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Long-term Follow-up of Pegylated Liposomal Doxorubicin and Oxaliplatin in Recurrent Ovarian Cancer

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Abstract

Oxaliplatin (LOHP) and pegylated liposomal doxorubicin (PLD) are active single agents in recurrent ovarian cancer (ROC). In this phase II study we explored safety and activity of combined LOHP and PLD in the treatment of ROC. Eligible patients had had disease recurrence following a paclitaxel/ carboplatin regimen or following cisplatinum or non-platinum-based second line chemotherapy. Other eligibility criteria were a performance status ≤ 2 and a life expectancy > 3 months. Treatment consisted of 120 mg/m^2 LOHP and 40 mg/m^2 PLD, given over 2 days, every 3 weeks. Forty-six patients with ROC were entered into the study between 10/2001 and 10/2005; 67.5% of patients were platinum-sensitive. Toxicity was moderate, with grade 3 or 4 neutropenia in 2% of patients, and grade 2 PPE in 7% of patients. Overall response rate was 67.5%. Median progression-free survival (PFS) was 27.5 months, while median overall survival was 44 months. We conclude that LOHP and PLD are active in ROC, and can be safely administered in pre-treated patients.

Keywords: Recurrent ovarian cancer; Salvage chemotherapy; Pegylated liposomal doxorubicin; Oxaliplatin

Introduction

Surgical debulking followed by carboplatin/taxane-based combination chemotherapy is the treatment of choice for patients presenting with advanced ovarian cancer [1]. Unfortunately, the majority of patients develop recurrent ovarian cancer (ROC) and need some form of salvage chemotherapy. Patients with disease recurrence 6 months or longer after first-line chemotherapy, may respond to the same drug, while patients who recur before 6 months are considered to be platinum resistant [2].

Doxorubicin, as well as cisplatin, are active in ovarian carcinoma. Their different mechanisms of action decrease the likelihood of cross-resistance [3].

Topotecan, gemcitabine and etoposide, have demonstrated some activity in patients that had failed previous paclitaxel-based chemotherapy [4]. Nonetheless due to the palliative role of chemotherapy [5], high toxicity should be not acceptable.

Liposome technology, reducing drug uptake by the reticuloendothelial system has helped to decrease toxicity. Therefore, pegylated liposomal doxorubicin (PLD) causes less myelotoxicity, cardiotoxicity, nausea and vomiting and alopecia compared to the parent compound, doxorubicin [6]. In addition, liposomal doxorubicin has been shown to be superior to topotecan [7] and active as second-line treatment even after prior failure of platinum- and paclitaxel-containing first-line chemotherapy. Oxaliplatin (LOHP), a platinum analogue active in ovarian cancer cells lines, has non-cross-resistance characteristics with platinum compounds such as cisplatin and carboplatin [8]. LOHP is active, as a single agent, in heavily pre-treated ovarian cancer patients, with objective responses in platinum-refractory patients [9]. The non-cross resistance of LOHP with platinum compounds and the activity of LOHP and PLD in second-line chemotherapy has suggested to conduct a phase I study in order to determine the maximum tolerated dose, the dose-limiting toxicities and the toxicity profile of LOHP in combination with PLD in the salvage treatment of patients with advanced ovarian cancer [10].

Here we report the results of an open label, multicentre phase II study of 46 consecutive patients with recurrent ovarian cancer (ROC), treated with the doses of LOHP and PLD, determined in the phase I study.

Patients and Methods

Patients

Patients who had either failed or relapsed after a paclitaxel/ carboplatin regimen or after cisplatinum or non-platinum-based second line chemotherapy, were eligible if they had histologically or cytologically confirmed epithelial ovarian cancer, measurable lesions of at least 2 cm. Other eligibility criteria included patient age ≥ 18 years and ≥ 75 years, a performance status ≤ 3 (ECOG scale) and an anticipated life expectancy of at least 3 months. The patients were required to have adequate haematological (WBC > 4000/ml, platelets > 100,000 /ml), hepatic (bilirubin level ≤ 1.5 mg/dl and AST ≤ double the upper limit of normal), renal (creatinine concentration ≤ 1.5 mg/dl) and cardiac function. Patients were excluded if they had clinically significant cardiovascular disease, previous chemotherapy, radiation or surgery to the metastatic site within 4 weeks of baseline, or a diagnosis of another malignancy. Patients were classified as platinum-resistant if they had a relapse within 26 weeks of completion of first-line platinum-based chemotherapy [7].

