Skin Toxic Effects of Polyethylene Glycol–Coated Liposomal Doxorubicin

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Objectives: To record the profile of toxic effects of polyethylene glycol–coated liposomal doxorubicin hydrochloride (Doxil) to the skin, and to evaluate whether the long circulation pattern and enhanced accumulation of liposomes in specific skin sites will result in any unique presentations.

Design: Patients were accrued in the frame of dose-range–finding studies that examine the toxic effects and antitumor activity of Doxil therapy in metastatic breast and prostate cancers. All patients receiving Doxil were instructed to report any skin eruption or discomfort. Skin examination was performed on a regular basis at every cycle of Doxil therapy and after specific complaints.

Setting: Outpatient day care unit of the oncology institute of a secondary-referral medical center.

Patients: Sixty patients (45 women and 15 men).

Main Outcome Measures: A basic severity scale of I through IV was adopted for toxic effects to the skin, based on National Cancer Institute common toxicity criteria.

Results: The following 4 patterns of skin eruptions were encountered: hand-foot syndrome (n=24), diffuse follicular rash (n=6), intertrigolike eruption (n=5), and new formation of melanotic macules (n=3). Another major toxic effect of Doxil was stomatitis, which was found to be the dose-limiting factor for the maximal single dose. Alopecia and extravasation injuries did not occur.

Conclusions: The profile of toxic effects of Doxil to the skin reflects its unique pharmacokinetics and tissue distribution. These skin reactions vary significantly from those associated with doxorubicin in non–liposome-encapsulated form.

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Drug delivery systems hold considerable potential for oncology use by allowing preferential drug accumulation in target tissues and reducing toxic effects to healthy organs. Encapsulation of doxorubicin hydrochloride in liposomes is a successful application of this concept that is gaining widening acceptance for several indications, including acquired immunodeficiency syndrome–related Kaposi sarcoma and ovarian cancer.

Liposomes are bilayer vesicles, formed by amphipathic lipids, generally phospholipids, entrapping a water-soluble phase. They serve as drug carriers when a drug is dissolved in the water phase. The resulting complex may have a totally different profile of pharmacokinetics and toxicity. This holds true especially for a liposomal formulation of doxorubicin coated with polyethylene glycol and known as Doxil (Alza Corp, Mountain View, Calif). Doxorubicin is an important antineoplastic agent with activity in a variety of solid tumors, but its use is limited by substantial toxicity, with adverse effects consisting of myelosuppression and myocardial damage. Doxil differs from doxorubicin significantly. Preclinical toxicologic studies and a phase I clinical study showed only mild myelosuppression, minimal alopecia, and no apparent cardiototoxic effects. It appears that Doxil accumulates preferentially in tissues of increased microvascular permeability, as is the case for tumors with active neoangiogenesis. Doxil formulation has a long circulation time and is highly stable, thus providing a slow release pool of drug to tumor and other tissues. However, Doxil is not devoid of adverse effects. Its toxicity profile is characterized by dominant and dose-limiting mucocutaneous reactions.

In this report, we illustrate and draw attention to the various skin reactions that are associated with the administration of
Doxil. Clinicians should be acquainted with this spectrum of mucocutaneous toxic effects, as this product is becoming better recognized and more widely prescribed.

RESULTS

Sixty patients were accrued (45 women and 15 men). The following 4 patterns of skin eruptions were seen: HF syndrome (grades II-IV) in 24 patients, diffuse follicular rash (grades I-II) in 6 patients, intertrigolike eruption (grades II-IV) in 5 patients, and new formation of melanotic macules in 3 patients.

HF SYNDROME

Also known as toxic acral erythema and palmar-plantar erythrodysaesthesia syndrome, HF syndrome is the most common skin reaction. The earliest sign is painful erythema of the palms, soles, and fingers that later becomes edematous, changes color to violet (Figure 1A), then dries off and desquamates (Figure 1B). In severe cases, blisters develop, later leaving erosive surfaces, with considerable impairment in function (Figure 2). Hand-foot syndrome is often the dose-limiting toxic effect, especially when Doxil is given on short schedules (3-week intervals) with dose intensities of greater than 12 mg/m² per week. The reaction tends to recur and increase with each subsequent administration.

