Palmar-Plantar Erythrodysesthesia

Gail M. Wilkes, MS, RNC, AOCN®, and Diane Doyle, MS, RNC

Case Study 1

M.J. is a 47-year-old woman who was diagnosed with epithelial ovarian cancer two years ago; she underwent total abdominal hysterectomy with bilateral salpingo oophorectomy and received adjuvant carboplatin and paclitaxel, but her cancer recurred within six months of completing adjuvant therapy. M.J. recently completed two cycles of liposomal doxorubicin 50 mg/m² every four weeks. The likelihood of obtaining a response with this regimen is 14%–20%, with stable disease reported in 30% of patients (Campos et al., 2001). M.J. arrives at the clinic and tells the nurse that she developed intermittent tingling, erythema, and slight swelling on the palms of her hands and fingers, as well as red blotches between her knees, three days after her last cycle of chemotherapy. M.J. is able to perform all self-care and work-related functions and reported that the red blotches are tender to touch but not painful. The affected skin is intact, and she denies fever, rash, urticaria, or pruritis; use of new detergents, lotions, or soaps; or exposure to any allergen. The clinical assessment confirms M.J.’s report, and the differential diagnoses include allergic reaction, palmar-plantar erythrodysesthesia (PPE), cellulitis, and contact dermatitis. The most likely diagnosis is PPE resulting from the recent liposomal doxorubicin chemotherapy.

Discussion

M.J. is diagnosed with grade 1 PPE on her hands and fingers, as well as the pressure points between her knees. PPE is a dermatologic toxicity characterized by erythema and dysesthesias on the palm and foot surfaces. Grade 1, which rarely affects the soles of the feet, is defined by mild erythema, swelling with or without tingling in fingertips, dry desquamation, and no alteration in function or ability to perform activities of daily living (ADL) (see Table 1). Liposomal doxorubicin-induced PPE appears to be schedule dependent and generally develops after two to three cycles of therapy. In most cases, PPE is mild and resolves in one to two weeks. Drug-dose modifications are based on the severity of the symptoms. Grade 2 PPE requires a delay in dosing for as many as two weeks or until resolved to grade 0–1; if symptoms are not resolved after two weeks, liposomal doxorubicin should be discontinued. Grade 3 PPE requires a dose delay for as many as two weeks or until resolved to grade 0–1, and the next dose should be reduced by 25%. If symptoms do not resolve after two weeks, liposomal doxorubicin should be discontinued. Patients with grade 4 PPE are bedridden or hospitalized, and dose delay and discontinuance guidelines are similar to those for grade 3 (Ortho Biotech Products, L.P., 2001).

Figure 1. Foot With Stage II Palmar-Plantar Erythrodysesthesia

Note. Photo courtesy of Cheryl Moore, RN, Cancer Center of Boston. Reprinted with permission.

Case Study 2

J.E. is a 73-year-old widowed woman recently diagnosed with synchronous breast and bowel lesions that were resected with a tumor histology that revealed a primary adenocarcinoma of the bowel, metastatic to the breast. The patient has a complicated history of severe coronary artery disease, hypertension, and type II diabetes mellitus. After a multidisciplinary team meeting, J.E. agrees to begin capecitabine (Xeloda®, Roche Pharmaceuticals, Nutley, NJ) 1,250 mg/m² given orally twice daily for 14 days followed by one week of rest. After her second cycle of capecitabine, J.E. arrives at the clinic complaining of pain on the soles of her feet, which has necessitated a change of shoes and caused a 75% reduction in the distance she is able to walk each day (see Figure 1). On examination, erythema, edema, dry desquamation, and pain on palpation of both soles of the feet are noted. The palms of her hands bilaterally are unchanged from baseline assessment, and her feet are warm, with excellent capillary refill of the nail beds. The differential diagnoses include PPE and diabetic atherosclerotic changes on the soles.
of her feet. PPE is the most likely diagnosis because of the timing of symptoms in relation to the capecitabine dosing.

Discussion

Symptoms of PPE related to capecitabine typically appear with the second cycle of therapy, which is consistent with J.E.’s situation. Grade 2 PPE includes painful erythema with swelling and discomfort that affect ADL. (see Table 2). When grade 2 or 3 PPE occurs within the first two cycles of treatment with capecitabine, the dosing should be discontinued until symptoms resolve or symptom intensity has reduced to grade 1. When patients develop grade 3 PPE, subsequent doses of capecitabine should be decreased (Abushullia, Saad, Munsell, & Hoff, 2002).

