Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia (‘hand-foot’ syndrome)

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Palmar-plantar erythrodysesthesia (PPE), also called hand-foot syndrome or hand-to-foot syndrome, is a distinctive and relatively frequent dermatologic toxic reaction associated with certain chemotherapeutic agents. Pegylated liposomal doxorubicin (PLD), a long-circulating formulation of doxorubicin in which doxorubicin hydrochloride is encapsulated within pegylated liposomes, is approved to treat patients with metastatic breast cancer, advanced ovarian cancer, and acquired immunodeficiency syndrome-related Kaposi’s sarcoma. The incidence of PPE is increased in patients receiving PLD compared with conventional doxorubicin. In studies that utilized the currently approved dose of PLD (50 mg/m² every 4 weeks), ~50% of all patients receiving PLD experienced PPE, and ~20% experienced grade 3 PPE. The pathophysiology of PPE, as it occurs with any drug with which it is associated, is not well understood. Studies evaluating the development of PPE specifically associated with PLD have not fully elucidated the mechanism; however, data support the roles of drug excretion in sweat and local pressure as contributors. When PPE develops, clinical interventions with respect to altering PLD administration include dose reduction, less frequent dosing, and ultimately, drug withdrawal with several consequences on treatment efficacy. This article will review the available data regarding the etiology and potential management strategies of PPE associated with PLD.

Key words: hand-foot syndrome, liposomal doxorubicin, pegylated

introduction

Palmar-plantar erythrodysesthesia (PPE), also called hand-foot syndrome or hand-to-foot syndrome, is a distinctive and relatively frequent dermatologic toxic reaction associated with certain chemotherapeutic agents [1]. The syndrome was first described in 1984 at the New England Deaconess Hospital by Lokich and Moore [2] during 5-fluorouracil (5-FU) continuous infusion. Since then, the syndrome has been associated with a number of other agents including pegylated liposomal doxorubicin (PLD), continuous-infusion doxorubicin, cytarabine, flouxuridine, high-dose interleukin-2, docetaxel, capecitabine, vinorelbine, and gemcitabine [3, 4].

clinical features

PPE typically presents with dysesthesia and tingling in the hands and feet, which usually appear 2–12 days after administration of chemotherapy. These symptoms may progress, 3–4 days later, into symmetrical edema and erythema of the palms and soles. Erythematous plaques with violaceous and edematous patches in the palms, soles, and other high-pressure areas are usually mild and resolve in 1–2 weeks. PPE, however, may evolve into blistering desquamation, crusting, ulceration, and epidermal necrosis if the next chemotherapy cycle is not delayed or the dose reduced.

Dysesthesias and erythema may occur on several other body surfaces, especially in areas where pressure or increased warmth occur, such as on the buttock, groin, under pendulous breasts, and in the axillae. Additional areas of involvement include the inginal, scrotal, and labial regions. On the basis of different body localizations and possibly on different histological and etiologic characteristics, a German author has recently published a paper distinguishing hand-foot syndrome from PPE but generally the terms are used as synonyms [5].

PPE can be uncomfortable and can interfere with the ability to carry out normal activities.

histological features

Histologically, PPE presents with few specific findings. Plantar punch biopsies show marked hyperkeratosis with parakeratosis in the stratum corneum of the epidermis and spongiosis with numerous pyknotic cells without associated lymphocytes in the stratum malpighii. The basal layer shows focal areas of vacuolization and the dermis contains a mild perivascular lymphocytic infiltrate and melanin deposition. Dermal changes include dilated blood vessels, papillary edema, and a sparse superficial perivascular lymphohistiocytic infiltrate [1].
PLD, a long-circulating formulation of doxorubicin in which doxorubicin hydrochloride is encapsulated within pegylated liposomes, is approved to treat patients with metastatic breast cancer where there is an increased cardiac risk, advanced ovarian cancer that has failed platinum-based chemotherapy, and acquired immunodeficiency syndrome-related Kaposi’s sarcoma. Encapsulating doxorubicin within these liposomes alters its pharmacokinetic and biodistribution profile, resulting in a decrease in doxorubicin-related toxic effects, particularly cardiotoxicity [6, 7]. The rate of PPE is, however, increased in patients receiving PLD compared with conventional doxorubicin [6, 7]. In studies that utilized the currently approved dose of PLD (50 mg/m² every 4 weeks), ~50% of all patients receiving PLD experienced PPE, and ~20% experienced grade 3 PPE [7, 8]. Available evidence indicates that altering the dosage schedule of PLD may reduce the incidence of PPE. This article will review the available data regarding etiology of PPE

