Biweekly pegylated liposomal doxorubicin in patients with relapsed ovarian cancer: results of a multicenter phase-II trial

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Background: The obvious benefit of pegylated liposomal doxorubicin (PLD) for tumour control in recurrent ovarian cancer is frequently offset by severe palmar-plantar erythrodysesthesia (PPE). There is evidence that dose reduction from 50 to 40 mg/m2 reduces the incidence of PPE without compromising cytotoxic activity. We set out to investigate whether biweekly application further improves the therapeutic index of PLD.

Patients and methods: Patients with recurrent ovarian cancer after surgery and adjuvant chemotherapy with platinum and taxane compounds were eligible to participate in this multi-institutional phase II study. PLD was administered at a dose of 20 mg/m2 every two weeks. Eligible patients had ECOG performance status of £2, and sufficient organ function. We employed an optimized two-stage design to test the hypothesis that biweekly application of PLD reduces the frequency of grade III and IV PPE from 25% to 10%. Response and survival were addressed descriptively.

Results: Between October 2001 and February 2004, 64 patients with median age of 59 (range 38–81) years were recruited onto this trial. We evaluated 553 (median 7, range 1–25) courses of PLD treatment. Most patients were in their third or fourth line of chemotherapy. PPE was noted in 30 patients (47.6%), but only three participants progressed to grade 3 severity (4.7%, 95% confidence interval 1.0–13.1%). Partial response, stable disease, and tumour progression were observed in 5, 13, and 24 patients, respectively. Median overall and progression-free survival were 18.2 (range, 1.4–34.0) and 4.3 (range 0.5–22.3) months.

Conclusions: Biweekly PLD may reduce the incidence of PPE while retaining efficacy in relapsed ovarian cancer. Our data support the need for a randomized trial to strengthen these assumptions.

Key words: ovarian cancer, pegylated liposomal doxorubicin, biweekly schedule, toxic skin reactions, palmar-plantar erythrodysesthesia

introduction

Pegylated liposomal doxorubicin (PLD) is a stealth formulation of doxorubicin, in which a polyethylene glycol layer surrounds a doxorubicin-containing liposome. In a randomized trial, PLD 50 mg/m² every 4 weeks was compared to Topotecan 1.5 mg/m² daily for 5 consecutive days every 3 weeks in recurrent ovarian cancer [1].

Long-term follow-up data suggest that PLD prolongs overall survival comparing with topotecan, although this benefit was of marginal significance. Of note, patients with platinum-sensitive disease lived about 35 weeks longer on PLD rather than topotecan treatment [2].

Palmar-plantar erythrodysesthesia (PPE) is a typical and serious toxicity of PLD. Its pathophysiology is still not fully understood, but there is evidence that PLD-secretion with sweat is an important trigger of this condition [3–6]. PPE impairs quality of life, and the gain in overall survival demonstrated in the mentioned RCT was paid by a 49% overall incidence, and a 23% incidence of grade 3 and 4 PPE.

PLD is approved by the FDA and other regulatory authorities for treating recurrent ovarian cancer at a monthly dose of
50 mg/m². Investigations in patients with ovarian, peritoneal, and tubal carcinoma suggest a lower incidence of dose-limiting PPE and stomatitis by lowering the dose to 40 mg/m², without compromising survival rates [7–12]. Modifying the application schedule could further reduce the risk of skin toxicity. A potentially successful approach is biweekly application, as demonstrated in patients with Kaposi’s sarcoma [13, 14].

These findings prompted us to conduct a multicenter phase-II study in patients with recurrent ovarian cancer, splitting the dosage into 20 mg/m² every 2 weeks. We sought to reduce severe PPE, and to evaluate response rates, overall and progression-free survival with this novel schedule.

**patients and methods**

**study design**

This was an open label, multi-institutional two-stage phase II study of PLD in women with histologically proven, relapsed ovarian cancer.

The study was performed according to Good Clinical Practice, and regulations issued in the World Medical Association’s Declaration of Helsinki. An independent monitoring institute was responsible for data control. Approval from local review boards was gained at each collaborating center, and written informed consent was provided by each participant.

