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ORIGINAL ARTICLE

Pegylated liposomal doxorubicin in heavily pretreated epithelial ovarian cancer patients

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Summary

Purpose: *While most patients with ovarian cancer respond to first-line treatment, 50-75% of these patients will eventually relapse. Pegylated liposomal doxorubicin (PLD) is an active agent indicated for the treatment of patients with disease that is refractory to both paclitaxel- and platinum-based regimens, but skin toxicity remains the dose-limiting toxicity of the drug. The primary objective of this retrospective study was to evaluate the activity and safety of this agent in patients with heavily pretreated ovarian cancer.*

Patients and methods: *Patients with platinum-refractory/resistant, paclitaxel-pretreated epithelial ovarian carcinoma were treated with PLD 50 mg/m^2 in 4-week courses until disease progression or unacceptable toxicity. All patients had progressive disease (PD) before starting PLD. Primary endpoints were response rate, progression free survival (PFS) and toxicity and secondary endpoints duration of response (DOS) and overall survival (OS).*

Results: *Seventeen heavily pretreated patients (median number of previous chemotherapy regimens 3, range 1-5) with taxane- and platinum-refractory disease were analysed. No complete response (CR) was achieved, while 3 (17%) partial responses (PR) and 2 (11%) cases with stable disease (SD) were observed. The median PFS was 15 weeks (range 10-21) and median OS 32 weeks (range 16-47). Palmar plantar erythrodysesthesia (PPE) occurred in 4 (23%) patients and was of grade 4 in 1 (6%) patient. Stomatitis occurred in 3 (17%) patients and was grade 3 in 1 (6%) patient. Grade 3-4 neutropenia occurred in only 2 (12%) patients. No febrile neutropenia was encountered.*

Conclusion: *Pegylated liposomal doxorubicin is an active and tolerable agent in heavily pretreated epithelial ovarian cancer patients.*

Key words: chemotherapy, ovarian carcinoma, pegylated liposomal doxorubicin, salvage therapy

Introduction

Ovarian cancer remains the leading cause of death among gynecologic malignancies in the USA [1]. The standard of care for first-line treatment of ovarian cancer is surgery for staging and cytoreduction, followed by chemotherapy with a platinum/taxane combination. Long-term survival for advanced-stage disease is only 30%, even among women who have had optimal cytoreduction and front-line combination therapy [2,3]. While most patients with ovarian cancer respond to first-line treatment, 50-75% of these patients will eventually relapse. In these patients, the goals of second-line chemotherapy include palliation of symptoms, preservation of quality of life, and prolongation of PFS. For patients with platinum-refractory or platinum-resistant tumors (no response or relapse within 6 months), treatment options are unsatisfactory but include a number of novel agents with unique mechanisms of action, such as docetaxel, etoposide, gemcitabine, oxaliplatin, topotecan and PLD [4,5]. Survival in patients with ovarian cancer has improved in recent decades, reflecting improvements in therapy [6].

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Doxorubicin has a wide spectrum of activity in human tumors, but the role of this agent is not very impressive in recurrent ovarian cancer and is of only limited benefit in front-line trials [7]. The use of doxorubicin is also limited by its myelosuppression, gastrointestinal toxicity and cumulative cardiac toxicity [8]. PLD is a unique formulation of conventional doxorubicin in which a polyethylene glycol layer surrounds the doxorubicin-containing liposome, a process termed pegylation. Pegylation protects the liposomes from detection by the reticuloendothelial system and increases the plasma half-life compared with conventional doxorubicin [9]. PLD has demonstrated efficacy as a single agent in the treatment of recurrent/relapsed ovarian cancer in several clinical trials with response rates ranging from 16 to 25%, while skin toxicity remains the dose-limiting toxicity of the drug [10-12].

In the USA PLD is approved by the Food and Drug Administration (FDA) for the treatment of metastatic ovarian cancer in patients with disease refractory to both paclitaxel- and platinum-based chemotherapy regimens [13]. Guidelines from the National Institute for Clinical Excellence advocate PLD as the drug of choice for many patients with advanced ovarian cancer for whom first-line chemotherapy has failed [14].

In the literature, PLD has been extensively studied in first relapse and to a lesser extend in second relapse, but not in heavily pretreated patients. In this study the efficacy and toxicity of single-agent PLD was evaluated in heavily pretreated, taxane- and platinum-refractory/resistant epithelial ovarian cancer patients.

Patients and methods

Patients with platinum-refractory/resistant, paclitaxel-pretreated ovarian cancer were treated with PLD and included in this retrospective study. Patients were surgically staged according to FIGO staging criteria. Eligibility criteria were: age 18-70 years; platinum- and taxane-pretreated epithelial ovarian cancer; PD with measurable or evaluable disease documented through imaging procedures; life expectancy >3 months; adequate bone marrow, renal and hepatic functions; normal cardiac function evaluated by both ECG and echocardiography (with left ventricular ejection fraction >52); Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. All patients had undergone clinical, blood/serum and imaging evaluation of PD prior to treatment administration.