The pathophysiology of PPE, as it occurs with any drug with which it is associated, is not well understood. It has been hypothesized that, following the local trauma associated with routine activities, PLD may extravasate from the deeper microcapillaries in the hands and feet; PLD has been detected in elevated concentrations in eccrine sweat glands in palms and planta, where it accumulates perhaps facilitated by the hydrophilic coating of the liposomes, and the higher number of eccrine glands in hands and feet could explain the preferred body localizations of the syndrome [9]. In a study of 10 patients receiving PLD for various malignancies, doxorubicin was observed in sweat located inside the excretory ducts of eccrine sweat glands [9]. Further, patient-specific sweat patterns may contribute to the development of PPE. In the same study, only the five patients who had hyperhidrosis of the palms and plantae developed PPE [9]. Regional temperature gradients in the distal extremities, rapid cell proliferation, gravitational forces, and vascular anatomy may contribute to the typical localization to the palms and soles [10, 11].

After extravasation, the drug may penetrate the stratum corneum and accumulate there, causing a local inflammatory tissue reaction, probably mediated by cyclooxygenase (COX)-2, as indicated by the response of capetabine-associated PPE to COX inhibitors [12]. Alternatively, a direct cytotoxic reaction has been hypothesized.

The contribution of local pressure or trauma to the skin was observed in a separate study [13]. Lyass et al. reported that in 45 patients receiving various doses and schedules of PLD for metastatic breast cancer, areas other than the hands and feet that were subjected to frequent pressure or microtrauma were also affected by PPE. These areas included the axillae, groin, and sacral area, among others.

management of PPE related to PLD

When PLD develops, clinical interventions with respect to altering PLD administration include dose reduction, less frequent dosing, and ultimately, drug withdrawal (Table 1) [14]. Early detection of PPE is most valuable as it will allow for early interventions that may potentially prevent the worsening of symptoms. Patient education is important for early detection of PPE to minimize discomfort and complications. At each visit the patient should be carefully asked about signs and symptoms following the last dose. Treatment measures must be started as soon as possible when necessary to help prevent progression of PPE.

preventive measures

Several pharmacologic and nonpharmacologic treatments have been utilized as prevention strategies for PPE. Nonpharmacologic interventions include avoidance of undue pressure or rubbing on the skin and avoidance of blood vessel dilation (e.g. hot showers or sun exposure) [15]. In a retrospective study, regional cooling with ice packs around the wrists and ankles, combined with consumption of iced liquids during PLD infusion, were reported to reduce the frequency and severity of PPE in 17 women compared with three women who did not utilize these measures [16]. Cooling is theorized to result in vasoconstriction, lessening circulation of drug to distal extremities. This in turn may lead to less drug extravasation into surrounding tissue with reduced cutaneous toxicity. It is also possible that lower temperatures stabilize the liposomal configuration, thereby reducing the concentration of unencapsulated doxorubicin [16].

Table 1. PLD dose modification guidelines for the management of palmar-plantar erythrodysesthesia [14]

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild erythema, swelling, or desquamation not interfering with daily activities</td>
<td>Redose unless patient has experienced previous grade 3–4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.</td>
</tr>
<tr>
<td>2. Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations &lt;2 cm in diameter</td>
<td>Delay dose up to 2 weeks or until resolved to grade 0–1. If after 2 weeks there is no resolution PLD should be discontinued.</td>
</tr>
<tr>
<td>3. Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing</td>
<td>Delay dose up to 2 weeks or until resolved to grade 0–1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution PLD should be discontinued.</td>
</tr>
<tr>
<td>4. Diffuse or local process causing infectious complications or a bed ridden state of hospitalization</td>
<td>Delay dose up to 2 weeks or until resolved to grade 0–1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution PLD should be discontinued.</td>
</tr>
</tbody>
</table>

PLD, pegylated liposomal doxorubicin.
Pharmacologic agents that have been evaluated for PPE prevention include pyridoxine (vitamin B₆), dexamethasone, amifostine, and COX-2 inhibitors [12, 17–23].

