

Extravasation of Liposomal Doxorubicin Induces Irritant Reaction without Vesicant Injury

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Abstract. Anthracycline extravasation is an uncommon but very serious complication. Very few data are available in the literature concerning the consequences and the management of extravasation of liposomal doxorubicin. This report describes the cases of two patients with liposomal doxorubicin extravasation who developed irritant reaction without vesicant or necrotic lesions. It is concordant with other cases described in the literature and suggests that extravasation of liposomal doxorubicin can be relatively well tolerated. The process applied to extravasations of irritant and non-vesicant agents could be used to manage extravasations of liposomal doxorubicin.

Extravasation is defined as the escape of a chemotherapeutic agent from a vessel into the surrounding tissues. Extravasation of anthracycline is one of the most dreaded complications and represents an extremely severe toxicity (1), with an incidence ranging between 0.01 and 1.0% (2). Myocet[®] and Caelyx[®]/Doxil[®] are liposomal formulations of the antineoplastic drug doxorubicin, with an improved therapeutic index compared with conventional doxorubicin (3). The encapsulation of doxorubicin within a macromolecular vector, the liposome, significantly modifies its distribution volume, diminishing its diffusion and, potentially, its toxicity in healthy tissues (4). However, consequences on skin and soft tissue are

unknown when an extravasation of liposomal doxorubicin occurs. The present report describes the cases of two patients with extravasation of liposomal doxorubicin.

Case Report 1

A 52-year-old woman was treated for breast cancer with liver and bone metastases in our institution. Chemotherapy with non-pegylated liposomal doxorubicin (Myocet[®]) at 60 mg/m² and cyclophosphamide at 600 mg/m² was administered. The third cycle of liposomal doxorubicin and cyclophosphamide was infused via an implantable central venous access device (CVAD) with a Huber needle for one hour and twenty minutes. During the infusion, the patient did not complain for pain and the nurse did not notice anything unusual. Two days later, the patient notified an erythema and three days later she contacted her physician because she felt pain around the CVAD. A large erythema measuring 19×10 cm, including a central inflammatory red, warm and painful lesion measuring 6×4 cm, were observed. No ulceration or necrosis was identified. She experienced no fever, blood cultures were sterile, and an ultrasound showed non-drainable fluid collection displayed around the CVAD. Local and systemic analgesics with systemic antibiotics were administered to the patient. Three days later, the size of the red, hot centre had increased and the erythema had become more painful (Figure 1). The plastic surgeon decided not to remove the CVAD and dexrazoxane was infused, although the extravasation had occurred 8 days earlier. Pain and warmth progressively decreased in two days. Erythema remained for 30 days with a cutaneous desquamation within the last 10 days. The patient recovered almost completely in three months with the persistence of a small area of hyperpigmentation (Figure 2).

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Figure 1. Day 8 after non-pegylated liposomal doxorubicin extravasation: irritant reaction without vesicant or necrotic lesion.



Figure 2. Three months after non-pegylated liposomal doxorubicin extravasation: recovery with an area of hyperpigmentation.

Case Report 2

The second case report concerns a 71-year-old woman treated with pegylated liposomal doxorubicin (Caelyx®) and carboplatin for ovarian cancer with brain and liver metastases. The first cycle of chemotherapy was given through her CVAD with a Huber needle. Fifteen minutes after the beginning of pegylated liposomal doxorubicin infusion, a red liquid was noted under the clean dressing. The infusion was stopped, and surgical washing and aspiration without debridement was performed. Intravenous dexrazoxane was given 24 hours after the extravasation. In the first 24 hours, the patient developed an inflammatory skin reaction with a mild erythema



Figure 3. Day 1 after pegylated liposomal doxorubicin extravasation: inflammatory erythema.



Figure 4. Three months after pegylated liposomal doxorubicin extravasation: complete recovery.

(Figure 3); she did not develop ulcerative or necrotic wounds. Four weeks later hyperpigmentation at the site of drug extravasation was noted, with complete recovery in two months (Figure 4).

Discussion

Chemotherapeutic agents are classified into two broad categories based on the degree of tissue damage related to extravasation: irritant or vesicant agents. Anthracyclines are the most common vesicant chemotherapy agents. They may cause severe and lasting tissue injury and necrosis, with serious aesthetic and functional sequelae in the long term. Management of anthracycline extravasation is an emergency and combines medical and surgical care, with dexrazoxane infusion (5) and early surgical management (2). Liposomal doxorubicin formulations have distinctive pharmacokinetics and toxicity profiles compared to those for free doxorubicin, with similar efficacy (6). Liposomes are vesicles consisting of spherical phospholipid bilayers, which encapsulate doxorubicin or other drugs. Liposomal doxorubicin was designed to reduce the cardiotoxicity of doxorubicin while preserving its antitumor efficacy. The rationale is based on the fact that intravenously injected liposomes cannot escape the vascular space in sites that have tight capillary junctions, such as the heart muscle. Preclinical studies have demonstrated that liposomal formulations reduce the peak distribution of doxorubicin because 90% of circulating drug is encapsulated in liposomes and free doxorubicin is progressively and slowly released into blood circulation. Compared to non-pegylated liposomal doxorubicin, pegylated liposomal doxorubicin presents a pharmacokinetic profile characterized by a longer duration of exposure and an accumulation in the skin and the mucosa, responsible for the occurrence of palmar-plantar erythrodysesthesia and mucositis. To the best of our knowledge, there are two other case reports (7, 8) describing irritant injury following extravasation of pegylated liposomal doxorubicin Caelyx[®]/Doxil[®]. Nevertheless, one instance of vesicant injury has been reported (9). In phase II and III clinical trials assessing liposomal doxorubicin efficacy and tolerance, two extravasations of non-pegylated liposomal doxorubicin Myocet[®] were reported. They resulted in mild inflammation without tissue damage (10). The two present reports reinforce the fact that extravasation of liposomal doxorubicin can be relatively well tolerated with mild cutaneous reaction and without necrosis or vesicant effect. The exact mechanism of lack of vesicant injury following extravasation of liposomal doxorubicin is unclear. It may be that liposomes protect skin and soft tissue from free doxorubicin and minimize tissue damage. Moreover, with the use of non-pegylated liposomal doxorubicin, cutaneous reaction seems to be delayed. Indeed, liposomal formulations delay liberation of free doxorubicin and explain the possible benefit of delayed administration of dexrazoxane. According to our experience, the management applied for extravasation of irritant and non-vesicant agents can be used to manage extravasation of liposomal doxorubicin.

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