Phase I study of liposomal doxorubicin and oxaliplatin as salvage chemotherapy in advanced ovarian cancer

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Oxaliplatin (L-OHP) and stealth pegylated liposomal doxorubicin (PLD) have been shown to be active in pre-treated advanced ovarian cancer (PAOC). The aim of this phase I study was to determine the maximum tolerated dose (MTD) of L-OHP, combined with fixed doses of PLD as salvage treatment of PAOC. Twenty patients with recurrent ovarian cancer previously treated with two (30%) or three lines (70%) of chemotherapy were entered into the trial. Patients had a median age of 64 years (52–77) and a median platinum-free interval of 13 months (range 6–35). Patients received a fixed dose of PLD 40 mg/m^2, combined with escalating doses of L-OHP from 80 to 130 mg/m^2 administered in 1 day, every 3 weeks. Dose escalation was interrupted if 30% or more patients of a given cohort (three patients) exhibited dose-limiting toxicity in the first treatment cycle. The MTD of L-OHP was 130 mg/m^2 as two out of three patients of this cohort showed dose-limiting thrombocytopenia and/or neutropenia during the first cycle of treatment. Amongst 20 evaluable patients, we observed an overall response rate of 55% (95% confidence interval 31.5–76.9%). With a median follow-up of 12 months (3.4 ± 19.2), median time to progression was 9.7 months, while median survival was not reached yet. We conclude that a combination of PLD and L-OHP has a manageable toxicity profile, and can be safely administered as outpatient chemotherapy for heavily pre-treated patients with relapsed ovarian cancer. Promising anti-tumor activity was observed. *Anti-Cancer Drugs* 14:633–638 © 2003 Lippincott Williams & Wilkins.

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Introduction

A combination of a platinum compound with an alkylating agent was considered as the standard treatment for patients with ovarian cancer; however, the introduction of taxanes in combination with cisplatin has recently been recommended as the new standard care [1]. The substitution of cisplatin with carboplatin has decreased the toxicity of this chemotherapeutic regimen and has rendered it suitable for administration to outpatients, resulting in improved quality of life with a similar response rate and overall survival [2].

In a randomized trial versus standard chemotherapy, this combination chemotherapy has yielded a favorable response rate with a median progression-free survival of 17.3 months and an overall median survival time of 36.1 months [2]. However, despite the high response rates (approximately 75%) obtained initially after cytoreductive surgery, the vast majority of patients (55–75%) with stage III or IV cancer develop disease recurrence and become candidates for salvage chemotherapy [3,4]. The treatment of recurrent ovarian cancer is further complicated by acquired platinum resistance [5]. Paclitaxel has been found to be an active drug in platinum-resistant advanced ovarian cancer [6]; however, second-line chemotherapy for patients with ovarian cancer in whom platinum and paclitaxel treatment has failed remains a therapeutic challenge. While a number of agents including topotecan, gemcitabine and etoposide have demonstrated activity giving modest response rates and response duration in patients that had failed previous paclitaxel-based chemotherapy [7–9], the treatment of patients with platinum-resistant disease is more complicated [10]. Doxorubicin is a drug known to be active in advanced epithelial ovarian carcinoma. Several single trials comparing a combination of doxorubicin with other active agents such as cisplatin and cyclophosphamide did not show any statistically significant advantage in terms of disease-free survival and overall survival. However, a meta-analysis showed that doxorubicin plus cisplatin and cyclophosphamide added a modest, but significant, 7% improvement in survival [11]. This meta-analysis has renewed interest in the use of anthracyclines in the treatment of ovarian carcinoma. Moreover, anthracyclines have a mechanism of action involving DNA intercalation and topoisomerase II inhibition [12] that differs from that of

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cisplatin, therefore decreasing the likelihood of cross-resistance.

