Phase II trial of biweekly pegylated liposomal doxorubicin in recurrent platinum-refractory ovarian and peritoneal cancer

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Pegylated liposomal doxorubicin (PLD) is active in recurrent platinum-refractory ovarian and peritoneal cancer as demonstrated in a prospective-randomized trial. Dose-limiting toxicity in the US Food and Drug Adminstration-approved application schedule of PLD (50 mg/m^2 every 4 weeks) was serious palmar–plantar erythrodysaesthesia (PPE). This phase II trial was aimed at reduction of the frequency of serious PPE without loss of efficacy by modifying both the application schedule and the total dose of PLD administered as palliative single-agent chemotherapy. Fifty patients were enrolled into this phase II trial. PLD was given via 30-min intravenous infusion at a dose of 20 mg/m^2 every 2 weeks. Primary endpoint of the trial was the best response to chemotherapy. Secondary goals were progression-free survival, overall survival, and toxicity. Four complete responses and 16 partial responses were found resulting in an overall best response rate of 40.0%. The median progression-free survival in the intention-to-treat-population was 4.1 months [95% confidence interval (CI), 2.8–5.4 months], whereas the overall survival was 16.5 months (95% CI, 12.3–20.7 months). Although 17 (34.0%) patients developed some PPE, only one progressed to grade 3 (NCI-CTC version 2.0; 1998). No grade 4 toxicity occurred. PLD 20 mg/m^2 biweekly is highly active in patients with recurrent platinum-refractory ovarian and peritoneal cancer. The frequency of grade 3 and grade 4 PPE was remarkably reduced in this trial, as compared with the frequency of serious PPE observed in patients who were administered the dose schedule of 50 mg/m^2 every 4 weeks. *Anti-Cancer Drugs* 19:541–545 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The majority of women with epithelial ovarian and peritoneal cancer will develop recurrent disease. Patients with recurrent ovarian and peritoneal cancer that is classified as platinum sensitive have a superior prognosis than platinum-refractory patients. The most promising treatment option for women with platinum-sensitive recurrent disease is the combination of carboplatin with paclitaxel or gemcitabine [1,2].

Chemotherapy in those women with platinum-refractory disease typically focuses on maximizing periods of symptom-free survival through the administration of antineoplastic therapy that controls tumor growth although maintaining tolerable side effects.

Currently, randomized trials support the use of either pegylated liposomal doxorubicin (PLD) or topotecan as second-line therapy in women with recurrent platinum-refractory ovarian cancer [3,4]. Whereas myelosuppression is the most frequent toxicity observed with the administration of topotecan, palmar–plantar erythrodysaesthesia (PPE) is frequently the only serious toxicity of PLD. PPE impairs the quality of life of these patients. Its pathophysiology is still not fully understood. However, there is evidence that PLD secretion with sweat is an important trigger of this condition. In the prospective-randomized trial published by Gordon *et al.* 2001 [3], a 23% incidence of NCI grade 3 and grade 4 PPE occurred.

PLD is approved by the Food and Drug Adminstration and other regulatory authorities for treating recurrent ovarian cancer at a monthly dose of 50 mg/m^2. Investigations in patients with ovarian, peritoneal, and tubal carcinoma demonstrated a lower incidence of dose-limiting PPE and stomatitis by decreasing the total monthly dose to 40 mg/m^2, with comparable survival rates [5,6]. Modifying the application schedule could further reduce the risk of skin toxicity.

A potentially successful approach is biweekly application of PLD, as demonstrated recently in patients with Kaposi's sarcoma and in recurrent platinum-sensitive and platinum-refractory ovarian cancer [7–9]. Dose splitting of this regimen may also be useful in tumor control of patients with platinum-refractory ovarian

cancer because of a possible rapid progression of disease with consecutive worsening of clinical conditions of some of these patients within a short time interval. We investigated PLD administered biweekly in patients with platinum-refractory ovarian and peritoneal cancer in a phase II trial.

Patients and methods

Patients with recurrent platinum-refractory ovarian and peritoneal cancer were included in this phase II trial. Platinum-refractory recurrent ovarian or peritoneal cancer was defined by either immediate progression of disease while on a platinum chemotherapy regimen or tumor progression within 6 months of completion of a platinum regimen.

