Case Report

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Management of Daunorubicin Extravasation with Dexrazoxane in a Child

Mitra Ardakani Moghadam[1] , Maryam Noory[2] , Mohammad Kaji Yazdi[1]

1. Pediatric Hematology and Oncology Department, Tehran University of Medical Sciences, Tehran, Iran.
2. Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran.

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Running Title Daunorubicin Extravasation Management with Dexrazoxane

ABSTRACT

The extravasation of anthracyclines during chemotherapy can harm the surrounding soft tissue, necessitating prompt management. In this report, we discuss a four-year-old boy who was treated with daunorubicin (an anthracycline) for acute lymphoblastic leukemia (ALL), during which extravasation occurred, and we addressed this issue using dexrazoxane. A four-year-old boy undergoing chemotherapy for ALL received daunorubicin, which extravasated. This led to cutaneous inflammation, prompting the discontinuation of the drug. Dexrazoxane was administered for three days, along with dimethyl sulfoxide spray. Severe cutaneous irritation and burning sensations occurred immediately after the application of the spray and continued until the site was washed. Subsequently, the patient developed a catheter-related infection, exhibiting severe dyspnea, hypotension, and pulmonary edema. He was admitted to the pediatric intensive care unit for appropriate treatment. Dexrazoxane is a valuable option for managing anthracycline extravasation; however, our case revealed a severe reaction to the initial dose of dimethyl sulfoxide spray, suggesting that dexrazoxane may be the safer choice for handling such extravasation cases.

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Introduction

Acute lymphoblastic leukemia (ALL) is the most frequently diagnosed cancer in children under 15 years of age, with a median diagnosis age of 15 years [1]. In 2019, it was estimated that nearly 6,000 new cases and 1,500 deaths from ALL would occur, reflecting an age-adjusted incidence rate of 1.38 per 100,000 individuals annually in the US, with the highest incidence observed between one and four years of age [2].

Daunorubicin is an anti-neoplastic drug that has received approval from the Food and Drug Administration (FDA) for use as remission induction therapy in conjunction with another cytotoxic agent for acute non-lymphocytic leukemias, including acute myelogenous, promyelocytic, and erythroid leukemias in adults, as well as ALL in both children and adults [3,4].

Clinical research indicates that daunorubicin extends the duration of complete remission in childhood ALL when combined with vincristine-prednisone,

*** Corresponding Author:**
Mohammad Kaji Yazdi
Address: *Pediatric Hematology and Oncology Department, Tehran University of Medical Sciences, Tehran, Iran.*
E-mail: *mkajiyazdi50@gmail.com*

compared to the use of vincristine and prednisone alone. However, there is no evidence regarding its effectiveness as part of consolidation therapy. In adult ALL, daunorubicin significantly enhances the complete remission rate from 47% to 83% when added to the triple therapy of vincristine, prednisone, and L-asparaginase; however, it does not influence the duration of complete remission [5]. Daunorubicin must be administered intravenously via rapidly flowing infusions. It cannot be given subcutaneously or intramuscularly, as this can lead to severe local tissue necrosis due to the extravasation of the drug into surrounding tissues. If extravasation occurs, the infusion should be halted immediately, and cold compresses should be applied [6].

Dexrazoxane has also been indicated for the prevention of tissue damage caused by the extravasation of anthracyclines, which can happen during the administration of these chemotherapeutic agents [7]. However, there is limited data on the use of dexrazoxane in cases of daunorubicin extravasation. Consequently, this study aims to report on a 4-year-old boy with ALL who experienced daunorubicin extravasation.

Case presentation

A four-year-old boy who underwent chemotherapy for ALL treatment two years ago received daunorubicin (25 mg in 100 cc normal saline) at this facility. During the last session, daunorubicin extravasated at the catheter insertion site (about 20 cc of the solution around the port catheter), leading to cutaneous inflammation and prompting an immediate halt to the drug administration.

For three days, dexrazoxane was administered alongside dimethyl sulfoxide spray (standard dose). Severe cutaneous irritation and a burning sensation occurred immediately after the spray application and persisted until the site was washed. We did not use any more of the dimethyl sulfoxide spray.

After receiving three doses of dexrazoxane (1000 mg/m^2 for the first two days and 500 mg/m^2 for the third), the patient developed diarrhea, which progressed to fecal incontinence. At this point, the sclera became icteric, prompting us to request serum liver function tests, which revealed a significant increase in hepatic enzymes. Hepatic involvement was treated with Livergel at 70 mg daily and Ursobil at 300 mg daily. The diarrhea lasted for four days without any response to treatment.