Considering the palliative effect of second-line chemotherapy in advanced ovarian cancer, high toxicity is not acceptable. Liposome drugs that are devoid of high toxicity have therefore been used. Encapsulation of doxorubicin by stealth pegylated liposomes (caelyx) decreases its uptake by the reticuloendothelial system, resulting in a significant prolongation of serum half-life to approximately 50 h compared with 10 min of the free drug [13]. Due to these pharmacokinetic considerations, PLD is associated with decreased myelotoxicity, cardiotoxicity, nausea and vomiting, and alopecia compared to doxorubicin [14], even if cutaneous and mucosal toxicity can be bothersome. PLD has demonstrated activity in the treatment of advanced ovarian cancer in patients previously treated with paclitaxel/carboplatin chemotherapy and superiority with respect to topotecan [15–17].

Oxaliplatin (L-OHP) is a diaminocyclohexane platinum analog active against human and murine cells both *in vitro* and *in vivo*, including ovarian cells lines, with non-cross-resistance characteristics with first- and second-generation platinum compounds such as cisplatin and carboplatin [18]. This compound, synthesized 20 years ago, is currently under investigation in phase II–III studies in several malignancies such as colorectal cancer and non-small-cell lung cancer. L-OHP has shown a 29% response rate as a single agent at hematologically subtoxic doses in heavily pre-treated ovarian cancer patients, with objective responses in platinum-refractory patients [19]. The non-cross resistance with platinum compounds and the activity in second-line chemotherapy of PLD and L-OHP has induced us to initiate this phase I study aimed at determining the maximum tolerate dose (MTD), the dose-limiting toxicities (DLTs) and the toxicity profile of L-OHP in combination with fixed doses of PLD in the salvage treatment of patients with advanced ovarian cancer.

Patients and methods

This phase I study conducted in accordance with the Declaration of Helsinki and the EU Guidelines on Good Clinical Practice was approved by the local Ethical Committee of the participating institutions, and written informed consent was obtained from each patient.

Eligibility criteria included patients aged 18 years of age or older with histologically or cytologically confirmed advanced ovarian cancer, recurrent after, or failing to achieve an objective response to paclitaxel/carboplatin chemotherapy or to a cisplatin or non-platinum-based second-line chemotherapy. Other eligibility criteria included: bidimensionally measurable or assessable disease, age ≤ 75 years, a performance status ≤ 3 (ECOG scale) and an anticipated life expectancy of at least 3 months. The patients were required to have an adequate hematological (WBC > 4000/ml, platelets $> 100\,000$/ml), hepatic [bilirubin level ≤ 1.5 mg/dl and alanine aminotransferase (AST) $\leq 2\times$ the upper limit of normal], renal (creatinine concentration ≤ 1.5 mg/dl) and cardiac function. Patients with additional malignancies, other than curatively treated skin and cervical cancer or with active cardiovascular disease, were excluded.

Patients with a performance status of 3 and a life expectancy longer than 3 months were included in this trial in order to make the results more applicable to a broader population of previously treated ovarian cancer patients. Patients were classified as platinum-resistant (relapse within 26 weeks after completion of first-line platinum-based chemotherapy) or platinum-sensitive (relapse after 26 weeks of completion of first-line platinum-based chemotherapy) [10]. Pre-treatment evaluation included medical history, clinical examination, complete blood cell count, determination of plasma urea and creatinine levels, electrolyte measurement, a liver function test, and serum CA-125 determination. Electrocardiogram, computed tomography (CT) scan of chest and abdomen, and X-rays of abnormal areas of bone scan uptake were performed. CT scan was used to evaluate hepatic lesions. Before each subsequent course of treatment all patients had a further blood cell count, plasma urea, electrolytes, serum creatinine, aspartate aminotransferase (ALT), AST, alkaline phosphatase (AP) and bilirubin measurement. In addition, a cell blood count was repeated weekly.

Toxicity and activity assessment

Standard WHO criteria for assessing response and toxicity [20] were used. Clinical tumor response and toxicity assessment were performed by physical examination and serum CA-125 determination before each course of chemotherapy. Cardiac function in patients previously treated with anthracycline therapy was evaluated by MUGA scan. Objective tumor response was measured by CT scan or magnetic resonance imaging of the abdomen and pelvis every two courses of chemotherapy or sooner if the patient appeared to have disease progression. Time to disease progression was calculated from the date of the first day of treatment to the first date when disease progression was observed. Survival was calculated from the first day of treatment to death. Both were assessed by with the Kaplan–Meier method [21].

