

Case Report

Severe Tissue Necrosis after Low-Concentration Cisplatin Extravasation: A Case Report and Review of Expert Guidelines and Literature

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Keywords

Cisplatin · Extravasation · Tissue necrosis · Cytotoxic

Abstract

A 65-year-old man was treated with a course of rituximab, cisplatin, and cytarabine. During the second cycle, a volume of 40–50 mL of 0.3 mg/mL cisplatin was extravasated. The patient was treated with a cold pack multiple times a day and cutaneous application of dimethyl sulfoxide cream three times a day for a week. In the months after the extravasation, the patient suffered from worsened swelling and redness and a black crust had formed on the wound. The patient was diagnosed with chemical phlebitis. After watchful waiting for 3 months, antibiotic therapy was started. After 7 months, the wound had healed. On the contrary to what is described in our case, no extravasation guideline classifies cisplatin in a concentration lower than 0.4 mg/ml as a vesicant. The different guidelines also present conflicting recommendations on how to treat the extravasation of cisplatin. In three previous case reports, severe effects of cisplatin extravasation after infusion at low concentration were described as well. We recommend that the findings from our case report are incorporated into extravasation guidelines to ensure optimal treatment of cisplatin extravasations.

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Introduction and Background

Extravasation of chemotherapy is the unintended subcutaneous or subdermal leakage of an intravenous administered cytotoxic agent [1]. Considering the cytotoxic effects of chemotherapy, the extravasation of these agents has the potential to cause significant damage to the patient. It is therefore of great importance to act quickly and appropriately when extravasation occurs. How to act depends on the characteristics of the agent and the extent to which it may cause tissue damage [1, 2]. In this case report, we describe the case of an extravasation of low-concentrated cisplatin leading to severe chemical phlebitis.

Case Presentation

In November 2018, a 65-year-old man was referred to our hospital for treatment of mantle cell lymphoma stadium III. In January 2019, the patient was treated in the study. Patients are treated with six alternating courses of rituximab, cyclophosphamide, doxorubicin, vincristine (R-CHOP), and rituximab, cisplatin, cytarabine (R-DHAP) followed by an autologous stem cell transplant and 3 years of rituximab maintenance therapy. During the second R-DHAP cycle in April 2019, cisplatin was administered over 24 h as a dose of 177 mg (100 mg/m^2 , Accord Healthcare, Ahmedabad, India) dissolved in 577 mL of 0.9% saline. During administration, the patient noticed that his arm was swollen and had turned red. It was then discovered that an estimated volume of 40–50 mL of cisplatin was extravasated. Several measures were taken after discovering the extravasation according to the extravasation protocol used in our hospital. The infusion was stopped and withdrawal of the extravasated fluid from the arm was attempted. This was unsuccessful. Then, the lesion was cooled for 1 h and dimethyl sulfoxide (DMSO) 500-mg/g cream was applied. Redness of the skin, which covered an area of $5 \times 6 \text{ cm}$, was marked. Then, cisplatin therapy was continued using a new peripheral intravenous line in the opposite arm. The patient was consequently treated with a cold pack multiple times during the next day and cutaneous application of DMSO three times a day for a week.

After 2 weeks, the wound was observed during a control visit. The wound was red, indurated, and a crust had formed. According to the patient, blisters had formed on the wound during the previous week. The patient was treated with amoxicillin 500 mg three times a day for a week.

One month after the extravasation, the patient came to the emergency room. The patient suffered from a worsening stinging pain, limiting movement of the arm. The arm was swollen, and a black crust had formed on the wound, see Figure 1. The patient described that his arm occasionally turned from red to purple. The patient was diagnosed with dry necrosis by chemical phlebitis. An expectative policy of watchful waiting was agreed upon.