In a patient with grade III HF syndrome, histopathological examination revealed vacuolar necrosis of basal keratinocytes and also vacuolar necrosis of keratinocytes in the lower third of the epidermis, with partial separation from dermis. Perivascular infiltrate was seen in dermis, composed of lymphocytes and a few eosinophils (Figure 3).

DIFFUSE FOLLICULAR RASH

This eruption consists of delicate, widespread scaly erythematous accentuation of the hair follicles (Figure 4). Most common over the lateral parts of the limbs, it can also be detected over the trunk. This exists to some extent in many patients but, being asymptomatic, it may go unobserved. Most patients experienced only grade 1 toxic effects. Often this eruption was noticed after a single

PATIENTS, MATERIALS, AND METHODS

PATIENTS

Patients were accrued in the frame of dose-range-finding studies that examined Doxil therapy for metastatic breast and prostate cancers. Detailed analyses of the toxic effects and antitumor activity of Doxil in these patients have been published separately. Participants were randomized to receive dose levels ranging from 35 to 70 mg/m², and the drug was administered as a 1- to 2-hour intravenous infusion.

This report focuses specifically on toxic effects to the skin observed during these clinical studies.

TOXIC EFFECTS SCALE

In this study, we adopted the following basic scale from the common toxic effects criteria of the National Cancer Institute for evaluation of skin lesions: grade I indicates scattered asymptomatic lesions; grade II, scattered symptomatic lesions without functional impairment; grade III, generalized eruption with functional impairment; and grade IV, erosive or ulcerated lesions. We slightly modified this scale for hand-foot (HF) syndrome and intertrigolike eruption as follows: grade I indicates asymptomatic, mild erythema, swelling, or desquamation; grade II, painful erythema, swelling, and desquamation not precluding normal physical activity; grade III, blistering, ulceration, or swelling interfering with regular activity, including ability to wear clothing; and grade IV, diffuse or local blistering and ulceration causing infections or bedridden state.

SKIN-LESION MONITORING

Patients were instructed to report any skin eruption or discomfort. Skin examination by a dermatologist or oncologist acquainted with Doxil toxicity was performed on a regular basis at every cycle of Doxil therapy and after specific complaints. It is possible that mild skin manifestations of short duration may not have been documented. Skin biopsy was performed in selected, representative cases.
course and did not recur after additional successive treatments. Histopathological examination revealed vacuolar changes in the basal layer of the epidermis, more pronounced near hair follicles, and perivascular and bandlike lymphocytic infiltrate in superficial dermis.

**INTERTRIGOLIKE ERUPTION**

This eruption on first glance highly resembles true intertrigo and consists of erythematous patches over skin foldings (eg, axillae, groin, and waist) (Figure 5). Other areas of friction are also subject to this eruption, including the belt region and skin under adhesive tape. Involved skin may become painful and erosive and require dose reduction. In 1 patient, an additional involvement of the elbow of the dominant arm was seen.

**NEW FORMATION OF MELANOTIC MACULES**

In this eruption, flat brown macules are seen on the trunk and extremities, including palms and soles (Figure 6). The histopathological examination revealed lentiginous melanocytic hyperplasia at the basal layer (Figure 7). New melanotic macules were not necessarily preceded by the HF syndrome.

**STOMATITIS**

Besides cutaneous manifestations, another major toxic effect of Doxil is stomatitis, which was found to be the dose-limiting factor for the maximal single dose. Stomatitis was most frequent at 60 to 70 mg/m² and was less dependent on schedule (ie, intervals between treatments). With the lower doses, most patients experienced only grades I to II toxic effects and did not require dose modifications. Melanotic macules were observed in the buccal mucosa of 2 patients who had had stomatitis earlier.