Treatment

The outpatient treatment was performed according to the following 1-day schedule: 15-min i.v. administration of dexamethasone 20 mg in 100 cm^3 of saline, 15-min i.v. administration an 5-HT_3 antagonist in 100 cm^3 of saline

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and PLD at the fixed dose of 40 mg/m^2 diluted in 250 ml of dextrose 5% in water, administered i.v. in 1 h. During administration of the drugs, both hands and feet were refrigerated in order to decrease the occurrence of palmar–plantar erythrodysesthesia. L-OHP was administered i.v. after PLD in 500 cm^3 of a 5% glucose solution in 3 h. The dose of L-OHP was escalated from 80 to 130 mg/m^2, in 10 mg/m^2 increments. At least three patients were enrolled in each cohort and dose escalation was interrupted if 30% or more patients of a given cohort exhibited DLT during the first cycle of treatment [22]. DLT was defined as grade 4 neutropenia persisting for more than 7 days or grade 4 thrombocytopenia or grade 4 non-hematological toxicity (except for nausea or alopecia). A delay longer than 1 week in administering the second cycle of therapy was also considered a DLT. There was no intra-patient dose escalation.

Although this study was designed to evaluate toxicity, patients were assessed for response after three courses of therapy. Additional therapeutic cycles were administered until progression if patients showed a partial or complete response, according to WHO response criteria. Patients exhibiting evidence of disease progression after two courses of chemotherapy were excluded from this study.

Results

Patient characteristics

All 20 patients, with a median age of 64 years, entering this study from March 2001 to June 2002 received at least two courses of treatment. Thirty percent of patients were stage III, while 70% had stage IV disease, as defined by the International Federation of Gynecology and Obstetrics (FIGO). Histology was as follows: papillary 55%, mucinous 5%, endometroid 25% and poorly differentiated 15%. The ECOG performance status was 0–1 in 12 patients, 2 in five patients and 3 in three patients (Table 1). The 20 patients received 130 courses of chemotherapy. The median number of courses administered per patient was 6.2 (range 2–16 courses). All patients had received at least four courses of paclitaxel/carboplatin as first-line chemotherapy: adjuvant after debulking surgery 15 patients, primary chemotherapy for stage IV disease five patients. Seventy percent of patients had received the CAP (cyclophosphamide, cisplatin, adriamycin) regimen as second-line chemotherapy, while 20 patients had received gemcitabine, taxotere, mitoxantrone, ifosfamide in various combinations.

Median interval from last platinum treatment was 14 months (range 5–75 months).

Table 1 Patient characteristics

Characteristics	No.	%
No. of patients	20	100
Age (years)		
median	64	
range	52–77	
Performance status (ECOG)		
0–1	12	60
2	5	25
3	3	15
FIGO stage		
III	6	30
IV	14	70
Histology		
papillary	11	55
mucinous	1	5
endometroid	5	25
poorly differentiated	3	15
Tumor grade		
1	1	5
2	7	35
3	12	60
Metastatic sites[a]		
peritoneal carcinomatosis	10	50
abdomen–pelvis	8	40
bone	6	30
liver	5	25
lung	1	5
Interval from last treatment (months)		
>6	6	30
<6	14	70
Prior lines of treatment		
taxol–carboplatin	20	100
cisplatin, adriamycin, cyclophosphamide	14	70
gemcitabine, taxotere, mitoxantrone, ifosfamide in various combinations	20	100

[a]Ten patients had two metastatic sites.