Study design

This study was a multicentre, phase II study of liposomal

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doxorubicin (Caelyx®, Schering-Plough International, Kenilworth, NJ, USA) plus oxaliplatin (Eloxatin®, Sanofi-Synthelabo Inc., Paris, France) for the treatment of ROC. Pre-treatment evaluation included a medical history and physical examination, complete blood count (CBC), serum chemistries and coagulation profile, serum CA-125 determination, abdomino-pelvic imaging scan, chest x-ray, ECG with ejection fraction evaluation with echocardiogram (ECHO). Follow-up included physical examinations, CBC, differential, serum chemistries, as well as serum CA-125, ECHO and imaging procedures or pelvic examination every 9 weeks. This phase II study was conducted in accordance with the Declaration of Helsinki and the EU Guidelines on Good Clinical Practice, was approved by the local Ethical Committees of the participating institutions and written informed consent was obtained from each patient.

Treatment

Treatment, repeated every three weeks, consisted of (IV) administration of dexamethasone (20 mg) and a $5HT_3$ antagonist and 1-hour administration of 20 mEq KCl and 4 mEq $MgSO_4$. PLD was given intravenously in 1 hour at the dose of 20 mg/m^2 (total dose in two days: 40 mg/m^2). During the administration of PLD, both hands and feet were refrigerated in ice water in order to decrease the occurrence of palmar-plantar erythrodysesthesia (PPE), while acetyl-l-carnitine was administered orally (500 mg twice a day), in order to decrease the likelihood of neuropathy. LOHP was administered intravenously after PLD in 2 hours at the dose of 60 mg/m^2, (total dose in two days: 120 mg/m^2) for a maximum of 9 cycles or until progression, unacceptable toxicity or patient refusal.

Response and toxicity evaluation

Response to treatment was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) [11]. Relapse was defined as the recurrence, following a period of response, of a former lesion, its enlargement or the formation of new lesions, including central nervous system disease. The date of relapse was defined as the time when recurrent disease was diagnosed. Progression-free survival (PFS) was defined as the length of time from the date of the first course of therapy to any relapse, or to the appearance of a second primary cancer or death, whichever occurred first. PFS and overall survival (OS) were estimated by means of the Kaplan-Meier product-limit method [12]. OS was measured from study entry to death. Standard World Health Organization (WHO) criteria for assessing toxicity were used.

Statistical analysis

Accrual was conducted according to Simon's optimal two-stage design [13]. The first stage required that three or more patients out of 17 had a confirmed response; the aim was to rule out an undesirably low response probability of 0.20 (P0) in favour of a desirable response probability of 0.40 (P1), with a 10% probability of accepting a poor agent ($\alpha = 0.1$) and a 10% probability of rejecting a good agent ($ß = 0.1$) before proceeding to the second stage. In the second stage, 37 assessable patients could be added, and if a total of 10 or more patients achieved a confirmed response, then the primary end point would have been met. Statistical analysis was performed with SAS statistical software. The log-rank test was used to compare PFS and OS of patients with platinum-resistant and platinum-sensitive disease.

Results

Patient characteristics

Patients were entered between October 2001 and October 2005. The 46 patients, with a median age of 68 years (range 49-74), were evaluated for response and toxicity. At study entry, 64% of patients had stage III disease, while 36% had stage IV (FIGO). Histological characteristics were: papillary 55%, endometroid 25%, poorly differentiated 15%, and mucinous 5%. The performance status (ECOG) was 0-1 in 31 patients and 2 in 15 patients (Table 1). All patients received a total of 311 courses of chemotherapy, and each patient had received, at least, four courses of paclitaxel/carboplatin chemotherapy. Forty-five percent of patients got one line of chemotherapy, while 55% of them received two or more lines.

Median interval from the last platinum treatment was 18 months for the 30 patients with platinum-sensitive disease, and 5 months for the 16 patients with platinum-resistant disease. Visceral disease and bone disease were present in 75% and 10% of patients, respectively.