Other inclusion criteria were either a bidimensionally measurable tumor or an elevated serum cancer antigen (CA) 125 ($\geq 2 \times$ upper limit of normal), if no measurable tumor was seen. More than one previous chemotherapy regimen was allowed. Patients were excluded from this trial if they had previously received an anthracycline-containing chemotherapy regimen.

WHO performance status 0–2, a life expectancy of at least 12 weeks, and age >18 years were also entry criteria to this phase II trial. Patients were required to have adequate bone marrow function (neutrophil count $\geq 1500/mm^3$, platelet count $\geq 100\,000/mm^3$), renal function (creatinine clearance >40 ml/min), and hepatic function (bilirubin $\leq 1.25 \times$ upper limit of normal; alanine aminotransferase, aspartate aminotransferase $< 1.5 \times$ upper limit of normal; and alkaline phosphatase $< 3 \times$ upper limit of normal).

Patients with brain or leptomeningeal metastasis with preexisting peripheral neuropathy $\geq$ G2 (NCI-CTC version 2.0, 1998), ototoxicity $\geq$ G2 or cardiac insufficiency $\geq$ G2 (echocardiogram required), history of pectangina, and myocardial infarction within the last 6 months were excluded. Additionally, patients who were pregnant, lactating, or of reproductive potential without the human chorionic gonadotropin (HCG) serum test and contraceptive use were not included in this trial. Patients with a history of other malignancies within the last 5 years or of any malignancy for which they received chemotherapy or radiation also were excluded. The trial received approval from the local ethics committee and all patients provided written informed consent. Characteristics of the 50 patients are summarized in Table 1.

Table 1 Patients' characteristics

50 patients (ovarian cancer: $n=46$, peritoneal cancer: $n=4$)
Median age: 66.6 years (range: 38–78 years)
WHO performance status 0: $n=10$; 1: $n=15$; 2: $n=25$
Number of previous chemotherapy regimen: range 1–7 (Median: 2.9)
Number of patients with more than one previous chemotherapy regimen: $n=39$
FIGO stage at primary diagnosis: Ia: $n=1$; Ic: $n=2$; IIc: $n=1$; IIIa: $n=1$; IIIb: $n=3$; IIIc: $n=34$; IV: $n=8$
Optimal surgical debulking at first operation: $n=38$
Progression of disease while on a platinum therapy: $n=31$
Progression within 6 months of completion of platinum therapy: $n=19$
Pretherapeutic serum CA 125 elevation ($\geq 2 \times$ upper limit of normal): $n=48$

FIGO, International Federation of Gynecology and Obstetrics, WHO, World Health Organization.

Treatment schedule

PLD was administered by 30-min intravenous infusion at a dose of $20\,mg/m^2$ every 14 days. Prophylactic use of vitamins was not allowed.

All patients received a standardized information sheet to prevent PPE. Patients were educated in monitoring pressure-sensitive areas for early signs and symptoms with this sheet. They should avoid tight clothes and shoes, vigorous pressure or friction to the skin, and rigorous activity and excess heat (including hot water). Treatment was continued until complete remission, partial remission without symptoms of disease lasting $\geq$ 4weeks, progressive disease, or limiting toxicity.

Toxicity

Toxicity was evaluated by the Common Toxicity Criteria (NCI-CTC version 2.0, 1998; National Cancer Institute, Bethesda, Maryland, USA). Neutropenic fever or neutrophil count $< 0.5 \times 10^9$/l despite secondary prophylaxis with granulocyte colony stimulating factor (GCSF), or nadir platelet count $< 25 \times 10^9$/l as well as PPE grade 3 and grade 4 were considered dose-limiting toxicities.

Other limiting toxicities were a lack of hematologic recovery within 2 weeks prolongation of interval between two consecutive courses and also nonhematologic toxicity $>$ G2, except for nausea or alopecia.

Treatment was discontinued if PPE grade 2 was observed. Treatment was resumed only if improvement to grade 1 toxicity within 2 weeks of prolongation of interval occurred.

Endpoints and statistical methods

Primary endpoint of this trial was the best response to chemotherapy. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity. This phase II study was planned based on the two-phase design published by Simon 1998 and should proceed to include 50 patients, if at least three complete responses (CR) or partial responses (PR) occurred in the first cohort of 17 patients [10]. A minimum of 14 patients with partial or complete response of 50 patients was considered a positive trial result.