Pathophysiology

The pathophysiology of PPE is not clearly understood. The most compelling hypothesis involves the tiny capillaries in the palms of the hands and soles of the feet, which lie deep under the dermis to protect them from pressure during walking and working. The hand and foot surfaces, while under pressure from walking or use, are believed to rupture the capillaries, releasing liposomal doxorubicin or capcitabine and causing an inflammatory reaction (Lin et al., 2002; Wilkes, 2003). Drugs with sustained or protracted serum levels such as liposomal doxorubicin and capcitabine are most likely to cause PPE. Liposomal doxorubicin has a half-life of 55 hours, and PPE has been described in as many as 48% of patients receiving liposomal doxorubicin. Protracted 5-fluorouracil (5-FU) infusions and capcitabine, a 5-FU prodrug that mimics continuous infusion, have a PPE incidence of 54%–68% (Abushullia et al., 2002; Lokich & Moore, 1984; Roche Pharmaceuticals, 2001). In addition, liposomal doxorubicin accumulates in tumor tissue by leakage through the tumor microvasculature, and the drug is believed to localize in the deeper microcapillaries of the hands and feet and other tissues with deep cutaneous pressure via leakage into the peripheral vasculature (Gabizon & Muggia, 1997). With continued drug administration, swelling, pain, blister formation, and cutaneous dry and moist desquamation develop on the palms of the hands and/or soles of the feet and other areas of significant cutaneous pressure.

Lin et al. (2002) suggested that the inflammatory reaction is mediated by cyclooxygenase-2. This response was demonstrated retrospectively when capcitabine was administered with celecoxib, a cyclooxygenase-2 inhibitor, and this resulted in a decreased incidence of PPE (grade 1: 12.5% versus 34.3%, \( p = 0.037 \); grade 2: 3.1% versus 17%, \( p = \text{not significant} \)). A significant decrease was reported for grade 2 or higher diarrhea in the celecoxib arm of the study, as well as a significant increase in the number of patients with stable disease (62.5% versus 22.8%, \( p = 0.001 \)).

Severe PPE can significantly decrease quality of life, rendering patients unable to wear shoes, walk, or use their hands to hold various instruments. At the very worst, moist desquamation can necessitate ongoing dressing changes to facilitate healing. Thus, assessment and early identification of significant PPE will lead to delay of drug administration or dose reduction until the underlying tissues heal and symptoms resolve, thereby obviating severe PPE and its resultant disability.

Nursing Interventions

Nurses play a key role in patient assessment and should reassess areas of PPE continually until symptom resolution, which often includes bringing patients into an ambulatory center for clinical examinations. Discuss patient symptoms and grade of PPE with the physician so that, if necessary, treatment is delayed or, when grade 3 or 4 PPE is present, subsequent doses are reduced.

Prospective clinical data from comparative trials are lacking for much of the recommended clinical care. Topical treatment includes skin hydration with a moisturizer to maintain skin integrity. If the skin begins to blister or ulcerate, patients should be instructed to soak the area with cool or tepid water for 10 minutes, then apply petroleum jelly to the wet skin to trap the moisture. Bag Balm® (Dairy Association Co., Inc., Lyndonville, VT) is used commonly to keep skin well moisturized and intact (Chin et al., 2001). Do not use topical corticosteroids or anesthetics because they may exacerbate symptoms. Pharmacologic options include vitamin B₉ (pyridoxine) 300 mg daily (Lau & Mortimer, 2001), but randomized prospective clinical trials are needed to confirm this treatment. Some studies have shown attenuation in the intensity of PPE.

Table 1. Grading Scale of Palmar-Plantar Erythrodysesthesia for Liposomal Doxorubicin

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Domain</th>
<th>Functional Domain</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild erythema, swelling and/or tingling sensation in fingertips and rarely on the soles of the feet, and dry desquamation</td>
<td>No alteration in function or ability to perform activities of daily living (ADL)</td>
</tr>
<tr>
<td>2</td>
<td>Pain on palms and/or soles of feet may be intense or burning, especially with pressure; palms of the hands and/or soles of the feet are uniformly deep red and edematous, may desquamate, and may have small blisters or ulceration less than 2 cm.</td>
<td>Interferes with ADL but still able to perform them</td>
</tr>
<tr>
<td>3</td>
<td>Increased pain with any pressure or contact, central pallor in areas of intense erythema, blisters, and ulceration more than 2 cm in diameter</td>
<td>Significant interference with function and ADL</td>
</tr>
<tr>
<td>4</td>
<td>Red, purulent, infected areas of ulceration, which are localized or involve large areas of the palms, fingers, soles of the feet, or other areas of cutaneous pressure</td>
<td>Bedridden or hospitalized; diffuse or local infection</td>
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Table 2. Palmar-Plantar Erythrodysesthesia Grading Scale for Capecitabine