**sample size**

Standard application of PLD at a dose of 50 mg/m² for 28 days induces PPE of grade 3 and 4 in about 25% of all patients. Reducing this rate by 15% was defined a clinically relevant difference.

We used Simon’s 2-stage design to optimize sample sizes. Setting test criteria to alpha = 5%, and beta = 20%, 26 patients had to be evaluated at the first stage. If less than two patients had developed severe PPE, recruitment was continued until a sample size of 54 patients was reached. Clinical success was achieved if fewer than six patients had grade 3 and 4 PPE. To account for a drop-out rate of 10%, 60 patients had to be allocated onto this trial.

**patient eligibility**

Patients ≥18 years with recurrent ovarian, peritoneal, or fallopian cancer and prior treatment with platinum and paclitaxel were invited to enter this trial.

Eligible subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of less than 3. Additional criteria included adequate renal function (serum creatinine ≤ 1.25 times the upper limit of normal, glomerular filtration rate greater than 60 ml/min), liver function (AST/ALT ≤ three times the upper limit of normal, bilirubin concentrations ≤ 1.25 the upper limit of normal), bone marrow function (neutrophil count greater than 1.5 × 10⁹/l, and a platelet count greater than 100 × 10⁹/l). Patients with a history of severe cardiac disease were excluded.

**treatment plan**

Patients received 20 mg/m² of PLD as a 30 minute infusion every 14 days. Concomitant prophylactic or therapeutic use steroids or vitamins were not allowed in this trial. If tumours did not progress, we strived for a minimum of four biweekly cycles. Given tolerability, treatment was continued until disease progression.

Dose reduction was defined in case of PPE, haematologic toxicity, elevated bilirubin, and stomatitis.

**examinations**

Within 14 days before the first application of the study drug, all patients underwent a medical history, and a physical examination. Disease was staged by radiological imaging (chest x-ray, ultrasound, CT, or MRI scan). The ventricular ejection fraction (LVEF) was assessed by multiply gated acquisition scan or echocardiogram. LVEF was also documented 4 weeks after the last dose of the study drug for all patients. Laboratory analyses comprised haematology, serum chemistry, urinalysis, and a pregnancy test for women of child bearing potential. All blood analyses were repeated every week while on study treatment. Physical examination was repeated after any four applications of chemotherapy, and in case of symptoms or signs of tumour progression. Radiological assessments (using the same methodology as was used at baseline) were performed every 8 weeks.

**toxicity determinations**

Safety analyses were performed on all patients who received at least one infusion of the study drug.

Electrocardiogram tracing was performed prior to every second course of chemotherapy, and blood samples for monitoring of haematology (hemoglobin, hematocrit, RBC, WBC, neutrophils, and platelets) and blood chemistry (serum creatinine, alkaline phosphatase, SGOT, SGPT, and total bilirubin) were collected prior to each treatment and on day 7 after chemotherapy.

Toxicity was graded according to the National Cancer Common Toxicity Criteria [7]. All documented effects were included, regardless of their relationship to the study treatment.

Primary supportive administration of granulocyte-colony-stimulating factor (G-CSF) was not permitted. A secondary prophylactic use of G-CSF was given only in case of severe leucopenia or neutropenic fever and a treatment delay due to leucopenia or neutropenia. The use of erythropoietin was permitted.

Chemotherapy was applied only if neutrophil count was greater than 1500/µl, and platelet count was greater than 100 000/µl.

The main focus of monitoring was placed on skin toxicity, specifically PPE.

Therefore, at the beginning of this study all patients were asked to report any symptoms of skin toxicities immediately to their nurse or physician. Additionally, patients were educated in monitoring pressure-sensitive areas for early signs and symptoms. In addition, patients should avoid tight clothes and shoes, vigorous pressure or friction to the skin, rigorous activity and excess heat (including hot water).

**response**

Response was determined according to UICC-criteria. Complete remission (CR) was defined as complete disappearance of all measurable and assessable disease, no new lesions, and no disease-related symptoms. Partial remission (PR) was assumed in patients with a ≥50% decrease in the sum of the products of bidimensional perpendicular diameters of all measurable lesions; progression of assessable disease and new lesions were not allowed. All patients who achieved CR or PR underwent a second radiological assessment to confirm response. Progressive disease (PD) was defined as a ≥25% increase in the sum of the products of bidimensionally measured lesions over the smallest sum obtained at best response, or reappearance of any lesion that had disappeared, or clear worsening of any assessable disease, or failure to return for evaluation because of death or deteriorating condition, or appearance of any new lesion on site. Patients were classified as having stable disease (SD) if they did not qualify for CR, PR, or PD.

