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Liposomal Cytarabine–Daunorubicin (CPX-351) Extravasation: Case Report and Literature Review

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Abstract. *Background: Liposomal formulation of anthracyclines provide better systemic and organ-specific tolerance, with potential for less local tissue damage during extravasation. Several small series have reported that most liposomal anthracycline extravasations are consistent with irritant injury without tissue necrosis. There have been no reports published regarding the clinical effects of extravasation of liposomal cytarabine-daunorubicin (CPX-351). Case Report: The patient received CPX-351 for relapsed acute myelogenous leukemia via a left chest wall port-a-catheter. The catheter became dislodged. Once symptoms developed, the infusion was discontinued, with observations demonstrating an 8-cm region of edema, warmth, no erythema, and no drainage. Limited supportive management was performed. Physical examination the following day demonstrated no evidence of necrosis, and erythema resolved completely without additional intervention. Conclusion: CPX-351 extravasation behaving as an irritant is consistent with the reports of other liposomal anthracyclines.*

Liposomal formulations of chemotherapies provide better systemic and organ-specific tolerance, with potential for less local tissue damage during extravasation. Several small series have reported that most liposomal anthracycline extravasations manifest as irritant injury without tissue necrosis. To our knowledge, there have been no reports published regarding the clinical effects of extravasation of liposomal cytarabine–daunorubicin (CPX-351), a formulation that has shown a survival advantage in patients undergoing induction therapy for secondary acute myelogenous leukemia (AML) (1). The aim of this publication is to describe a case of CPX-351 extravasation that is consistent with an irritant injury, and then compare our experience with cases of other liposomal anthracyclines that have been reported.

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Anthracycline extravasation. In the context of cancer therapy, extravasation refers to the leakage of a chemotherapeutic drug from an intravenous (*i.v.*) administration site into the surrounding subcutaneous or subdermal tissue. Extravasated drugs are classified based on their potential for harm as a vesicant or irritant. Vesicants, such as daunorubicin and doxorubicin, are defined by their ability to cause necrosis and long-lasting damage of the tissue at the site of extravasation. For instance, vesicant-related wounds typically lack granulation tissue and may expand instead of heal, resulting in permanent damage to underlying nerves, muscles, and vasculature. Irritants, such as cytarabine, pose less risk to patients and typically cause temporary symptoms of inflammation that include subjective burning and pain, without desquamation or tissue necrosis (2). However, these distinctions are not absolute and a chemotherapeutic drug can exhibit characteristics of both. It has been suggested that irritants can display vesicant-like properties with increasing amounts of extravasation (3). Therefore, in addition to the classification of a drug, the amount of drug extravasated may also be an important factor affecting the amount of tissue damage or necrosis that occurs. Management of extravasation of a vesicant requires discontinuation of the therapy, elevation of the affected extremity, aspiration of fluid out of the line/catheter, and emergent medical therapy with evaluation for surgical intervention. Medical therapy for anthracycline extravasation includes dexrazoxane, or dimethyl sulfonamide when dexrazoxane is not immediately available (4).

In the past several decades several liposomal anthracycline formuIations have been developed and approved by the United States Food and Drug Administration. Single-agent liposomal anthracyclines were developed in order to reduce toxicity while possibly enhancing antitumor effects by means of superior tissue distribution and pharmacokinetics. These therapies include liposomal doxorubicin (Myocet), liposomal and pegylated doxorubicin (Doxil), liposomal daunorubicin (DaunoXome). In

addition to better systemic and organ-specific tolerance, the liposomal formulation of these anthracyclines has the potential for less local tissue damage during episodes of extravasation. This may be mediated by the liposomal formulation reducing the diffusive capacity of the anthracycline into nearby tissue. Several case reports and case series have reported that almost all liposomal anthracycline extravasations have been consistent with irritant injury without tissue necrosis (5-8). In 2017, the FDA approved liposomal cytarabine-daunorubicin (CPX-351) for the treatment of newly-diagnosed secondary acute myelogenous leukemia AML. To our knowledge, there have been no reports published regarding the clinical effects of extravasation of liposomal cytarabine-daunorubicin.