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Domain</th>
<th>Functional Domain</th>
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<tbody>
<tr>
<td>1</td>
<td>Numbness, paresthesias, dysesthesias, tingling, painless swelling, or erythema</td>
<td>Discomfort that does not affect normal activities of daily living (ADL)</td>
</tr>
<tr>
<td>2</td>
<td>Painful erythema with swelling</td>
<td>Discomfort that affects ADL</td>
</tr>
<tr>
<td>3</td>
<td>Moist desquamation, ulceration, blistering, severe pain, or discomfort</td>
<td>Unable to work or perform ADL</td>
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Note. Based on information from Roche Pharmaceuticals, 2001.
but not prevention of its occurrence, whereas others suggest as much as a 15% decrease in the incidence of PPE related to capecitabine with pyridoxine prophylaxis (Hussein et al., 1998; Longfield, Hasan, & Romie, 2001; Patel, 1999; Yee, Safran, & Jeffers, 1998). Some researchers have suggested that dexamethasone alone or in combination with pyridoxine may reduce the incidence and severity of PPE associated with liposomal doxorubicin (Kollmannsberger et al., 2000; Titgan, 1997). Early research by Kingsley (1994) showed that the use of nicotine patches prevented 5-FU–induced PPE in one patient, but this currently is undergoing investigation. Theoretically, vasoconstriction caused by nicotine could decrease drug delivery to the deep microcapillaries. In addition, analgesics often aid in decreasing local discomfort.

Anecdotal evidence exists that an altered treatment schedule of liposomal doxorubicin may be successful in avoiding severe PPE. Schedules include delaying therapy for one week and/or reducing the dose from 50 mg/m² to 40 mg/m². Retrospective analyses of patients treated with liposomal doxorubicin at doses of approximately 40 mg/m² every four weeks have shown a low incidence of PPE without loss of efficacy (Campos et al., 2001; Perez, Domenech, Frankel, & Vogel, 2002; Rose, Maxson, Fusco, Mossbruger, & Rodriguez, 2001).

Patient Education

Patient education is key in the early detection of PPE to minimize discomfort and complications. Patients should be instructed to (a) assess pressure-sensitive areas, (b) report signs and symptoms of PPE as soon as possible, and (c) use restorative and prophylactic strategies to minimize the likelihood or degree that PPE may develop. Because PPE occurs after patients return home and most often after receiving two or more cycles of chemotherapy, patient teaching, including self-assessment and strategies to discourage PPE, is extremely important.

To prevent dilation of deep capillary vessels that would increase drug extravasation, patients should be instructed to avoid activities such as sun exposure, taking hot baths and showers, and using a hot tub or whirlpool for 24 hours before and three to five days after the administration of liposomal doxorubicin. For patients receiving capecitabine, when the dose is taken twice daily for 14 days followed by a seven-day rest, these instructions are continuous. Cooling methods such as cold or cool baths are recommended but are dependent on patient tolerance. Patients may find comfort in using cool compresses or ice packs applied for 20 minutes and removed for 20 minutes.

In addition, to prevent pressure on the deep capillaries that can cause injury, patients should be instructed to avoid tight-fitting shoes and repetitive rubbing pressure (e.g., using scissors to cut many sheets of paper). Patients should avoid vigorous washing or rubbing pressure-sensitive points such as the soles of the feet and palms of the hands. Obese patients also should avoid vigorous washing under the breasts, axillae, and inguinal skin folds. Patients should be taught to protect the skin integrity by wearing gloves for hand activities and using topical emollients such as Bag Balm, Udderly Smooth® (Redex Industries, Inc., Salem, OH) cream, or Aquaphor® (Beiersdorf Inc., Wilton, CT) cream (Chin et al., 2001).

Patient Outcomes

The goal of care for PPE is to prevent toxicity grades 3 and 4 from occurring. If patients develop PPE, further injury should be minimized and recovery of the tissue hastened with resolution of symptoms. In case study 1, M.J. had grade 1 PPE, which did not necessitate the delay of her subsequent treatment cycle. Her PPE did not worsen and resolved by the next cycle reassessment. M.J. was very careful to keep her knees separated; as a result, after the erythema and tenderness resolved, PPE did not recur in this area. She continued to receive additional cycles without progressing beyond grade 1 PPE. Similarly in case study 2, J.E. had just finished her 14-day course of capecitabine and was beginning her seven-day rest period. Cycle 3 was delayed by four days until her PPE resolved to grade 0–1. In addition, because evidence supported that using a capecitabine dose of 1,000 mg orally twice per day is as effective with less toxicity, J.E.’s dose for cycle 3 was reduced to this amount (Michaud et al., 2000; O’Shaughnessy & Blum, 2000).

PPE is a potential toxicity of certain antineoplastic agents with protracted serum levels (e.g., liposomal doxorubicin, capecitabine). Thorough patient assessment and meticulous patient teaching are necessary to prevent its development or to identify early changes so that complications of severe pain, loss of cutaneous integrity, and disability can be avoided.

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References