Response and survival

Forty-six patients (Table 1) were evaluable for toxicity and response on an intent-to-treat basis. 6 patients (13%) had a complete response, 26 patients (57%), and a partial response, for an objective response rate (RR) of 70% (95% Confidence Intervals, 50-81%). Stable disease was observed in 12 patients (26%), and progressive disease in 2 patient (4%). After a median follow-up of 89,8 months (range 10-227), median PFS (Figure 1) was 27.5 months (range 9.6-117). Median OS was 44 months (range 9.7-227) (Figure 2). The 1-year and 2-year survival rates were 93% and 71%, respectively. No statistically significant difference was observed between patients with platinum-sensitive and platinum-resistant disease. The tumor marker CA-125 showed a statistically significant decrease from baseline values, both in platinum-sensitive ($P < 0.01$) and platinum-resistant disease ($P < 0.001$).

Toxicity

No treatment-related death occurred. The toxicity profile (Table 2) was acceptable, with grade 3 or 4 neutropenia in 2% of patients.

Characteristics	No.	%
No of patients	46	100
Age, years		
median	68	
range	49-74	
Performance status (ECOG)		
0-1	31	67
2	15	33
Platinum sensitive disease	30	65
" resistant disease	16	35
Metastatic sites		
viscera	35	76
bone	5	11
other	6	13
Number of chemotherapy courses	311	
median	7	
Response to chemotherapy		
PR	26	57
CR	6	13
SD	12	26
PD	2	4

PR: partial response; CR: complete response; SD: stable disease; PD; progressive disease

Table 1: Patient characteristics.

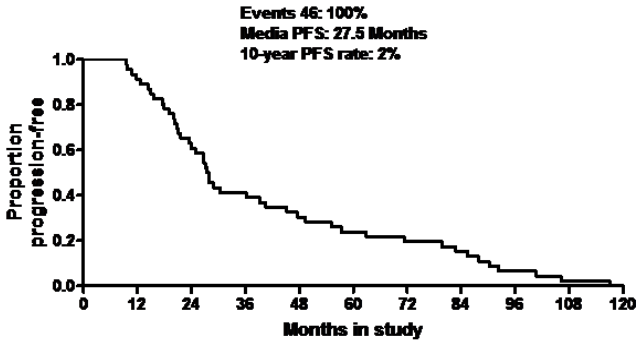

Figure 1: Progression-free survival. Events 46: 100%, MedianPFS: 27.5 Months.

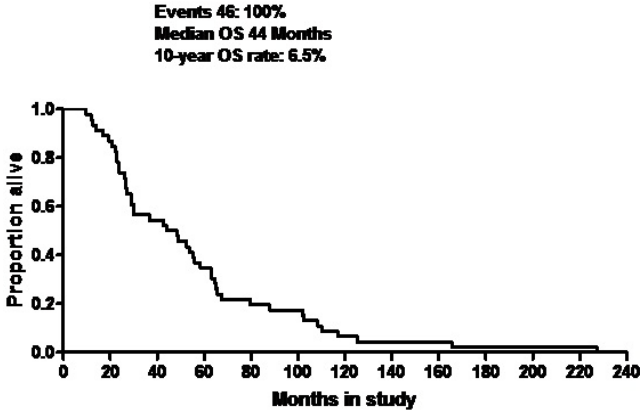

Figure 2: Overall survival. Events 46: 100%, Median OS 44 Months.

Grade 2 PPE was observed in 3 patients (7%). Gastrointestinal toxicity consisting of grade 2 and 3 mucositis was observed in 6% and 5% of patients, respectively. Cutaneous WHO grade 1 and 2 toxicity was observed in 6 patients (14%). No patients showed a reduction of left ventricular ejection fraction below 55%.

Discussion

Patients with ovarian cancer and other solid tumors, with long-time responses to first line chemotherapy, may benefit from the same drugs given as second-line [14].

The probability of response to further platinum-based therapies, in patients with partially platinum-sensitive tumors, is lower (between 15% and 30%), and in platinum-resistant disease, the probability of response is less than 10% [15].

