

## Hand-Foot Syndrome Related to Liposomal Doxorubicin

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**K**.M. was a 69-year-old woman who presented to her primary physician with bloating, abdominal cramping, and constipation over the previous weeks. She also noted some fullness in her right groin. She underwent an abdominal ultrasound, which revealed an adnexal mass on the right side of her abdomen, and a computed tomography (CT) scan, which demonstrated a large complex mass in the region of the right ovary along with fluid in the peritoneal cavity consistent with ascites. She had a cancer antigen 125 (CA-125) blood test for ovarian cancer drawn. The result was well above normal at 1,050 U/ml (normal range is up to 35 U/ml).

Because of these findings, K.M. had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy performed, and the pathology showed a serous adenocarcinoma of the ovary. It was staged as IIIC ovarian cancer with involvement of right ovary, omentum, and peritoneal lymph nodes. The surgeon noted that she had an optimal cytoreduction of the cancer and, during the surgery, she had a peritoneal port-a-cath placed for future treatment with intraperitoneal chemotherapy.

After approximately one month of healing, K.M. began treatment with a combination of intraperitoneal and IV chemotherapy with cisplatin and paclitaxel. She received six cycles of this treatment administered every three weeks. Unfortunately, within two months of completing her initial chemotherapy regimen, progression of her cancer was detected with an elevated CA-125 and an abdominal CT scan showing a new soft tissue mass adjacent to the spleen.

K.M. began treatment with pegylated liposomal doxorubicin (Doxil®, Centocor Ortho Biotech, Inc.) at 50 mg/m<sup>2</sup> IV every four weeks (the U.S. Food and Drug Administration [FDA]-approved dose for ovarian cancer). Doxil is doxorubicin encapsulated in a liposome, which increases the drug delivery and effectiveness and improves the adverse event profile com-

pared to conventional doxorubicin (Centocor Ortho Biotech, Inc., 2007).

K.M. did well through three cycles of treatment, experiencing a response to the therapy and only mild fatigue and mucositis following the treatments. However, prior to cycle four, K.M. reported skin peeling on the lateral aspects of her feet and along the lateral aspect of the big toe on her right foot. No pain, tingling, or erythema were reported with this side effect. The oncology nurse noted that these were possible early symptoms of palmar-plantar erythrodysesthesia (PPE) associated with liposomal doxorubicin treatment and instructed K.M. to begin applying a moisturizing cream twice daily to the palms of her hands and the soles of her feet. K.M. also was instructed to avoid undue pressure on the skin, such as tight shoes or restrictive clothing, and activities that cause blood vessel dilation such as hot showers or sun exposure (Markman, Kulp, & Peterson, 2004).

Prior to cycle five, K.M. experienced worsening symptoms of PPE with peeling of the skin, particularly along the lateral portions of her feet and blistering on the lateral aspect of the right big toe. She also experienced hyperpigmentation (a darkening of the skin) and a painful rash involving her anterior lower extremities, behind her knees, beneath both breasts, and in both axillary regions. K.M.'s ability to complete normal daily activities was limited by the pain she experienced. The medical oncologist withheld her treatment for two weeks and reduced her liposomal doxorubicin dose by 25% when treatment resumed. She continued to receive liposomal doxorubicin at the reduced dose until she experienced progressive disease. She had no resumption of PPE symptoms.

### Palmar-Plantar Erythrodysesthesia

PPE, also known as hand-foot syndrome, is a common side effect of liposomal doxorubicin, capecitabine, and continuous infusion 5-fluorouracil. This

review is restricted to skin toxicities associated with liposomal doxorubicin, as the origin, presentation, and treatment of PPE associated with other agents such as multikinase inhibitors may be slightly different (Anderson et al., 2009). PPE is the most common toxicity experienced by patients receiving liposomal doxorubicin for ovarian cancer and can be a dose-limiting toxicity (von Moos et al., 2008). PPE is more common among patients who are receiving liposomal doxorubicin treatment using a higher dose or a condensed schedule. Almost 50% of all patients treated with liposomal doxorubicin at 50 mg/m<sup>2</sup> every four weeks experience some degree of PPE (Centocor Ortho Biotech, Inc., 2007); therefore, modified dosing of liposomal doxorubicin using 40 mg/m<sup>2</sup> every four weeks reduces the incidence and severity without compromising clinical efficacy (Al-Batran et al., 2006; Rose, 2005).

