Skin toxicity associated with pegylated liposomal doxorubicin (40 mg/m²) in the treatment of gynecologic cancers

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Abstract

Objectives. To characterize the incidence of skin toxicity of pegylated liposomal doxorubicin (PLD) administered at a lower dose (40 mg/m²) in the treatment of advanced gynecologic malignancies.

Methods. Medical charts of all patients who initiated PLD at a starting dose of 40 mg/m² from 1997 to 2003 for the treatment of gynecologic cancers were retrospectively reviewed. PLD was infused over 1–2 h and administered every 4–6 weeks. No patient had previously received doxorubicin. All patients were clinically assessed for adverse reactions including skin toxicity.

Results. Ninety patients (mean age 62 years, range 45–82 years) were included in this analysis. There were 55 ovarian, 16 endometrial, 2 fallopian, and 17 primary peritoneal cancers. The median cumulative dose of PLD was 120 mg/m² (range 40–855 mg/m²) with a median of 3 cycles (range 1–25). 33/90 (37%) developed a skin reaction during therapy. The overall incidence of grade 1, 2, and 3 skin toxicity was 23 (26%), 9 (10%), and 1 (1%), respectively. Of the 23 cases of grade 1 toxicity, 16 (70%) occurred within 1–3 cycles. All 9 cases of grade 2 toxicity occurred within 1–3 cycles. The only case of grade 3 toxicity occurred after the first cycle. 28/30 (93%) patients who continued treatment did not experience further episodes of skin toxicity with subsequent cycles after a dose reduction (5–20 mg/m²). PLD was stopped in only 2/90 (2%) cases due to a skin reaction.

Conclusions. Severe skin toxicity (≥grade 2) associated with PLD occurs infrequently when initial doses of 40 mg/m² are administered. When skin reactions appear, they usually occur early in the course of treatment, respond to dose reduction, and do not appear to limit the duration of treatment.

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Keywords: Liposomal doxorubicin; Skin toxicity; Palmar–plantar erythrodysesthesia; Gynecologic cancer

Introduction

Primary therapy for cancers of the reproductive tract is of curative benefit in many women. A significant number of patients with advanced stage cancers, however, will develop recurrence. For these women, no good curative options exist, and further therapy is aimed at palliating symptoms, halting disease progression, and improving quality of life. Doxorubicin has demonstrated cytotoxic activity in advanced ovarian cancer [1–4]. Despite its utility, substantial toxicity related to its myelosuppressive and cardiotoxic effects has limited its use [5,6].

Pegylated liposomal doxorubicin (PLD) was developed to deliver equal benefit without the serious side effects of doxorubicin [7,8]. Pegylation of liposomal capsules alters the pharmacokinetic profile of its parent compound with a resultant decreased volume of distribution, increased area under the curve (AUC), and prolonged circulation time [9–11]. In a phase 1 study, PLD was associated with adverse side effects of total alopecia, nausea and vomiting, bone marrow suppression, and even cardiotoxicity [7].
Phase 2 studies established PLD to be an active cytotoxic agent in platinum- and paclitaxel-refractory ovarian cancer when administered at a dose of 50 mg/m² every 3 weeks [12]. At this dosage, however, an unacceptable number of patients experience skin reactions, the most common being palmar–plantar erythrodysesthesia (PPE, “hand–foot syndrome”), requiring dose reductions and treatment delays which negatively impact on women’s treatment and quality of life. In extreme cases, patients may be rendered crippled by diffuse epidermolysis of the soles [13]. PPE severity appears directly related with cumulative dosing. In an attempt to reduce the incidence of PPE, many clinicians have experimented using lower doses and longer treatment intervals with demonstrable activity [14–16].

This current study examines our institutional experience and the incidence of skin toxicity using PLD at 40 mg/m² administered every 4 weeks in the treatment of gynecologic malignancies.