PLD 50 mg/m^2 was dissolved in 250 ml of 5% glucose and infused i.v. over 1 h; cycle repetition was every 28 days. Standard antiemetic treatment was given to all patients. Delays or dose modifications were based on toxicity present on the treatment day. Patients continued therapy until PD or unacceptable toxicity.

Primary endpoints were response rate, PFS and toxicity and secondary endpoints duration of response and OS. Staging procedures included standard physical examination, ultrasound and computed tomography scan of the abdomen and pelvis, and two-view chest X-ray. Objective responses were evaluated every 3 cycles by repeating the staging procedures following the Response Evaluation Criteria for Solid Tumors (RECIST) [15]. CA125 levels were evaluated at baseline and after each cycle. Patients who showed PD after 3 cycles were taken off treatment. Response criteria were defined as follows: CR: disappearance of all known disease lesions for at least 1 month; PR: ≥50% decrease of known lesions, without appearance of new ones, for a minimum of 1 month; SD: >25% decrease or <25% increase of known lesions, without appearance of new ones; PD: >25% increase of any known lesion or appearance of new lesion(s).

Hematological and non-hematological toxicities were assessed by utilizing the National Cancer Institute Common Toxicity Criteria (NCI CTC 3.0).

Statistical considerations

PFS and OS were calculated with the Kaplan-Meier method. SPSS (Statistical Package for Social Sciences) v.11.5 software was used for statistical analysis.

Results

Seventeen heavily pretreated patients (median number of previous chemotherapy regimens 3, range 1-5) with taxane- and platinum-refractory/resistant disease were enrolled. Their median age was 55 years (range 35-75). Patients received a total of 60 cycles of PLD (median 3, range 2-9). All patients were evaluable for clinical response, 16 for serological response, and all of them were evaluable for toxicity. ECOG performance status of the patients ranged from 0 to 2 (mean 1) and renal, hepatic and hematological functions were adequate. Patient characteristics are illustrated in Table 1.

No patient showed CR, while there were 3 (17%) PRs and 2 (11%) patients showed SD, for an overall disease control rate of 28%. Median follow-up was 8 months (range 2-19). The median PFS was 15 weeks (range 10-21) and median OS 32 weeks (range 16-47; Figures 1 and 2). PPE occurred in 4 (23%) patients and was of NCI CTC grade 4 in one (6%) patient.

Table 1. Patient characteristics (n=17)

	n	*%*
Median age, years, (range)	55 (35-75)	
Median performance status (ECOG), (range)	1 (0-2)	
No. evaluable for clinicoradiologic response	17	100
No. evaluable for toxicity	17	100
FIGO stage		
IIIA	4	24
IIIB	5	29
IIIC	6	35
IV	2	12
Histology		
Papillary-serous	12	72
Clear cell	1	5
Endometrioid	3	18
Undifferentiated	1	5
Localization of recurrence		
Ascites	7	41
Pelvis	3	18
Liver	7	41
Pleural effusion	2	12
Lung	6	35
Prior neoadjuvant chemotherapy	4	24
Prior adjuvant chemotherapy	17	100
Prior chemotherapy with paclitaxel/platinum	17	100
Prior anthracycline-based chemotherapy	2	12
Prior cyclophosphamide-based chemotherapy	4	24
Prior chemotherapy with topotecan only	11	65
Prior chemotherapy with gemcitabine only	10	59
Prior chemotherapy with docetaxel/platinum	8	47

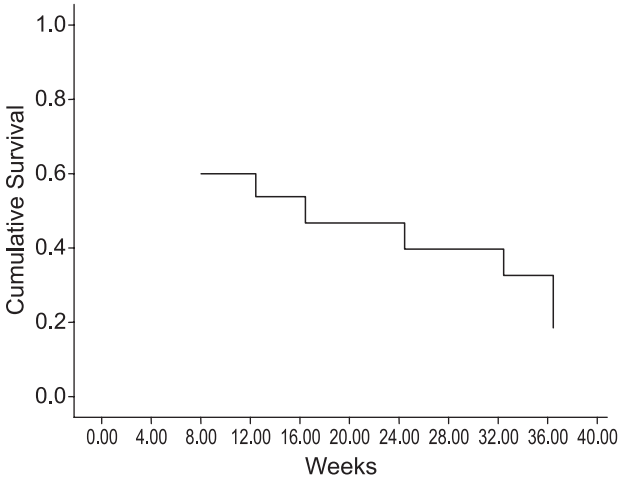

Figure 1. Progression free survival (Kaplan-Meier). The median progression free survival was 15 weeks (range 8-36).