PPE usually starts with a localized tingling sensation on the palms of the hands or the soles of the feet. PPE also can affect other common pressure points, such as the waistline and bra lines. It progresses to a painful erythema in those areas and can be associated with dryness, cracking, edema, and rash. If the offending drug is continued, burning pain, blistering, ulceration, and desquamation of the skin may occur. Patients describe the symptoms as if they are walking on hot sand or have gravel in their shoes (Webster-Gandy, How, & Harrold, 2007).

The etiology of PPE associated with liposomal doxorubicin is not well understood. The drug may accumulate in the microcapillaries of the hands and feet. Liposomal doxorubicin has been detected in eccrine sweat glands, which are more numerous in the palms of the hands and soles of the feet. As the drug accumulates in these tissues, it may cause a local inflammatory tissue reaction (Lorusso et al., 2007).

Toxicity grading is important because it determines when the treatment should be delayed or the dose should be reduced. The Common Terminology Criteria for Adverse Events™ [v.3.0] (Cancer Therapy

Evaluation Program, 2006) is used to grade PPE toxicity and determine dose modifications for liposomal doxorubicin (Centocor Ortho Biotech, Inc., 2007). Grade 1 is when painless erythema with mild swelling, numbness, or tingling is present. Supportive care is recommended at this grade. Grade 2 occurs when the patient experiences skin changes (peeling, blisters, bleeding, and edema) that do not interfere with daily functions. If grade 2 toxicity occurs, the drug should be stopped until the toxicity resolves to grade 0 or 1 and restarted at a full dose. Grade 3 is when ulcerative dermatitis or skin changes (moist desquamation, ulceration, and blistering) occurs with pain that interferes with daily functions. If grade 3 toxicity occurs, the drug should be stopped until the toxicity resolves to grade 0 or 1, and the dose should be reduced by 25% when the drug is restarted. Patients should be prepared for PPE and instructed to report signs and symptoms immediately to a healthcare provider. If the drug is continued while patients are experiencing PPE, a very painful condition may arise that can compromise additional therapy.

## Side-Effect Management

Patients should be instructed about the potential of experiencing PPE and to look for early signs and symptoms of PPE during liposomal doxorubicin treatment. Figure 1 lists recommendations to prevent the condition, although it should be noted that most of these recommendations are based on anecdotal data with limited research. When PPE does develop, reducing dose intensity (increasing interval or reducing dose) often is the most crucial intervention to prevent progression of PPE to a more serious and painful condition (von Moos et al., 2008.) Oral pyridoxine

- Regularly apply moisturizing or urea-containing creams to hands and feet.
- Avoid skin irritants such as perfumes and cleaning agents.
- Avoid constrictive clothing, shoes, or jewelry.
- Avoid extreme hot or cold temperatures, pressure points, and friction.
- Wear rubber gloves when doing dishes.
- Avoid getting a sunburn.

### Figure 1. Recommendations to Prevent Palmar-Plantar Erythrodysesthesia

Note. Based on information from Lorusso et al., 2007; Markman et al., 2004; Tanyi et al., 2009.

(vitamin B<sub>6</sub>) 300 mg per day has been tested in patients receiving liposomal doxorubicin and found to be ineffective at reducing the severity or frequency of PPE (Rossi & Catalano, 2007).

A prospective study tested the effectiveness of dexamethasone for the prevention of PPE and found that a tapering dose of oral dexamethasone beginning on the day prior to treatment and continuing for five days was effective in preventing dose delays and reductions in patients with ovarian cancer who were receiving liposomal doxorubicin (Drake et al., 2004). More research is needed to test the intervention because of the limitations of a small, single-institution study. A potential risk factor previously thought to put patients at risk for PPE was a greater body mass index; however, a retrospective review found that body mass index did not correlate with PPE (Gordinier et al., 2006).