In July 2019, the patient was hospitalized for an autologous stem cell transplant. During hospitalization, the black crust was still present, and the redness of the wound worsened (see Fig. 2). The patient was treated with flucloxacillin 1,000 mg four times a day which was continued after hospitalization. In September 2019, this was converted to amoxicillin/clavulanic acid 500/125 mg three times a day.

In October 2019, the patient was seen during a control visit. The patient still suffered from the pain of the wound on his arm and the wound had an unpleasant smell. A microbiological culture of the wound was taken which proved positive for *Klebsiella pneumoniae* and *Citrobacter freundii* complex. Based on the established sensitivity of the bacteria, the patient was treated with trimethoprim/sulfamethoxazole 800/160 mg twice a day for a month. In November 2019, the wound had healed, see Figure 3.



Fig. 1. Wound 1 month after the extravasation.

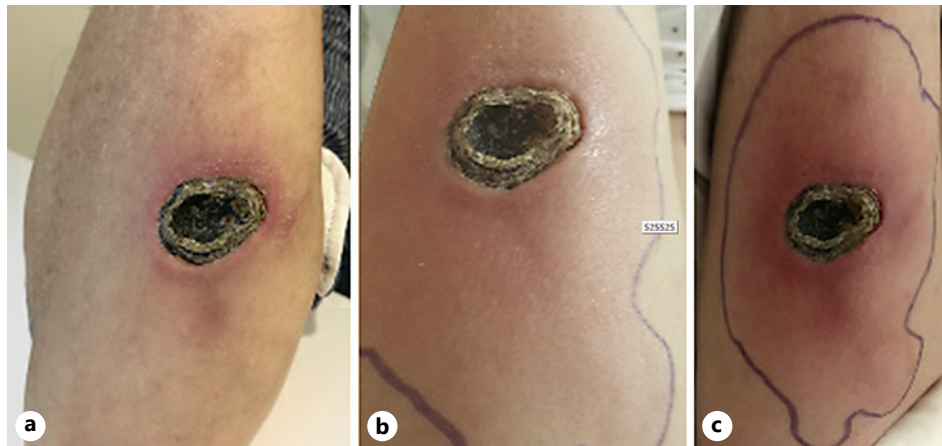


Fig. 2. Developing inflammation 2 months after the extravasation. Pictures were taken in a time span of 1 week during hospitalization. Increasing redness and swelling can be seen.

Discussion and Conclusion

As soon as an extravasation occurs, rapid intervention to minimize negative effects is crucial. In order to allow healthcare staff to perform the required steps in a timely manner, most clinics have emergency treatment procedures available at hand at any location where chemotherapy is administered. These procedures usually contain a description of general measures such as cessation of the infusion and subsequent attempts to aspirate the chemotherapeutic agent, followed by a list of drug-specific treatments that should be applied. For this drug-specific management, several national or international guidelines exist. In our country, the overall procedure for the extravasation of cytotoxic drugs has been compiled by

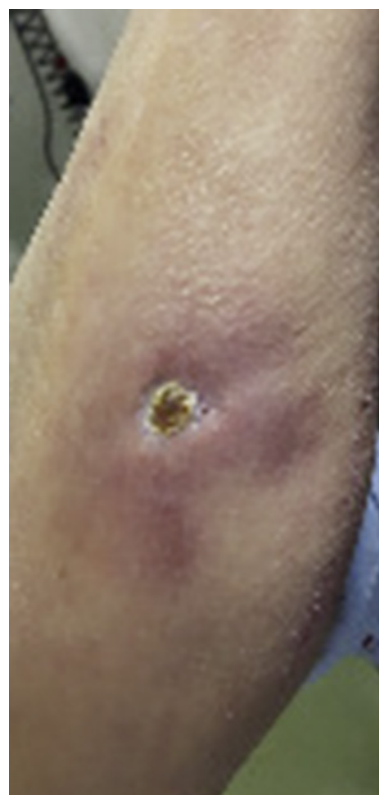


Fig. 3. Cured wound. The picture was taken 7 months post extravasation.