Stomatitis occurred in 3 (17%) patients and was of grade 3 in 1(6%). Grade 3-4 neutropenia occurred in only 2 (12%) patients. No febrile neutropenia was encountered and no patient stopped chemotherapy because of toxicity. No cardiac toxicity occurred. Toxicity profile is illustrated in Table 2.

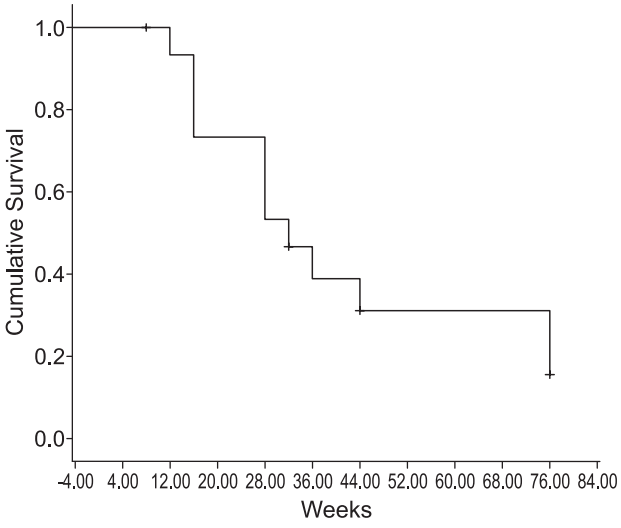

Figure 2. Overall survival (Kaplan-Meier). The median overall survival was 32 weeks (range 16-76).

Table 2. Toxicity with pegylated liposomal doxorubicin

Toxicity	*n*	*%*
Palmar-plantar erythrodysesthesia		
Grade 1-2	3	18
Grade 4	1	6
Stomatitis		
Grade 1-2	2	12
Grade 3	1	6
Neutropenia		
Grade 3-4	2	12

no febrile neutropenia and no cardiac toxicity occurred

Discussion

Despite aggressive surgery and chemotherapy, most advanced epithelial ovarian cancers recur, and chemotherapy remains as an important part of salvage treatment [16]. Platinum-containing regimens can be re-administered for platinum-sensitive tumors, while doxorubicin, topotecan, gemcitabine or weekly paclitaxel [17] are considered as potential salvage therapy for platinum-resistant or refractory tumors.

An ideal drug for salvage therapy of a heavily pretreated patient should provide a satisfactory response and low toxicity. The usage of doxorubicin has been limited due to its cardiac toxicity, and the relatively recent development of liposomal doxorubicin may spare this toxicity and provide a potential resolution. PLD has demonstrated efficacy as a single agent in the treatment of recurrent/relapsed ovarian cancer in several clinical trials [10-12]. The first of these was a phase II study of 35 patients with platinum- and paclitaxel-refractory/

resistant ovarian cancer who received PLD 50 mg/m^2 every 3 weeks. The overall response rate was 25.7% (1 CR and 8 PRs). In a second phase II study, 89 patients with platinum- and paclitaxel-refractory ovarian cancer were treated with PLD at slightly lower dose intensity: 50 mg/m^2 every 4 weeks. Tumor response was observed in 16.9% of the patients, with 1 CR and 14 PRs. Recently, phase III randomized controlled trials have been conducted in patients with platinum-resistant ovarian cancer. In a study by Mutch et al. gemcitabine was compared with PLD for efficacy and safety in taxane-pretreated platinum-resistant ovarian cancer patients [18]. In the gemcitabine and PLD groups, median PFS was 3.6 vs. 3.1 months, respectively (p=0.87); median OS was 12.7 vs. 13.5 months, respectively (p=0.99); and overall response rate was 6.1% vs. 8.3%, respectively (p=0.58). Another active and relatively well-tolerated combination is gemcitabine plus PLD. In one report of 31 platinum-refractory/resistant patients receiving 21-day cycles of gemcitabine and PLD, objective response rate was 33%, and median PFS and OS were 4 and 16 months, respectively [19]. In a study by Chura et al. heavily pretreated patients with ovarian cancer were administered bevacizumab and cyclophosphamide combination and were evaluated for efficacy and safety. The overall response rate was 53.3% (2 CR and 6 PRs) and SD was 20% (3 patients) [20].

In our study, PLD was administered as single-agent. All of the patients were platinum refractory/resistant and heavily pretreated. Clinical response rate and SD were determined at 17% and 11%, respectively, median PFS was 15 weeks and median OS 32 weeks. Toxicity was generally mild, with only 1 patient experiencing grade 4 PPE, and only 2 patients developing grade 3-4 neutropenia. There were no treatment-related deaths. Toxicities are illustrated in Table 2.

In conclusion, single-agent PLD is a feasible and moderately effective treatment in heavily pretreated advanced ovarian cancer patients. This retrospective analysis of heavily pretreated epithelial ovarian cancer patients who received PLD provides further evidence on efficacy and tolerability of this agent and strengthens its usage without special limitations. Our study shows that PLD is an active and safe agent in this kind of patient population.

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