Response evaluation

Patients who received at least three courses of chemotherapy were evaluated for response. Response was

evaluated initially after 12 weeks. All 50 patients were evaluated by abdominal computed tomography (CT) scan at baseline.

In patients with normal serum CA 125 baseline values, measurable lesions were evaluated by CT scan every 12 weeks, if clinical symptoms of progression occurred, and at the end of chemotherapy.

In those patients with elevated CA 125 baseline levels ($\geq 2 \times$ upper limit of normal), CA 125 serum concentrations were evaluated every 12 weeks, if clinical symptoms of progression occurred and at the end of chemotherapy. In addition, preexisting measurable lesions were only monitored by CT scan in these patients, if a doubling of serum CA 125 concentrations occurred, or at the end of therapy.

A CR was defined as the disappearance of all measurable disease assessed by imaging, the disappearance of clinical signs and symptoms, and normalization of CA 125 serum values without clinical evidence of progression for ≥ 4 weeks. A PR was defined as the reduction of $\geq 50\%$ of the summation of the perpendicular parameters for each of all measurable lesions, without appearance of new lesions for ≥ 4 weeks, no enlargement of any existing lesion, and decrease of elevated CA 125 values $\geq 50\%$ from the pretherapeutic level.

Progressive disease was defined as any increase of $> 50\%$ of the summation of the perpendicular diameters of any measurable lesion, the appearance of new lesions, or a doubling of the baseline CA 125 serum value, if there was no measurable lesion. Stable disease was any outcome that did not meet the criteria for response or disease progression.

Results

From May 2001 to October 2006, 50 patients were enrolled in this study, and their characteristics are outlined in Table 1. The median patient age was 66.6 years (range 38–78 years). Thirty-nine patients (78.0%) had more than one previous chemotherapy regimen (range 1–7/median 2.9); 31 cases progressed while on a platinum therapy, whereas 19 had shown a progression within 6 months of completion of platinum therapy. A total of 417 courses (range 2–29/median 8.3) of PLD were administered to the 50 patients.

Efficacy

The overall best response rate was 40.0% [95% confidence interval (CI) 28–51%]. CR was observed in 4/50 patients (8.0%), whereas 16/50 (32.0%) had a PR. Eight patients (16.0%) had a stable disease for median of 16.5 weeks (range 9–23 weeks).

Table 2 Acute toxicity (CTC criteria of NCI Clinical Trials Group version 2.0; 1998)

	NCI-CTC grade of toxicity			
	G1	G2	G3	G4
Anemia	17	9	0	0
Neutropenia	5	2	2	0
Thrombocytopenia	5	0	0	0
Infection	2	10	1	0
Nausea	2	2	0	0
Mucositis	4	4	1	0
PPE	**6**	**10**	**1**	**0**
Sensory neuropathy	15	3	0	0
Skin	2	5	1	0

The median PFS of all patients in the study population was 4.1 months (95% CI, 2.8–5.4 months), whereas the OS was 16.5 months (95% CI, 12.3–20.7 months). The median PFS was 7.2 months (95% CI, 4.3–10.2 months) in patients who responded to this therapy and 2.5 months in nonresponder patients (95% CI, 2.0–2.9 months).

Toxicity

All 50 patients were evaluable for toxicity. No grade 4 toxicity (NCI-CTC version 2.0; 1998) was observed in this study population. Adverse events are summarized in Table 2. Grade 1 and grade 2 anemia was the most frequent hematologic toxicity in 17 and nine patients. Grade 3 neutropenia was only observed in two patients, and no grade 4 neutropenia occurred. Neither GCSF nor erythropoietin was used in primary or secondary prophylaxis of neutropenic fever or anemia. No thrombocytopenia $>$ G1 was seen in this phase II trial.

Although 17 patients (34.0%) developed PPE, only one progressed to a limiting toxicity grade 3. Stomatitis $\geq$ G2 occurred in five patients (10.0%); all of them also had a skin reaction $\geq$ G2. Urosepsis, esophageal ulceration without infection, and a rapid worsening of a preexisting crural ulcer were the only other grade 3 nonhematologic toxicities.

Discussion

PLD is active as single-agent therapy for recurrent platinum-refractory ovarian and peritoneal cancer with evidence from a prospective-randomized trial [3]. Although PLD has significantly enriched the spectrum of chemotherapeutic agents for these patients, the onset of severe PPE strongly affects the risk–benefit calculation.

