side-effects were mostly moderate and primarily represented by gastrointestinal and neurological toxicities. Four cases (20%) of grade 3 stomatitis were observed, but grade 1–2 stomatitis was reported in another five patients (25%). Four patients (10%) complained of grade 2 asthenia. Grade 3 nausea/vomiting was recorded in 28% of cases. Grade 1–2 peripheral neurotoxicity was observed in two patients (10%). Mild grade 1 renal toxicity was observed in two patients. No patient developed any signs of left ventricular failure, but one patient showed a 15% reduction in the left ventricular ejection fraction. All patients had grade 2–3 alopecia. No allergic hypersensitivity reactions were seen.

Discussion

Despite the fact that PTX administration represents considerable progress in the management of AEOC, clinical results are still unsatisfactory, especially if OS is considered as the main endpoint [1–4]. The majority of patients show recurrent disease and will ultimately die even if they experience impressive regression after PTX plus platinum [4–9]. Although the addition of anthracycline to cisplatin/cyclophosphamide regimen (CAP) may represent an advantage in terms of OS, the role of anthracycline drugs in the management of AEOC as well as the possible combination with other drugs are still not fully understood [14–18]. The CAP regimen was shown to be equiactive to single-agent carboplatin AUC [6] and to the PTX/carboplatin regimen in the ICON trials [4]. Therefore, this trial was carried out with the aim of developing a feasible and effective poly-chemotherapeutic regimen including three of the most active drugs against AEOC. The sequence employed in this study was based on the suggestion of reduced toxicity with the taxane given before platinum compounds from the study of Rowinsky *et al.* [23].

In our trial, the DLT was febrile neutropenia, which occurred in two out of three patients treated with EPI 100 mg/m^2 plus PXL 140 mg/m^2 (Level 5) or EPI 80 mg/m^2 + PXL 160 mg/m^2 (Level 7). The MTD was then identified at Level 6, i.e. EPI 80 mg/m^2 plus PXL 140 mg/m^2. Prophylaxis with G-CSF was not employed since the use of G-CSF has been reported to be ineffective in permitting drug dose escalation or improvements in dose intensity when the PTX/cisplatin regimen is given with or without the addition of EPI [24,25]. The data achieved in the phase I part of the study are consistent to those reported by Papadimitriou *et al.* [26], Neumann *et al.* [27] and Nardi *et al.* [28], which employed cisplatin in combination with PTX and adriamycin or EPI. Comparison of our data to those reported by other authors who employed carboplatin instead of cisplatin is not appropriate because carboplatin may cause significantly more myelosuppression than cisplatin [26,29]. However, we agree with the comments made by Du Bois *et al.* [25] concerning the substitution of cisplatin with carboplatin or adriamycin with EPI. Neither of these approaches resulted in an increase of anthracycline DI.

This three-drug regimen is, however, very effective in terms of ORR as witnessed by the 79% ORR with a 29% CR rate (phase I and II pooled data) reported in the present study. These figures are in the range reported with similar regimens in AEOC [25–28]. These impressive data have been obtained mostly in phase I–II studies which enrolled a highly selected series of fit patients with optimal performance status and low co-morbidity rate. Therefore, caution must be used in interpreting these results, and in employing this regimen in settings different than an experimental trial, since expected

toxicity may be quite significant. The results of a phase III trial by Du Bois *et al.* [30], however, showed no difference in clinical outcome with carboplatin AUC 5 and PTX 175 mg/m^2 with EPI 60 mg/m^2 or without. In our trial EPI dosage was higher than that utilized in the latter trial with a lower dose of PTX which avoided severe neurotoxicity.

In conclusion, our study confirms that the PTX, EPI and cisplatin regimen may be safely administered to fit patients with advanced epithelial ovarian carcinoma. This three-drug regimen seems extremely active in terms of response rate in both untreated or suboptimally debulked patients. However, these data have been achieved in a selected population of fit patients and therefore this regimen should not be considered a routine therapy. The activity of this three-drug combination should be tested in a future wider head-to-head study.

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