**RECALL PHENOMENA TO PHYSICAL INJURY**

Anecdotal cases included a recall phenomenon of sunburn in vitiliginous areas of a patient who denied any recent sun exposure (Figure 8A) and a severe radiation therapy recall on the right chest wall in a patient who had undergone irradiation to the ribs previously (Figure 8B).

**COMMENT**

Skin and mucosal toxic effects of the soluble form of doxorubicin include generalized alopecia and mucositis of varying severity.1 Hand-foot syndrome has been reported with doxorubicin, especially when administered as a protracted continuous infusion.10 Other adverse effects include extravasation injuries and recall phenomena, ie, the exacerbation of past physical injuries in the absence of the provoking agent, such as sunburn or radiodermatitis.11

Doxil is associated with a wider range of toxic effects to the skin, some shared by the nonencapsulated
drug and some unique to the encapsulated form. The most common effect is the HF syndrome, which is more pronounced, frequent, and disabling with short dose intervals (<4 weeks). Cumulative damage seems to occur with repeated courses, and the time to resolution is prolonged, enforcing treatment delays and reduced dose intensity. In extreme cases, patients became crippled by diffuse epidermolysis of the soles. We observed some degree of HF syndrome in as many as one third of patients, a ratio much above that reported for soluble doxorubicin. Because of the variations in dose and schedule in our patient population, this study cannot give an accurate estimate of the incidence of HF syndrome for a particular Doxil regimen. However, at comparable dose intensities, these results are consistent with the incidence reported by Ranson et al and Muggia et al. With other liposome formulations of shorter circulation time, no HF syndrome has been reported.

We coined the term intertrigolike dermatitis to discriminate skin lesions that may have resulted from the same mechanism of HF syndrome but definitely constitute a separate morphologic entity. Other authors have observed similar reactions.

The diffuse follicular rash and the intertrigolike eruptions are not mentioned among common skin eruptions due to doxorubicin or any other chemotherapeutic agents. Although the follicular rash is mostly asymptomatic, the intertrigolike toxic effect to the skin is most disturbing.

Accelerated formation of nevi was reported in children who had received chemotherapy for hematologic malignant neoplasms. We suggest that some melanotic macules observed herein, which now represent melanocytic hyperplasia, may develop into melanocytic nevi.
Interestingly, alopecia, which is the rule for patients receiving doxorubicin, was not observed in our patients. Likewise, Doxil did not cause extravasation injuries. In fact, liposome encapsulation protects patients from the vesicant action of doxorubicin.\(^\text{17}\)

The rapid turnover rate of keratinocytes makes these cells most susceptible to cytotoxic damage induced by chemotherapy.\(^\text{18}\) The pattern of damage is dictated not only by the inflicting drug but also by the method of administration. Compared with doxorubicin, Doxil has an extremely long circulation time, and it preferably localizes in the skin and deposits a substantial fraction of the administered drug there.\(^\text{19}\) Inflamed skin is especially susceptible to liposome localization, as was demonstrated in a murine model of psoriatic lesions.\(^\text{20}\) The palms, soles, and areas of repeated friction or trauma apparently achieve increased concentrations of Doxil as a result of the rich capillary network at their thickened papillary dermis and increased blood flow. The increased concentrations of the drug damage the skin, as does the protracted in situ slow-release effect. Another analogous example is fluorouracil. Its rapid intravenous infusion is associated mainly with mucositis and conjunctivitis, whereas continuous intravenous infusions are associated with significant HF syndrome.\(^\text{21}\)

Treatment of HF syndrome is mainly palliative and consists of wet dressings and emollient creams. Medium- and high-potency topical corticosteroids have proven to be of little value.

The profile of toxic effects of Doxil to the skin reflects its unique pharmacokinetics and tissue distribution. Although the soluble and the liposomal formulations contain doxorubicin as their active component, their toxicities are those of 2 different drugs.

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