Three days later, the patient developed fever, severe dyspnea, hypotension, and pulmonary edema. He was admitted to the Pediatric Intensive Care Unit (PICU), where Lasix and antibiotics were administered due to suspicion of septic shock from a vascular catheter infection, as there were signs of cellulitis at the catheter site. An ultrasonogram was performed, revealing vascular catheter thrombosis. The vascular access was removed, and the patient was treated and discharged in good condition, without the need for a graft at the extravasation site.

Discussion

Chemotherapy extravasation, which refers to the accidental leakage of cytotoxic drugs into adjacent tissues, represents a major complication in cancer treatments, potentially resulting in significant tissue damage and long-lasting effects [8]. Daunorubicin belongs to the anthracycline class of antibiotics. It demonstrates its anti-neoplastic effects through several mechanisms, including both anti-mitotic and anti-cytotoxic actions. The drug intercalates between DNA base pairs, leading to the uncoiling of the DNA double helix and inhibiting the topoisomerase II enzyme, which results in both single- and double-strand breaks, thereby hindering DNA and RNA synthesis [9].

The extravasation of antineoplastic agents such as daunorubicin is an unfortunate and troubling occurrence that can happen quite easily. It may lead to severe and irreversible local damage. If not addressed, vesicant chemotherapy extravasation can potentially result in tissue necrosis, functional impairment, and permanent disfigurement [10]. In this study, we present a case of a 4-year-old boy diagnosed with ALL who experienced daunorubicin extravasation. Our patient developed cutaneous inflammation and irritation shortly after the infusion of daunorubicin. The administration of the drug was halted, and we prescribed dexrazoxane for this condition, along with dimethyl sulfoxide spray. The spray caused significant acute irritation and was quickly washed off the skin.

Dimethyl sulfoxide is an organosulfur solvent that is applied topically to enhance the absorption of the extravasated agent [11]. It also possesses free-radical scavenging abilities. Its effectiveness has been noted in a few studies [12]. The application of topical dimethyl sulfoxide (99%) as an antidote for anthracycline extravasation and mitomycin C is supported by level IV-B evidence [13,14]. Dimethyl sulfoxide is available in solvent form, and a dropper

is typically utilized to apply drops onto the affected skin. It is recommended to use a topical application of 99% dimethyl sulfoxide, administering four drops per 10 cm², up to twice the size of the extravasation area. In instances of anthracycline extravasation, the combination of dimethyl sulfoxide and cooling is frequently described as the initial treatment for minor extravasation, particularly when dexrazoxane is unavailable [15]. We administered dimethyl sulfoxide, and our patient experienced severe symptoms such as irritation and burning. A systematic review indicated that dimethyl sulfoxide may lead to various adverse reactions, which are generally transient and mild. The dosage of dimethyl sulfoxide is crucial in determining the likelihood of adverse reactions. It appears to be safe for use in small doses [16]. We prepared the medication at the standard dose, and a severe reaction was noted after just one spray. To our knowledge, there are few reports concerning severe cutaneous reactions associated with dimethyl sulfoxide. However, it is possible that dimethyl sulfoxide spray is accompanied by more skin reactions in paediatrics, and this issue should be investigated in further studies.

As previously recommended in the studies mentioned above, dexrazoxane is more effective than dimethyl sulfoxide for managing extravasation. The common side effects associated with dexrazoxane include dose-limiting myelotoxicity, such as neutropenia, leukopenia, granulocytopenia, and thrombocytopenia, which closely resemble the side effect profile of anthracyclines. Consequently, it can be difficult to differentiate the adverse effects resulting from dexrazoxane from those associated with anthracycline chemotherapy. Additional side effects may include nausea and vomiting, increased renal excretion of iron and zinc, hair loss, mucositis, and inconsistent elevations in liver enzymes (alanine aminotransferase/aspartate aminotransferase), as well as injection site reactions like pain and superficial phlebitis. This has led to the recommendation that dexrazoxane be administered through a large vein [17-19]. In our case, these adverse effects were not observed, and the drug was effective and safe. It should be noted that we could not find any correlation between extravasation and catheter infection; they were different events, but simultaneous. Similarly, Romero et al. reported that dexrazoxane is a preferred option for managing the extravasation of liposomal anthracyclines [20]. Therefore, it appears that further studies are needed to evaluate the effects of dexrazoxane to support its recommendation as a treatment option for extravasation management.

Our case pertained to a catheter-related infection, which is a prevalent type of infection among pediatric patients with catheters in hospitals [21]. We handled the case effectively, and the patient was discharged in stable condition. This case was particularly noteworthy due to its severe reaction to dimethyl sulfoxide and the positive response to dexrazoxane.

Conclusion

Dexrazoxane is an effective option for managing anthracycline extravasations and can adequately address this issue in patients. While some research has suggested the use of dimethyl sulfoxide for treating extravasation, our case revealed a significant acute skin reaction (including inflammation and burning). It appears that oncologists should be informed about this reaction, as it has been reported less frequently.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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