Background of liposomal daunorubicin-cytarabine (CPX-351). CPX-351 is a liposomal formulation of a fixed concentration of cytarabine and daunorubicin. The two drugs are present inside the liposome in a 5:1 molar ratio. The liposome membrane is composed of distearoylphosphatidylcholine, distearoylphosphatidylglycerol and cholesterol in a 7:2:1 molar ratio. These liposomes have a nominal diameter of approximately 100 nm and are suspended in sucrose (9). The phase III trial of CPX-351 for secondary AML in elderly patients included 309 patients who were randomized to 100 units/m^2 CPX-351 days 1, 3 and 5 *versus* standard 7+3 chemotherapy (100 mg/m^2 cytarabine days 1-7, 60 mg/m^2 daunorubicin days 1-3). At a median follow-up of 21 months, a median overall survival (OS) of 9.5 months *versus* 5.9 months favored CPX-351 compared to standard 7+3 induction chemotherapy (p=0.003). Kaplan–Meier estimates of 2-year OS were 31% and 12%. Importantly, there were more patients in the CPX-351 arm who went on to receive allogeneic hematopoietic stem cell transplantation (HSCT) than in the 7+3 arm (34% *vs.* 25%, p=0.049) (1).

There was a chemotherapy exposure–response analysis of the aforementioned phase III trial. The cumulative doses of cytarabine and daunorubicin required to achieve survival benefit with CPX-351 were 77% lower than the cumulative doses used in the standard 7+3 arm (10). Furthermore, it has been demonstrated in animal studies that the relative heart exposure to daunorubicin is 100-times less with CPX-351 compared to free drug (11). These phenomena suggest that the liposomal formulation of CPX-351 may also have less of a potential to result in the typical sequelae seen when anthracyclines extravasate into the surrounding tissue. Instead, perhaps extravasation with CPX-351 may behave more similarly to chemotherapy agents classified as irritant.

Case Report

The patient's oncologicaI history dates to December 2007 when she developed excessive bleeding after colposcopy at 31 years of age. Complete blood count revealed the presence of peripheral blast cells. Bone marrow biopsy revealed AML and normal female cytogenetics; molecular studies were not performed. She received induction therapy with idarubicin and cytarabine, followed by a second cycle of induction of the same agents. Bone marrow biopsy after the second induction cycle demonstrated hypocellular marrow but with the presence of excess blasts. Subsequently, she received high-dose cytarabine. Approximately 6 months after the initial diagnosis of AML, bone marrow biopsy demonstrated complete remission. She underwent allogeneic HSCT at that time from an ABO-incompatible sibling matched-related donor. The conditioning regimen included total body irradiation, cytarabine, and cyclophosphamide. Bone marrow biopsy performed approximately 14 months after allogeneic HSCT revealed relapsed AML involving 90% of the marrow. The patient then received CPX-351 on clinical trial for relapsed AML. The dose prescribed was 44 mg/m^2 daunorubicin plus 100 mg/m^2 cytarabine on treatment days 1, 3, and 5. Bone marrow biopsy following salvage therapy demonstrated no excess blasts, with fluctuations of the absolute neutrophil count and platelet count above and below the thresholds for complete remission. Repeat bone marrow biopsy approximately 10 weeks after salvage CPX-351 revealed relapsed AML involving 40% of the marrow.

She then received another course of CPX-351 (44 mg/m^2 daunorubicin plus 100 mg/m^2 cytarabine on treatment days 1, 3, and 5) with the goal of eradicating excess blasts prior to proceeding with second transplantation. The infusion of CPX-351 was *via* a left chest wall port-a-catheter that had been placed prior to induction therapy approximately 2 years earlier. The port had been accessed successfully multiple times in the recent past. On treatment day 3 of CPX-351 (December 3, 2009), the patient got out of the hospital bed to use the bathroom. She recalled stepping on the *i.v.* line that was infusing CPX-351 into her port-a-catheter. Approximately 15 minutes into the 90-minute infusion of CPX-351 she noticed swelling around the site of the port-a-catheter. The infusion was discontinued immediately and the patient was examined by the covering physician who documented an 8 cm region of edema, mild warmth, no erythema, and no drainage. Aspiration of the drug was attempted. The diagnosis of chemotherapy extravasation was made. She was reassessed by the covering physician 45 minutes later at which time she had developed pain and mild erythema at the site. The small region of erythema was demarcated.

