

## 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