**Pyridoxine treatment**

Pyridoxine has been investigated because of the resemblance of PPE to acrodynia, a condition observed in pyridoxal phosphate-depleted rodents [17] and one uncontrolled study indicated that pyridoxine may reduce both the incidence and severity of PPE associated with 5-FU continuous infusion [18]. Additionally, preclinical evidence supports a role for pyridoxine in preventing PLD-associated PPE. In a placebo-controlled randomized study of pyridoxine in dogs receiving PLD for non-Hodgkin’s lymphoma, dogs receiving oral pyridoxine had a significantly reduced risk of serious PPE and PLD dose reduction (P = 0.032) [19]. The efficacy of anticancer treatment was not impaired. Dogs on pyridoxine were able to receive a higher median cumulative dose of PLD (P < 0.028). Limited clinical data regarding pyridoxine use for preventing PLD-associated PPE exists. In a phase 1 study of PLD, pyridoxine was administered to 23 patients with solid tumors [20]. The treatment regimen consisted of PLD 20–40 mg/m² every 21 days in combination with paclitaxel and cisplatin. Pyridoxine 50 mg orally three times daily was given on days 2–21 of each cycle. No case of grade 3–4 PPE was reported; grade 1–2 PPE occurred in four of 18 patients (22%) who received more than two cycles of chemotherapy. Because pyridoxine is a relatively nontoxic and inexpensive treatment, in several European hospitals, physicians administer 150–200 mg of pyridoxine daily for prophylaxis during PLD treatment. Phase III randomized trials of pyridoxine versus placebo for prevention of PPE are ongoing.

**Corticosteroids treatment**

Dexamethasone has been evaluated by several investigators for the prevention of PPE [21–23]. Kollmannsberger et al. [21] evaluated the maximum tolerable dose intensity of PLD that could be given to patients with solid tumors who were given concurrent oral dexamethasone and pyridoxine to reduce the frequency and severity of PPE. At the time of the report, 27 patients had begun treatment, receiving oral dexamethasone 8 mg twice daily, days 1 through 5 of each cycle and pyridoxine 100 mg twice daily continuously along with PLD. Only one of 12 patients developed grade 3 or higher PPE at a dose level of 60 mg/m² every 4 weeks, and this patient discontinued dexamethasone on day 2. Premedication with dexamethasone was studied in a prospective case study [22]. Twenty-three patients with recurrent gynecologic malignancies were treated with PLD 50 mg/m² every 28 days without dexamethasone. Nine patients developed grades 2–4 PPE and had the drug withheld until PPE resolution and then restarted. Upon restarting therapy, six of the nine patients received dexamethasone 8 mg twice daily from the day before the infusion for 5 days, then tapered over the next two days. All six of the patients receiving dexamethasone were able to continue chemotherapy without further delay or dose reduction for an average of seven cycles, while those not receiving dexamethasone experienced dose reduction and delays. This same premedication schedule of dexamethasone was used in a patient who developed PPE after three cycles of PLD [23]. Initiation of dexamethasone was successful in preventing further dermatological side-effects and a total of eight cycles of PLD were administered without delay or dose reduction.

Other agents of interest are amifostine [24] and celecoxib [12]. Lyass et al [24] reported a reduced incidence of grade 3/4 PPE in 22 patients with solid tumors receiving i.v. amifostine 500 mg on days 1, 3, or 4, and eight during treatment with PLD 45 to 60 mg/m² every 21 days compared with historical control patients. Celecoxib, a COX-2 inhibitor, has been reported to reduce the incidence and frequency of capecitabine-induced PPE [12]. Studies are currently underway to evaluate COX-2 inhibitors in the prevention of PLD-associated PPE.