Dose-finding study

The major toxicities encountered in this study were neutropenia, palmar–plantar erythrodysesthesia and thrombocytopenia. No treatment-related death was observed. Toxicity data are illustrated in Table 2. Three patients were entered at the first dose level (PLD 40 mg/m^2 and L-OHP 80 mg/m^2). This dose level was very well tolerated. Thirty courses of chemotherapy were delivered to the three patients, of whom two had a partial response and one exhibited a pathological complete response to second-look surgery. The first patient received 16 courses of chemotherapy because she continued to respond slowly and her CA-125 value kept decreasing constantly. The incremented dose of L-OHP 90 mg/m^2 was also well tolerated. Twelve courses of chemotherapy were delivered, resulting in one partial response, and one disease stability and mild toxicity. After 21 courses of chemotherapy delivered at the dose of 100 mg/m^2, one complete pathological response, one partial response and one case of disease stabilization were observed. Various grades of mild hematological toxicity occurred. At the next dose level of 110 mg/m^2, disease stability was observed in the three patients enrolled. One of the patients had undergone two courses of liver chemoembolization for unresectable liver metastases. Two patients enrolled at the dose level of 120 mg/m^2 had disease stability, while a third patient had a complete pathological response observed in the third operation. This patient suffering from a neurological lower extremities paraneoplastic syndrome had an improvement of her symptoms for 12 months.

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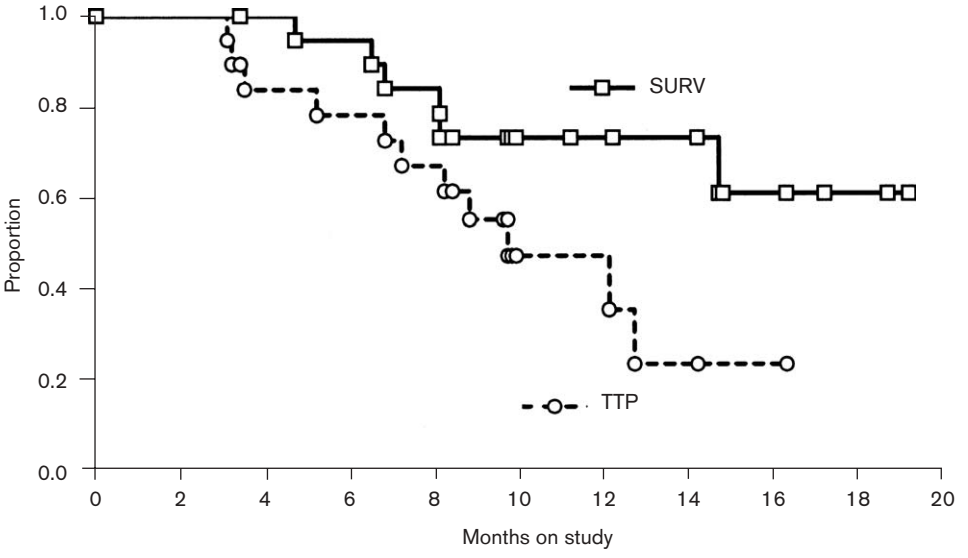
Table 2 Dose escalation scheme, DLT and response

Dose level of oxaliplatin (mg/m^2)	Patients	Cycles	DLT	Type of toxicity	Response
80	3	30	0	neutropenia	1 pathological CR 2 PR
90	3	12	0	mucositis	1 PR, 1 SD 1 PD
100	3	21	0	neutropenia	1 pathological CR 1 PR, 1 SD
110	3	16	0	neutropenia, anemia, PPED	3 SD
120	3	17	0	neutropenia, anemia, PPED	1 pathological CR 2 SD
130	3	23	2	2 G4 neutropenia, 1 G3 thrombocytopenia	3 PR
Total	18	119	2		

PPED, palmar–plantar erytrodysesthesia; CR, complete response; PR, partial response; SD, stable disease.

Fig. 1



Time to progression (TTP): there were 11 events (55%) and nine censored patients (45%). Median TTP was 9.7 months. Overall survival (SURV): there were six events (30%) and 14 censored patients (70%). Median SURV was not reached after a median follow-up of 12 months.

Two cases of grade 2 neutropenia and two cases of palmar–plantar erythrodysesthesia were observed. The sixth dose level of 130 mg/m^2 was toxic: two out of three patients had grade 4 neutropenia lasting 10 days and grade 3 thrombocytopenia at the first cycle of treatment. Further treatment was delivered at the lower dose level without problems. The last two patients were treated with PLD 40 mg/m^2 and L-OHP 120 mg/m^2, considered the dose for a phase II study that will follow this study.

In the case of hematological toxicity occurring after the first course of chemotherapy, doses were reduced by 20%. The median WBC and platelet nadir occurred on day 14 (range 4–18), with a median hematological recovery observed by day 21.