Nevertheless, many new agents have demonstrated activity in the treatment of both platinum-sensitive and also in platinum-resistant/refractory diseases, with responses between 7% and 36% [16]. Anthracyclines have activity in advanced ovarian cancer, but have a significant toxicity profile when added to taxane/cisplatin-based chemotherapy regimens [3]. In order to improve its tolerability, the doxorubicin molecule has been encapsulated in a liposomal structure. The liposomes containing doxorubicin have been shown to reduce alopecia, nausea, vomiting and even the risk of cardiomyopathy, without reducing its efficacy. In addition, the uptake of the drug by macrophages is decreased, prolonging its half-life and improving its deposition in pathological exudates [9]. PLD has demonstrated activity both in platinum-resistant or platinum-refractory disease with a 17% response rate and a 40% disease stability rate [17].

The dose of 20 mg/m^2 given over two days, was shown to be active and devoid of toxicity in a previous phase II study [15]. PLD was chosen for its non-cross-resistance with cisplatin, while LOHP was chosen because it may be able to overcome the platinum-resistance [11]. Moreover, LOHP lacks renal and auditory toxicity and is marginally haematotoxic at the recommended doses [18].

In a previously reported phase II study, the combination of PLD and LOHP was administered on a different schedule to 43 patients with ROC [19]. In that study, the dose intensity of LOHP was 17.5 mg/m^2 /week, while the dose intensity of PLD was 8.125 mg/m^2/week; in our study, the dose intensity of LOHP was doubled (40 mg/m^2/w), while the dose intensity of PLD was 13.3 mg/m^2/w. However, even considering the limitations of comparing different study populations, our higher dose-intensity was not accompanied by a higher toxicity

	WHO grade											
	0		1		2		3		4		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic												
Leucopenia	18	39	13	28	12	26	2	5	1	2	46	100
Thrombocytopena	30	65	6	13	9	20	1	2	0	0	46	100
Anemia	31	67	10	22	5	11	0	0	0	0	46	100
Infection	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal												
Oral	35	76	6	13	3	6	2	5	0	0	46	100
Nauseaandvomiting	40	86	3	7	3	7	0	0	0	0	46	100
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0
Hepatic	38	82	4	9	9	17	0	0	0	0	46	100
Neurotoxicity	40	86	3	7	3	7	0	0	0	0	46	100
Cutaneous												
Alopecia	0	0	0	0	0	0	0	0	0	0	0	0
Skin	40	86	3	7	3	7	0	0	0	0	46	100

Table 2: Toxicity according to WHO criteria.

profile, especially for neutropenia and PPE. This is probably due to the different administration schedule, to the refrigeration of the patients' extremities and to the administration of acetyl-l-carnitine. Moreover, we were able to administer weekly dose intensities for LOHP and PLD that were 96.2% and 95% of the planned dose, respectively, in all patients.

A study of the combination of PLD and carboplatin to treat patients with advanced ovarian cancer with platinum-sensitive disease has been recently reported [20]. In the study by Ferrero et al., the results were very similar to those obtained in our patients with platinum-sensitive disease in terms of the response rate (63% vs. 67.5%), PFS (9.4 months vs. 10.8 months) and OS (30.5 months vs. 32 months). The concurrence of the results of the two trials confirms the activity of the combination of liposomal doxorubicin and a platinum analogue.

In the attempt to prolong PFS with maintenance therapy, 486 women with relapsed platinum-sensitive ovarian cancer were randomly assigned to receive a treatment with cediranib or placebo. Women randomized to maintenance treatment had a median PFS of 11 months, while patients randomized to placebo had a PFS of 8.7 months [21].

Determination of serum CA-125 was useful for predicting the outcome of therapy in both platinum-sensitive and platinum-resistant patients. In fact, this tumor marker significantly decreased in responding patients and in patients with stable disease both in platinum-resistant and platinum-sensitive disease. These data show that this regimen was effective in both kinds of disease, even if it could not alter the natural history of these patients. Significant responses to therapy were seen in visceral sites.

In conclusion, even with the limitation of a non-randomized study, the combination of PLD and LOHP is an active regimen and may be safely used, with a low toxicity profile, for treating ROC in patients with both platinum-resistant and platinum-sensitive disease.

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