**Treatment**

Methods reported to treat established PPE are topical measures. Nonpharmacologic treatments that may relieve the symptoms of PPE include emollients, aloe vera lotion, and moisturizing creams such as Bag Balm®, a topical petroleum–lanolin-based ointment with the antiseptic ingredient hydroxyquinoline sulphate, to maintain skin integrity. Bag Balm® was evaluated in a study of 39 patients receiving various chemotherapy agents [25]. In this study, 13 patients developed PPE including two of six patients on liposomal doxorubicin. Toxicity severity in the 13 patients was grade 1 in four patients, grade 2 in eight, and grade 3 in one. All 13 patients applied Bag Balm® three times daily to the affected areas. Twelve of these patients reported improvement in appearance (photographs of the hands and feet at baseline and subsequent visits were obtained), Rotterdam Symptom Checklist assessment (for quality-of-life assessment), and objective grading of severity according to the NCI-National Cancer Institute Common Toxicity Criteria. In addition to topical creams, some clinicians recommend using cooling measures with ice packs to relieve discomfort or pain associated with PPE.

One pharmacologic topical agent, dimethyl sulfoxide (DMSO), has been investigated for its potential benefit in PPE management because of its potent free-radical scavenging properties. DMSO rapidly penetrates tissues following topical application and has been used successfully to treat extravasation of conventional doxorubicin [26]. The experience of two patients who developed grade 3 PPE while receiving PLD 50 mg/m² every 4 weeks has been reported [27]. Each applied topical 99% DMSO four times daily to the affected areas for 14 days. Symptoms resolved over 1–3 weeks. The data should be taken with caution on the basis of recent experimental data indicating that DMSO could increase the rate of permeability of encapsulated form of doxorubicin theoretically worsening the cutaneous syndrome.

None of the studies summarized here are randomized controlled trials. Most are observational in nature with unspecified study designs. Inclusion and exclusion criteria are frequently not stated and the duration of antidiote treatment is often unknown. At present no randomized clinical trial exists in order to define the best treatment of PLD-related PPE.
dose level and pharmacokinetic aspects contributing to PPE

Characteristics of PLD administration and pharmacokinetics appear to affect the incidence and severity of PPE. Clinical data indicate that PLD is more likely to develop after multiple injections of PLD [13, 28]. For example, in the study by Lyass et al. [13], PPE developed only after a minimum of two courses of therapy.

Several clinical and preclinical studies have evaluated the effect of varying doses and schedules of PLD on the incidence of PPE. The study by Lyass et al. [13] as well as a study by Ranson et al. [28] evaluated different doses and schedules on the incidence of PPE in patients with breast cancer. These studies found that shorter schedules were associated with greater toxicity (Table 2). This effect appeared to be generally independent of dose intensity. A correlation analyses of dose and pharmacokinetic parameters with PLD toxic effects revealed that while the severity of stomatitis and leukocyte nadir correlated strongly with dose and Cmax, the severity of PPE only correlated significantly with half-life (t1/2) [12]. In orthotopically implanted mammary tumors mice (4TI), the accumulation of PLD in cutaneous tissues was reduced by lengthening the dosing interval, and the incidence of PPE-like lesions was lowered [29]. A 4-week dosing interval (as compared with 1- and 2-week intervals) resulted in complete clearance of doxorubicin from cutaneous tissues between doses and in a negligible incidence of PPE lesions.