## Other Associated Skin Toxicities

Although less common than PPE, other skin toxicities that have been reported with liposomal doxorubicin include diffuse follicular rash, pruritis, skin discoloration, and vesiculobullous or maculopapular rash (Cady, Kneuper-Hall, & Metcalf, 2006; Centocor Ortho Biotech, Inc., 2007). Patients also should be monitored for other skin toxicities during liposomal doxorubicin.

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# Clinical Highlights: Hand-Foot Syndrome and Liposomal Doxorubicin

## Definition

Palmar-plantar erythrodysesthesia (PPE), also known as hand-foot syndrome, is a common side effect of liposomal doxorubicin, capecitabine, and continuous infusion 5-fluorouracil. PPE is the most common toxicity experienced by patients receiving liposomal doxorubicin for ovarian cancer and can be a dose-limiting toxicity (von Moos et al., 2008). PPE usually starts with a localized tingling sensation on the palms of the hands or the soles of the feet. It also can affect other common pressure points and progresses to a painful erythema in those areas associated with dryness, cracking, edema, and rash. If the offending drug is continued, a burning pain, blistering, ulceration, and desquamation of the skin may occur.

## Pathophysiology

The etiology of PPE associated with liposomal doxorubicin is not well understood. The drug may accumulate in the microcapillaries of the hands and feet. Liposomal doxorubicin has been detected in eccrine sweat glands, which are more numerous in the palms of the hands and soles of the feet. As the drug accumulates, it may cause a local inflammatory tissue reaction (Lorusso et al., 2007). PPE is more common among patients who are receiving liposomal doxorubicin treatment using higher doses or a more condensed schedule; a modified dose has been proposed to reduce the incidence and severity of PPE in recurrent or relapsed ovarian cancer (Al-Batran et al., 2006; Rose, 2005).

## Toxicity Grading and Interventions

Toxicity grading is important because it determines when the treatment should be delayed or the dose should be reduced. The Common Terminology Criteria for Adverse Events™ [v.3.0] (Cancer Therapy Evaluation Program, 2006) is used to grade PPE toxicity and determine dose modifications for liposomal doxorubicin (Centocor Ortho Biotech, Inc., 2007). Grade 1 is when painless erythema with mild swelling, numbness, or tingling occurs. Supportive care is recommended at this grade. Grade 2 is when the patient experiences skin changes (peeling, blisters, bleed-

ing, and edema) that do not interfere with daily functions. If grade 2 occurs, the drug should be stopped until the toxicity resolves to grade 0 or 1 and restarted at a full dose. Grade 3 is when ulcerative dermatitis or skin changes (moist desquamation, ulceration, and blistering) occur with pain that interferes with daily functions. If grade 3 occurs, the drug should be stopped until the toxicity resolves to grade 0 or 1 and the dose should be reduced by 25% when the drug is restarted.

## Nursing Implications

PPE is an important dose-limiting toxicity of liposomal doxorubicin. Oncology nurses should instruct patients about the potential of experiencing PPE and to look for early signs and symptoms of PPE during liposomal doxorubicin treatment. Liposomal doxorubicin also may be associated with other skin toxicities, such as diffuse follicular rash, pruritis, skin discoloration, and vesiculobullous or maculopapular rash (Cady, Kneuper-Hall, & Metcalf, 2006; Centocor Ortho Biotech, Inc., 2007). When a patient presents for treatment, nurses should assess the patient's skin for PPE, including a careful assessment of the feet and hands. In addition, patients should be monitored for other skin toxicities during liposomal doxorubicin. Dose modifications and delays for recovery from PPE are an important part of maintaining active treatment with liposomal doxorubicin. Patients should be advised to apply moisturizing lotion or urea-containing creams to hands and feet regularly and to avoid skin irritants; constrictive clothing, shoes, or jewelry; extreme temperatures; and sunburn (Lorusso et al., 2007; Markman, Kulp, & Peterson, 2004; Tanyi et al., 2009). A treatment that has shown promise in preventing PPE is a tapering dose of oral dexamethasone beginning on the day prior to treatment and continuing for five days for patients with ovarian cancer who were receiving liposomal doxorubicin (Drake et al., 2004). However, more research is needed to test this intervention. Patients should be instructed to report signs and symptoms of PPE to their healthcare provider immediately. If the drug is continued while they are experiencing PPE, it can progress to a very painful condition that may compromise additional therapy.

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