Methods and materials

We performed a retrospective chart review of all patients who initiated PLD at a starting dose of 40 mg/m² from 1997 to 2003 for the treatment of gynecologic cancers. We extracted information pertaining to age, surgical stage and histologic grade of disease, prior chemotherapy treatment, number of cycles and total cumulative doses of PLD, and all adverse side effects experienced by patients.

Patients received PLD at an initial dose of 40 mg/m² in 250 cc D5W with treatment repeated every 28 days. During the initial course, PLD was administered as a 2-h infusion. To further prevent a reported 7–9% hypersensitivity reaction with primary infusions [17], diphenhydramine (50 mg), dexamethasone (20 mg), and famotidine (20 mg) were given intravenously prior to the initial treatment. In the absence of a hypersensitivity reaction, subsequent courses of PLD were infused over 1 h and premedications were withheld. Excluding the use of dexamethasone during the initial cycle, prophylactic emetics were not used. All patients were clinically assessed for adverse reactions. Skin toxicity was graded according to NCI/GOG criteria (Table 1).

Table 1
Skin toxicity criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Signs</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild erythema, swelling, and/or desquamation not interfering with normal daily activities</td>
</tr>
<tr>
<td>2</td>
<td>Erythema, swelling, and/or desquamation interfering with but not precluding normal daily activities</td>
</tr>
<tr>
<td></td>
<td>Blisters and/or ulcers &lt; 2 cm in diameter</td>
</tr>
<tr>
<td>3</td>
<td>Swelling, blisters, and/or ulcers interfering with normal daily activities and/or walking</td>
</tr>
<tr>
<td></td>
<td>Unable to wear regular clothing</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse or local process causing infectious complications</td>
</tr>
<tr>
<td></td>
<td>Bedridden state</td>
</tr>
<tr>
<td></td>
<td>Hospitalization</td>
</tr>
</tbody>
</table>

PLD treatment was delayed in any patient exhibiting ≥grade 2 PPE on the day of her scheduled treatment until the toxicity had resolved. For all patients who developed PPE, the PLD dose was reduced by 25% to 30 mg/m² for subsequent courses. Further episodes of skin toxicity resulted in an additional dose reduction to 20 mg/m². If signs and symptoms of PPE persisted for ≥6 weeks, patients either stopped therapy or underwent further dose reductions accordingly. In addition, the dose interval was extended for patients with persistent grade 1–2 PPE or requesting adjournment from treatment.

The Cleveland Clinic Foundation Institutional Review Board approved this study.

Results

Of the 103 patients who had received PLD for recurrent or refractory gynecologic tumors, we identified 90 patients who initiated PLD at a dose of 40 mg/m². The mean age of this group was 62 years (range 45–82). Median follow-up was 6 months (range 1–48). There were 55 ovarian, 16 endometrial, 2 fallopian, and 17 primary peritoneal cancers (Table 2).

Table 2
Patient characteristics (n = 90)

<table>
<thead>
<tr>
<th>Diagnosis (no. of patients)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer: 55</td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer: 16</td>
<td></td>
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<tr>
<td>Fallopian tube cancer: 2</td>
<td></td>
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<tr>
<td>Primary peritoneal cancer: 17</td>
<td></td>
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</tbody>
</table>

Prior chemotherapy regimen* (no. of patients)

<table>
<thead>
<tr>
<th>Median</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>0–6</td>
</tr>
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</table>

No. of patients who had previously received doxorubicin: 0

Course of liposomal doxorubicin

<table>
<thead>
<tr>
<th>Median</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>1–25</td>
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</table>

* Retreatment with either a platinum agent or paclitaxel is considered a single regimen.

No. of patients stopping PLD due to skin toxicity: 2 (2%).

Table 3
Skin toxicity results (n = 90)

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23 (26%)</td>
</tr>
<tr>
<td>2</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Of the 103 patients who had received PLD for recurrent or refractory gynecologic tumors, we identified 90 patients who initiated PLD at a dose of 40 mg/m². The mean age of this group was 62 years (range 45–82). Median follow-up was 6 months (range 1–48). There were 55 ovarian, 16 endometrial, 2 fallopian, and 17 primary peritoneal cancers (Table 2).