Previous preclinical data have supported an association between PPE severity and dose intensity [30]. Together, these data indicate that lengthening the PLD dosing schedule does indeed mitigate PPE; however, the role of altering dose intensity and the resulting clinical impact remain unclear and require further controlled clinical trials to ascertain.

clinical effects of a different PLD treatment schedule in ovarian cancer

On the basis of the preclinical and clinical data that indicate the incidence and/or severity of PPE can be reduced by altering either the PLD dosing interval length and/or dose intensity, it is reasonable to further evaluate the effects that these strategies have on both PPE and clinical efficacy. Rose et al. [31] compared a dose of 40 mg/m² every 4 weeks (for an overall dose intensity of 10 mg/m²/week) to a dose of 30 mg/m² every 4 weeks (overall dose intensity 12.5 mg/m²/week) in a single-center retrospective analysis of 78 patients with platinum-refractory ovarian, peritoneal, or tubal carcinoma. Response rates were similar for patients receiving different PLD doses: one complete and four partial responses were registered in the 40 mg/m² treated-group while one complete and two partial responses were reported in the 50 mg/m² treated patients (13.5% vs 7.7%, respectively; P = 0.07). Stable disease, defined as less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions without the appearance of new lesions, was also observed in 18/37 patients (48.6%) at 40 mg/m² and 20/39 patients (51.3%) at 50 mg/m². Median progression-free survival was the same (4 months), and median overall survival was similar for both groups (7 months versus 10 months, respectively; P = 0.25). A significant difference was observed in the proportion of patients requiring dose reductions for PPE (0% versus 25%, respectively; P < 0.001). Fewer patients in the 40-mg/m² group experienced dose delays but the difference was not significant (16% versus 32%, respectively; P = 0.14). In the phase III trial of PLD 50 mg/m² every 4 weeks (delivered dose intensity of 11.6 mg/m²/week) in recurrent ovarian cancer by Gordon et al. [8], the incidence of grade 3 PPE was 22%. By contrast, the rate of grade 3 PPE in four studies of different schedules utilizing either planned or delivered dose intensities of 10.0–10.8 mg/m²/week was 3%–8% [32–35]. These data are summarized in Table 3.

In a retrospective analysis by Campos et al. [32], the authors reported a 27% response rate with a median time to progression of 5.3 months in 72 platinum- and paclitaxel-resistant ovarian cancer patients. The incidence of PPE of any grade was 21% and of grade 3, 8%. No grade 4 PPE was reported.

A prospective clinical trial utilizing 40 mg/m² every 4 weeks was conducted in 49 platinum- and paclitaxel-refractory ovarian cancer patients [33]. In this phase II trial, four of 44 assessable patients (9%) demonstrated objective responses. The incidence of PPE of any grade was 18%. No grade 3 or higher PPE was observed. Six patients (12%) required dose reductions for treatment-related toxic effects. On the basis of these data many

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients in treatment arm</th>
<th>Frequency (weeks)</th>
<th>Dose (mg/m²)</th>
<th>Planned dose intensity (mg/m²/week)</th>
<th>Incidence of grade 2–4 PPE (%)</th>
<th>Mean incidence in frequency subgroup (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyass et al. [13]</td>
<td>11</td>
<td>3</td>
<td>35</td>
<td>11.7</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td>Lyass et al. [13]</td>
<td>5</td>
<td>3</td>
<td>45</td>
<td>15</td>
<td>40</td>
<td>40</td>
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<tr>
<td>Ranson et al. [28]</td>
<td>26</td>
<td>4</td>
<td>45</td>
<td>15</td>
<td>65</td>
<td>65</td>
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<tr>
<td>Ranson et al. [28]</td>
<td>13</td>
<td>2</td>
<td>60</td>
<td>20</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Ranson et al. [28]</td>
<td>32</td>
<td>4</td>
<td>45</td>
<td>11.3</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Lyass et al. [13]</td>
<td>5</td>
<td>5</td>
<td>50</td>
<td>12.5</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Lyass et al. [13]</td>
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<td>6</td>
<td>60</td>
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<td>Lyass et al. [13]</td>
<td>6</td>
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<td>17</td>
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<td>Lyass et al. [13]</td>
<td>12</td>
<td>6</td>
<td>70</td>
<td>11.7</td>
<td>33</td>
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</table>

PLD, pegylated liposomal doxorubicin; PPE, palmar-plantar erythrodysesthesia.
authors believe that sufficient clinical evidence exists to support use of a modified dose schedule of PLD (40 mg/m² every 4 weeks) in patients with recurrent or relapsed ovarian cancer; however, a prospective phase III study would be required to adequately compare the relative efficacy and tolerability of this regimen to that of 50 mg/m² every 4 weeks.