**statistical analysis**

Data were presented as proportions, means, medians, and rates, and their adequate measures of distribution. We used a one-sample test of proportions to address the primary hypothesis. All other endpoints were evaluated in an exploratory fashion, and 95% confidence intervals (CI) were computed where appropriate.
Progression-free survival and overall survival were defined as the interval from the first day of study drug application until disease progression or death due to any cause, and were calculated by the Kaplan-Meier method.

**results**

**patient characteristics**

Between September 2001 and February 2004, 64 patients with a median age of 59 years (range, 38 to 81 years) were enrolled at six German institutions. Table 1 summarizes the demographic profile.

Patients received 553 cycles of chemotherapy, with a median of seven courses each patient (range, 1 to 35).

Fifty-seven patients had received first-line platinum chemotherapy, 46 of whom had had a combination of platinum and paclitaxel. Most patients \( (n = 43, 75.4\%) \) were platinum sensitive, as defined by a progression free interval of six months after the last course of first-line chemotherapy.

Thirteen patients had undergone a single course of prior chemotherapy. Twenty-six patients had a second, 15 had a third, and another 10 patients had fourth- or fifth-line chemotherapy before study entry.

**toxicity**

All patients were assessable for documentation of toxicity. There were no episodes of sepsis, or chemotherapy-related fatality.

Although 30 patients (47.6\%) developed PPE, only three progressed to CTC grade 3 (4.7\%, 95\% CI 1.0–13.1\%), one-sample test of proportions \( P = 0.0002 \). There was no grade 4 skin toxicity.

All other adverse events were generally mild. No unexpected non-hematological toxicity, specifically cardiotoxicity, occurred in the present investigation. Alopecia was the most commonly noted side effect, but was mostly pre-existing.

Three patients experienced grade 3 anemia. A single case of grade 3 thrombocytopenia was recorded. Table 2 summarizes non-hematological and hematological event rates.

**response, survival, and follow-up**

Forty-four patients were considered assessable for response, of whom two subjects showed complete remission (CR). Another five patients had partial remission (PR), 13 patients had stable disease (SD), and 24 patients had progressive disease (PD).

Accounting for all patients who had received at least one infusion of PLD, the response rate was 7 of 64, or 10.9\% (95\% CI 4.5–21.2\%), and the tumor control rate (including SD) was 20 of 64 (31.3\%, 95\% CI 20.2–44.1\%).

In all assessable patients, the response rate was 7 of 44 (15.9\%, 95\% CI 6.6–30.1\%), whereas the tumor control rate was 20 of 44 (45.5\%, 95\% CI 30.4–61.1\%).

Figure 1 illustrates survival rates. Median follow-up was 11.4 months (range 0.2–26.5 months). Median progression-free survival in this study was 4.3 months (range 0.5–22.3 months). Median overall survival was 18.2 months (range 1.4–34 months). At the time of final analysis, 30 patients were still alive.

**discussion**

Treatment goals after failure of first-line treatment for ovarian cancer are (i) controlling or preventing disease-related

**Table 1. Patient profile**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median age, years (range)</th>
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<tr>
<td></td>
<td>Median number of cycles (range)</td>
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<td></td>
<td>ECOG* performance status</td>
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<tr>
<td></td>
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</table>