Neutropenic fever requiring hospitalization was observed in three patients. The use of granulocyte colony stimulating factor was not allowed in this study. Various grades of anemia were observed in 11 patients who were treated with erythropoietin. No patient required a blood transfusion for a hemoglobin value below 7 g/100 ml. Eight courses of chemotherapy (6%) were delayed for 1 week due to myelosuppression. The dose intensity of PLD and L-OHP was 96 and 95%, respectively, for all patients. Non-hematological toxicity was acceptable. Nausea and vomiting were severe (grade 2–3) in only six patients (30%) due to the appropriate administration of 5-HT$_3$ antagonists and dexamethasone. Grade 3 alopecia occurred in 90% of patients and was not prevented by head hypothermia. Such a high rate of

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alopecia was unexpected. In fact these two drugs, used as single agents, have been described to give low-grade alopecia. Most likely the combination of the two drugs gives a cumulative toxicity on hair loss. Standard WHO criteria for assessing response and toxicity [20] were used, and one patient (5%) exhibited a transient elevation in the concentration of liver enzymes. Eight patients developed various grades of palmar–plantar erythrodysesthesia. This toxicity was partially avoided, after the first course of chemotherapy, by refrigerating hands and feet during the administration of PLD.

Response and survival

Although response to therapy was not the endpoint of this study, patients who had completed at least two cycles of chemotherapy were evaluated for response on an intent-to-treat basis. Twenty patients were evaluated for toxicity and response. Objective overall remission was observed in 11 patients (response rate 55%, 95% confidence interval 32–77%). A complete or partial response was observed in three (15%) and eight (40%) patients, respectively. Disease was stable in eight (40%) patients and progressed in one (5%) patient. Median time to disease progression (Fig. 1) was 9.7 months (range 3.1–16+). Median overall survival had not yet been reached after a median follow-up of 12 months, since 14 patients were still alive (Fig. 1). The 1-year survival rate was 73%. By February 2003, 14 patients (70%) remained alive and eight (40%) were progression-free between 3.4 and 19.2 months after initiating treatment. One patient with diffuse liver metastases exhibited a complete response after six courses of chemotherapy.

Discussion

The liposome containing doxorubicin presents, externally, the hydrophilic polymer methoxypolyethylene glycol that has been shown to reduce alopecia, nausea, vomiting and even the risk of cardiomyopathy without reducing its efficacy [23]. The stealth technology has improved the pharmacology of liposomal doxorubicin, decreasing the uptake of the drug by macrophages, prolonging its half-life (from 45 to 70 h) and improving the deposition of the drug in pathological exudates [13]. This is exactly the situation encountered in ovarian cancer with malignant ascites.

The dose chosen was 40 mg/m^2 as this dose level was shown to be active and devoid of toxicity in a previous phase II study [16]. PLD was chosen for its non cross-resistance with cisplatin due to its different mechanism of action, while oxaliplatin was chosen because it has been shown that it may be able to overcome the platinum resistance that complicates the treatment of recurrent ovarian cancer [10]. Moreover oxaliplatin lacks the renal and auditory toxicity, and is marginally hematotoxic at the recommended doses [24].

As expected, myelosuppression and palmar–plantar erythrodysesthesia were the DLTs. The activity of this regimen was encouraging, with a response rate of 50%. Responses were observed at all dose levels, indicating a wide margin of activity for this regimen. This regimen was successfully administered to three patients with a performance status of 3. These patients had a considerable improvement of their performance status.

Since neutropenia appears to be one of the main side-effects of this combination chemotherapy, it may be possible to increase the dose of L-OHP with the use of hematopoietic growth factors, leaving unchanged the dose of PLD that is the cause of palmar–plantar erythrodysesthesia. The weekly dose intensities for L-OHP and PLD were 96.2 and 95% of the initial dose, respectively, for all patients. In conclusion, PLD 40 mg/m^2 and L-OHP 120 mg/m^2 are the recommended doses for a phase II study. This study demonstrates that the association of PLD and L-OHP is feasible in the treatment of advanced, pre-treated ovarian cancer, has an acceptable toxicity profile and gives longer than expected responses.

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