Management was initiated shortly thereafter with the plan for topical dimethylsulfoxide (DMSO) every 8 hours, 1,000 mg/m^2 dexrazoxane for 3 consecutive days, and empiric *i.v.* vancomycin. The episode was immediately reported to the regulatory agency and study sponsor. Physical examination on the following morning, less than 8 hours after the episode, demonstrated no evidence of necrosis, and erythema receding away from the previous zone of demarcation. The region was

tender and warm to palpation. Upon further discussion amongst the attending physician, study sponsor medical director and the patient, the decision was made to discontinue CPX-351 and all medical interventions for extravasation (DMSO, dexrazoxane). Withdrawal of treatment was implemented because the patient was doing well and it was not known whether these agents would react with the liposomal formulation of the chemotherapies. By that time, the patient had received one dose of dexrazoxane and one dose of topical DMSO. The mild signs and symptoms of irritation at the extravasation site completed resolved after several days without any signs of necrosis or infection manifesting. The subsequent hospital course was complicated by worsening liver tests and persistent peripheral blasts. Workup included transjugular liver biopsy, demonstrating moderate hepatic venous outflow obstruction with the clinical correlation consistent with veno-occlusive disease, which ultimately contributed to the patient's death shortly thereafter.

Discussion

Conventional daunorubicin, an anthracycline, has been described as a well-known vesicant. Extravasation of Iiposomal daunorubicin (DaunoXome) has been reported to result in mild injury without tissue necrosis or long-term sequelae in a case series of four patients who received this therapy for Kaposi sarcoma (12). Preclinical data using a mouse model suggest that liposomal pegylated doxorubicin has less vesicant behavior compared to that shown in historical experiments (13, 14). The preclinical evidence has been supported by several human case reports that describe only irritant injury after extravasation of pegylated and non-pegylated liposomal doxorubicin in patients with metastatic disease (5, 6, 7, 15). Furthermore, a phase II clinical trial evaluating non-pegylated liposomal doxorubicin for lymphoma in patients of advanced age or with cardiac disease described two patients who experienced extravasation, both resulting in mild inflammation without tissue damage (8). Nonetheless, there have been reports of extravasation injury more consistent with vesicant classification with pegylated liposomal doxorubicin (16).

Our current case of CPX-351 extravasation behaving as an irritant is consistent with the aforementioned reports of liposomal anthracycline extravasation. Our patient developed localized edema, mild warmth and pain without erythema, and drainage shortly after extravasation of CPX-351 occurred. Unlike the typical clinical progression of vesicants, the patient did not display any signs of necrosis and erythema began to recede less than 8 hours after extravasation, and had completely resolved several days later. The improvement occurred despite receiving only a single dose of DMSO and dexrazoxane. It is unlikely that the single dose of these agents prevented tissue necrosis. Given the temporary and inflammatory nature of the patient's symptoms, extravasation of CPX-351 more closely aligned with the behavior of an irritant compared to the vesicant nature of conventional daunorubicin. Unfortunately, the amount of extravasated drug is not known and may have been a confounding variable in the patient's clinical course. Our current experience suggests that at least some cases of extravasation of CPX-351 can be managed as irritant extravasation without the need for dexrazoxane or surgical intervention. More data are required to further support the possibility that CPX-351 is an irritant when extravated.

Consent for Publication

The case report includes a description of a patient who is deceased. The University of California Internal Review Board has approved this study and considers it exempt since it does not contain any identifying information.

Availability of Data and Materials

The data generated and/or analyzed during the current study are not publicly available due to that fact that this is a case report and all data are contained within the electronic medical record. Additional data are available from the corresponding author on reasonable request.

Competing Interests

GH declares that he has no completing interests. CO is a sub-investigator on a clinical trial that is funded by Jazz Pharmaceuticals. GS is the principal investigator on a clinical trial that is funded by Jazz Pharmaceuticals.

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