Patients received a median of 2 (range 0–6) prior courses of chemotherapy. No patient had previously received doxorubicin. The median cumulative dose of PLD administered to the patients in this series was 120 mg/m² (range 40–855 mg/m²) with a median of 3 cycles (range 1–25).

Thirty-three of 90 (37%) patients developed a skin reaction during therapy. The overall incidence of grade 1, 2, and 3 skin toxicity was 23 (26%), 9 (10%), and 1 (1%), respectively (Table 3). There were no grade 4 skin toxicities.
Seventy-five percent (25/33) of skin toxicities were categorized as PPE, with the remaining cases presenting as either diffuse follicular rash or intertrigo-like eruption.

Of the 23 cases of grade 1 toxicity, 16 (70%) occurred within 1–3 cycles. All nine cases of grade 2 toxicity occurred within 1–3 cycles. The only case of grade 3 toxicity occurred after the first cycle. This patient required two dose reductions and remains active after her eleventh cycle at 20 mg/m².

Of the 30 patients with skin toxicity who continued treatment, 28 (93%) did not experience further episodes of skin toxicity with subsequent cycles after dose reduction (5–20 mg/m²). PLD was stopped in only 2/90 (2%) cases due to a skin reaction. The remaining patient (1%) declined further therapy unrelated to her PPE.

Discussion

Water-soluble drugs are effectively carried in plasma by liposomes, bilayer vesicles composed of insoluble amphiphatic lipids [13]. Greater than 90% of plasma doxorubicin remains encapsulated within these liposomes [18]. Liposome encapsulation results in a smaller volume of distribution, greater AUC, and slower clearance rate of doxorubicin [9]. Pegylation covers the liposomal surface with a methoxypolyethylene glycol polymer. This, in turn, decreases recognition and subsequent destruction by the reticuloendothelial system [11]. Pegylated liposomes are approximately 100 nm in diameter. Due to its size, PLD extravasates through wide gaps between endothelial cells found in such vessels typically associated with tumor-derived growth [19]. Although this results in effective delivery of PLD to solid tumors, extravasation may occur in other areas of microvascular permeability. PPE involves the palms and soles, which are well vascularized by small, fragile capillaries [10,13,20,21]. With repeated friction and trauma, these vessels become damaged, and PLD escapes into the surrounding tissue. Keratinocytes are particularly susceptible to cytotoxic damage due to their high turnover rate [22].

PPE represents the most common manifestation of PLD skin toxicity and is the agent’s most frequent dose-limiting side effect. Patients initially suffer painful erythema affecting their palms, soles, and/or fingers. Gradually, the affected skin becomes edematous and discolored with subsequent drying and desquamation. In severe cases, patients may develop blisters and be incapable of using their hands or even walking [13]. PPE has been described with other anti-neoplastic agents including fluorouracil, vinorelbine, cytarabine, and capecitabine [23,24]. Three-quarters of our patients experiencing skin toxic effects had complaints of PPE.

Other less common skin eruptions include diffuse follicular rash and intertrigo-like eruption. Diffuse follicular rash presents as a non-pruritic, scaly erythematous accentuation of hair follicles affecting the lateral limbs and/or trunk [13]. Eight women manifested these signs. Erythematosus patches involving skin foldings (e.g., axilla, groin) and areas of friction (e.g., bra-line, waist) are characteristic of intertrigo-like eruption. These lesions are often painful and erosive. Only three women suffered from this condition. Less common, but serious side effects include sunburn and radiation recall [13].