**Table 2. Worst hematological and non-hematological toxic effects in 64 patients. Total number of events, percentages in parentheses. Numbers in brackets are 95% confidence intervals. The upper 97.5% confidence limit for null events is 5.6%**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CTC-Grade I (percent)</th>
<th>CTC-Grade II (percent)</th>
<th>CTC-Grade III (percent)</th>
<th>CTC-Grade IV (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>24 (37.5% [25.7–50.5%])</td>
<td>16 (25.0% [15.0–37.4%])</td>
<td>3 (4.7% [1.0–13.1%])</td>
<td>0</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>18 (28.1% [17.6–40.8%])</td>
<td>8 (12.5% [5.6–23.2%])</td>
<td>0 0</td>
<td></td>
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<tr>
<td>Neutropenia</td>
<td>7 (10.9% [4.5–21.2%])</td>
<td>2 (3.1 [0.4–10.8%])</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>4 (6.3% [1.7–15.2%])</td>
<td>0</td>
<td>1 (1.6% [0.1–8.4%])</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>18 (28.1% [17.6–40.8%])</td>
<td>4 (6.3% [1.7–15.2%])</td>
<td>0 0</td>
<td></td>
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<tr>
<td>PPE</td>
<td>18 (28.1% [17.6–40.8%])</td>
<td>9 (14.1% [6.6–25.0%])</td>
<td>3 (4.7% [1.0–13.1%])</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18 (28.1% [17.6–40.8%])</td>
<td>5 (7.8% [2.6–17.3%])</td>
<td>1 (1.6% [0.1–8.4%])</td>
<td>1 (1.6% [0.1–8.4%])</td>
</tr>
</tbody>
</table>
symptoms, (ii) maintaining quality of life, and (iii) prolonging progression-free survival. PLD has significantly enriched the spectrum of chemotherapeutic agents for this challenging condition, but the onset of severe PPE strongly affects risk-benefit-calculations. Agents like DMSO and steroids, as well as regional cooling were proposed as prophylactic modalities, but none of them have been evaluated by randomized clinical trials [15, 16].

Until pharmacological or physical interventions prove efficacy and effectiveness in preventing PLD, modifying both application schedules and totally administered doses remain a responsible, ambitious, and essential field of research.

In this study, delivery of 40 mg/m² of PLD in two separate fractions any two weeks proved feasible and tolerable, and produced a remarkably low incidence of severe PPE.

The results from this investigation match the available evidence on reducing PPE incidence by tuning the dose from 50 to 40 mg/m². Kim observed a single grade 3 PPE among 90 patients with gynecological cancers treated with 40 mg/m² of PLD (1.1%, 95% CI 0.0–6.0%) [10]. Campos noted grade 3 cutaneous toxicity in 6 of 72 patients (8.3%, 95% CI 3.2–17.3%) under PLD monotherapy at 40 mg/m² [11].

Despite further dose reductions of the PLD compound to 30 mg/m², incidences up to 34% have been observed in combination treatment with gemcitabine [15–17].

Varying studies suggest that monthly PLD doses ranging from 40 to 50 mg/m² are equally effective to an overall dose intensity of 10.0 to 12.5 mg/m² each week, which is regarded a sufficient dose-density by the oncology community. Figure 2 summarizes the response rates observed in the relevant investigations, enrolling 223 participants [10–12]. There is no evidence of a difference in response rates between the current and previous studies. Of note, variance-weighted response rates with 40 mg/m² of PLD are very similar to those with 50 mg/m², as reported by Gordon and colleagues (n = 239, 19.7%, 95% CI 14.8–25.3%). [1, 2]

It is open to debate whether response rates are the appropriate endpoint in palliation trials. With regard to median survival, the present data support the hypothesis that dose reduction does not compromise anti-tumor activity of PLD. The 18.2 months of overall survival observed herein compare well with previously published intervals, ranging from 7.0 to 15.5 months [10, 11].

We stress that this study enrolled a large proportion (50 of 64 or 78.1%) of patients who underwent third- to fifth-line treatment.

Limits with the study design and sample size merit discussion. Since no internal control was used, our findings must be regarded as preliminary, and hypothesis-generating. Survival was only investigated as a secondary endpoint, preventing conclusive inferences on the effectiveness of biweekly PLD. Specifically, non-inferiority to conventional application remains to be proven on a larger scale.

It is obviously difficult to decide about the causal principle behind the low incidence of PPE observed in this study. There is convincing evidence that the PLD dose can be safely reduced from 50 to 40 mg/m², but randomized trials are needed to prove that dose-splitting further decreases the likelihood of severe skin toxicity.

In conclusion, biweekly application of 20 mg/m² of PLD is a promising new treatment approach that may help to improve the therapeutic index in the management of relapsed ovarian cancer.
acknowledgements

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references