The pathophysiology of PPE is not well understood. It has been hypothesized that, following the local trauma caused by routine activities, PLD may extravasate from the deeper micropapillaries in the hands and feet. PLD has been detected in elevated concentrations in eccrine sweat glands in palms and planta, where it accumulates. It may be facilitated by the hydrophiling coating of the liposomes [11].

The effects of prophylactic modalities such as steroids, pyridoxine treatment, COX-2 inhibitors, topical application of dimethylsulfoxide, or regional cooling are not evaluated in randomized clinical trials [12–14]. Experimental pharmacokinetic results in murine breast cancer confirmed clinical observation that longer dose intervals of PLD reduce the incidence and severity of PPE [15]. In the mentioned study a PLD dose of 27 mg/m^2 per week was given. Lengthening the dose interval to every 4 weeks resulted in a negligible incidence of PPE-like lesions but reduced therapeutic activity. Half-lives for elimination of the drug from skin and tumor were longer than that for plasma. Drug leakage rates in the different tissues play an important role in the therapeutic activity and the toxicity of liposomal drug formulations. Differences exist between the various liposomal drug formulations [16]. PLD produced the highest total doxorubicin concentration in all tissues of interest and had the best therapeutic activity of the formulations tested.

According to the preclinical results, we revised the application schedule as well as the total PLD dose administered in comparison to the phase III trial published by Gordon *et al.* 2001 [3] and reduced the frequency of grade 3 and grade 4 PPE from 23 to 2%. Only one patient progressed to grade 3 PPE in our study. The same low frequency of grade 3 and grade 4 PPE in 3/64 patients (4.7%) under single-agent chemotherapy with PLD 20 mg/m^2, every 2 weeks was observed by Sehouli *et al.* [9].

Although it was suggested that an altered regimen with a shorter application interval and a lower dose per week (10 mg/m^2) may impair the efficacy of PLD, we found one of the highest response rates ever described in phase II trials with platinum-free single-agent chemotherapy in recurrent platinum-refractory ovarian and peritoneal cancer. Median OS of 16.5 months was observed here, and this compares well with a recently published phase II study, which also included platinum-sensitive patients with expected better prognosis [9].

Evidence of a high therapeutic benefit of this single-agent chemotherapy exists for patients with platinum-refractory ovarian and peritoneal cancer. Response rate and OS in this phase II trial are better than those in ovarian cancer trials with a PLD dose of 50 mg/m^2 or 40 mg/m^2, every 4 weeks as well as with other single-agent antineoplastic regimens in platinum-resistant recurrent ovarian cancer [3,17–23].

However, there is a remarkable difference between the relatively short median PFS of 4.1 months and the median OS of 16.5 months in our study. A reasonable explanation for this is the discontinuation of PLD therapy according to protocol if a partial remission occurred and tumor-related symptoms disappeared. Eleven out of 16 patients with PR had a discontinuation and a later reinduction therapy with PLD, and therefore showed a short PFS but a long-term median OS. Furthermore, this difference can be explained by the feasibility and efficacy of subsequent therapies with other agents. Even patients who progressed immediately under PLD therapy had more than two subsequent regimens with topotecan, oxaliplatin, taxanes, etoposide, or treosulfan because of lack of persistent toxicity by this drug.

No febrile neutropenia or other serious nonhematologic toxicity occurred. A high rate of dose modifications occurred in 57.3% of all patients, including premature stop of therapy in 9.6% in the PLD-arm of the above-mentioned prospective-randomized trial published by Gordon *et al.* 2001 [3] because of nonhematologic toxicity, especially PPE. The low frequency of dose-limiting toxicity caused by grade 3/4 PPE with this application schedule of PLD is a possible causal explanation for the higher response rate compared with other studies in platinum-refractory ovarian and peritoneal cancer.

Thus, there is evidence that the PLD dose can be safely reduced from 50 mg/m^2 to 40 mg/m^2, every 4 weeks. Randomized trials are needed to prove that additional reductions in PLD dose and dose splitting decrease the likelihood of severe skin toxicity without lack of efficacy.

Biweekly application of PLD, 20 mg/m^2, every 2 weeks, represents a promising treatment for patients with recurrent platinum-refractory ovarian and peritoneal cancer and improves the therapeutic index. This regimen can be used in prospective, randomized, phase III trials to clarify which regimen/dose is the optimal therapy for these patients.

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