In a phase 2 study evaluating 35 women with platinum- and paclitaxel-resistant ovarian cancer, PLD 50 mg/m² administered every 3 weeks, demonstrated a 26% clinical response with a median overall survival of 11 months and progression-free survival of 5.7 months. Although PLD demonstrated antineoplastic activity in this unfavorable group of patients, 11% (4/35) and 29% (10/35) developed grade 2 and 3 skin toxicity, respectively [12].

In an attempt to minimize dose-limiting PPE, investigators increased the treatment interval to every 4 weeks while maintaining a PLD dose of 50 mg/m². While reasonable anti-neoplastic activity was noted, patients continued to experience a fairly substantial overall incidence of PPE (approximately 40%). Grade 3 skin toxicity was observed in 10–20% of individuals participating in these trials, and in one study, 3.4% of patients withdrew from therapy due to this side effect of treatment [25,26]. In a phase 3 study of 239 patients comparing PLD (50 mg/m² every 4 weeks) to topotecan in advanced ovarian cancer, 49% of women receiving PLD developed PPE, with 22% experiencing grade 3, and 0.8% grade 4 toxicities. Over 57% of patients required dose reduction with 4% withdrawing from the study due to skin toxicity [27].

To further reduce the incidence of PPE, several groups (including our own) reduced the initial dose of PLD in the treatment of gynecologic malignancies to 40 mg/m² administered every 4 weeks. In both endometrial cancer and platinum-resistant ovarian cancer, objective responses have been observed at this dose level, with a lower overall incidence of PPE, particularly grade 3–4 side effects [14,16]. For example, in one second-line ovarian cancer trial, an overall incidence of PPE of 18% was observed, with no patient suffering either grade 3 or 4 toxicities [14]. A similar experience was noted in a smaller experience with the agent in endometrial cancer (11% incidence of grade 1 PPE, no grade 2–4 toxicities) [16]. A retrospective evaluation of 72 platinum- and paclitaxel-sensitive and resistant ovarian cancer patients treated with PLD observed an overall skin toxicity incidence of 23%, with 10% being grade 3. Dose reductions and delays in delivering therapy were required in 8% and 3% of patients, respectively [15].

In the current expanded analysis of the experience of the Cleveland Clinic Gynecologic Cancer program evaluating a total of 90 patients initiating PLD at a dose of 40 mg/m², only one (1%) individual experienced grade 3 PPE (no episodes of grade 4). Additionally, only two (2%) patients discontinued treatment with the agent due to skin toxicity. From our observations and prior studies [28], it is reasonable to conclude that the lower dose of PLD results
in a substantially reduced incidence of PPE, compared to the FDA-approved dose level of 50 mg/m² delivered every 4 weeks. Furthermore, the published experience with PLD in platinum-resistant ovarian cancer strongly supports the use of the 40 mg/m² dose, which results in an acceptable objective response rate and favorable toxicity profile [12,14,15,25–28].

Management of PPE requires careful monitoring and prompt response with either dose reduction or treatment delay. Use of moisturizing creams, wet dressings, loose clothing, and avoidance of sharp objects or heavy activity are helpful conservative measures. Single studies have suggested that pyridoxine, prostaglandins (e.g., misoprostol), and/or 99% DMSO may ameliorate and accelerate resolution of PLD-induced PPE [29–31]. In our study, prompt dose reduction allowed 28 (93%) patients to continue PLD treatment.

Unfortunately, for many patients living with refractory or recurrent gynecologic cancer, second-line therapy is often palliative with short response durations. Survival is only marginally improved if at all. The goal of such therapy should then focus on optimizing a woman’s quality of life. PLD serves this goal well. Absence of total alopecia and minimal nausea and emesis results in more palatable treatment. Given its reduced cardiotoxicity, therapy for prolonged cycles is likely safer and requires less monitoring than doxorubicin [32]. Using a convenient 4-week dosing interval, patients spend less of their valuable time in the clinic receiving treatment. Our data, and that of others, suggest that PLD at 40 mg/m² administered every 4 weeks represents a reasonable therapeutic option in this palliative setting.

References

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