Sehouli et al. [34] evaluated a 20-mg/m² q 14 days schedule in 64 patients with recurrent ovarian cancer previously treated with platinum or taxanes. In 44 assessable patients, the response rate was 16%. Median progression-free survival was 4.3 months and median overall survival was 18.2 months. The incidence of PPE of any grade was 48%; however, only 5% developed grade 3 PPE and no grade 4 PPE was reported.

Our group evaluated PLD at the dose of 35 mg/m² every 21 days in a prospective, open-label phase II study [35]. Thirty-seven heavily pretreated patients (median number of previous chemotherapy regimens two, range 1–6) with recurrent ovarian cancer received at least two courses of chemotherapy and all were evaluated for response. Response rates were 0% complete response, 13.5% partial response, and 48.6% stable disease. The median time to response was 12 weeks (range 8–16). The median duration of response was 22.8 weeks (range 4–68) and the median duration of stable disease was 17.6 weeks (range 4–28). PPE occurred in eight patients (21.6%) and was of grade 3 in one patient (2.8%). In this patient population, we used premedication with corticosteroids (methylprednisolone 20 mg i.m. 12 h and 6 h before drug infusion) in order to prevent allergic reactions. The low rate of PPE reported in our study could be related not only to the different drug schedule but also to the corticosteroid premedication. At present, we are investigating if corticosteroid premedication may explain the low incidence of PPE in our population.

collection

The currently approved dose of PLD is 50 mg/m² every 4 weeks; however, the literature supports the use of different schedules to optimize clinical efficacy and minimize the occurrence of drug-related toxicity. Given the chronic course of ovarian cancer, an improved safety profile of PLD may translate into an improved quality of life for patients with advanced ovarian cancer.

references


Table 3. Incidence of PPE and clinical efficacy in trials with PLD at different doses and schedules for recurrent ovarian cancer

<table>
<thead>
<tr>
<th>Study/population</th>
<th>N</th>
<th>PLD regimen</th>
<th>Mean dose intensity of PLD (mg/m²/wk)</th>
<th>Response rate (%)</th>
<th>Median progression (months)</th>
<th>Incidence of PPE (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al. [8], platinum-resistant OC</td>
<td>239</td>
<td>50 mg/m² q 4 weeks</td>
<td>11.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.7</td>
<td>PFS: 3.7</td>
<td>49 22 1</td>
</tr>
<tr>
<td>Lorusso et al. [35], heavily pretreated OC</td>
<td>37</td>
<td>35 mg/m² q 3 weeks</td>
<td>10.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13.5</td>
<td>TTP: 6.6</td>
<td>22 3 0</td>
</tr>
<tr>
<td>Campos et al. [32], recurrent OC, 40% platinum-paclitaxel-resistant disease (retrospective analysis)</td>
<td>72</td>
<td>40 mg/m² q 4 weeks (in 93% of patients)</td>
<td>10.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26.7</td>
<td>TTP: 5.3</td>
<td>21 8 0</td>
</tr>
<tr>
<td>Markman et al. [33], platinum–paclitaxel-refractory OC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>49</td>
<td>40 mg/m² q 4 weeks</td>
<td>10.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.0</td>
<td>NR</td>
<td>18 0 0</td>
</tr>
<tr>
<td>Sehouli et al. [34], recurrent OC</td>
<td>64</td>
<td>20 mg/m² q 2 weeks</td>
<td>10.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15.9</td>
<td>PFS: 4.3</td>
<td>48 5 0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Delivered.
<sup>b</sup>Planned.
<sup>c</sup>Ovarian, peritoneal, or tubal carcinoma.
PPE, palmar-plantar erythrodysesthesia; PLD, pegylated liposomal doxorubicin; OC, ovarian cancer; PFS, progression-free survival; TTP, time to progression; NR, not reported.