the National Society of Hospital Pharmacy (NVZA) and is updated every year [2]. According to this guideline, severe reactions to cisplatin are not to be expected. This is in accordance with the European guideline from the European Society of Medical Oncology (ESMO) and European Oncology Nursing Society (EONS), which classifies cisplatin as an irritant rather than a vesicant [1]. Several other guidelines make a distinction in the effects of cisplatin extravasation based on the concentration of the infusion [3–6]. Notably, no guideline that has been published in the literature classifies cisplatin as a vesicant or necrosis-causing agent when diluted further than 0,4 mg/mL. Table 1 gives an overview of the classification and treatment of cisplatin extravasation from published guidelines. Interestingly, most guidelines advocate the application of cold compresses. This can help reduce pain and local inflammation by causing vasoconstriction, which will reduce the further spreading of the drug. In contrast, the ESMO-EONS guideline proposes hot compresses, possibly with the aim of causing vasodilatation leading to reabsorption of the drug from the tissue site. In general, cold is recommended for DNA-binding agents, and cisplatin falls into this class [4–7]. Thus, we propose to follow the majority of guidelines when choosing between hot and cold compresses for cisplatin, irrespective of its concentration.

A relatively large number of case descriptions where highly concentrated cisplatin caused tissue damage and necrosis has been published between 1980 and 2010. An excellent review of these cases is available in Mader et al. [7]. In addition, a large case series reporting on the outcome of multiple chemotherapy extravasations including 18 cisplatin cases as well as an open prospective study into the efficacy of topical DMSO for extravasation including 44 cisplatin cases, are available [8, 9]. Unfortunately, neither of these two publications provide data on the concentration of the cisplatin infusions. Another study looking specifically at platinum in various biopsies of 3 patients who experienced extravasation after a platinum infusion (cisplatin in 2 cases and oxaliplatin in 1 case) describes platinum concentrations of

Table 1. Cisplatin extravasation effects and management in published guidelines

Guideline	Country	Classification of cisplatin	Management of cisplatin extravasation	Ref
NVZA	The Netherlands	No serious reactions	Local cooling and DMSO [§] 3 times daily for 7 days	[2]
ESMO-EONS	Pan-European	Irritant	Warm compresses	[1]
ASORS*	Germany	>0.4 mg/mL: vesicant <0.4 mg/mL: irritant	>0.4 mg/mL: dry cooling and DMSO [§] 4–6 times per day for not less than 7 days, sodium thiosulfate 4% iv [#] or sc [#] (2 mL per mg of cisplatin extravasation)	[3]
CEPSP – CEPO*	Canada	≥0.4 mg/mL: vesicant <0.4 mg/mL: irritant	Cold dry compresses and DMSO [§] 4 drops/10 cm ² every 6–8 h for 7–14 days	[4]
Up to Date	USA	>0.5 mg/mL: vesicant	>0.5 mg/mL: sodium thiosulfate 4% sc [#] (2 mL per mg of cisplatin extravasation)	[5]
NSW gov-EviQ	Australia	>0.5 mg/mL: vesicant	Cold compresses	[6]

*ASORS, The German Working Group for Supportive Care in Cancer; CEPSP, Comité de l'évolution de la pratique des soins pharmaceutiques; CEPO, Comité de l'évolution des pratiques en oncologie; NSWgov, New South Wales government.

[#]iv, intravenous; sc, subcutaneous.

[§]DMSO, dimethylsulfoxide 99–100%.

50 times higher in connective tissue from the extravasation site as compared to tissue samples from other body sites. In addition, the biopsies showed necrosis in subcutaneous fat tissue [10]. However, this study also refrains from mentioning the concentrations of the administered cisplatin infusions.

Three case reports describe severe effects of cisplatin extravasation after infusion at low concentration. The eldest case report describes a 70-year-old female receiving cisplatin (160 mg in 1,000 mL of Saline 0.9% = 0.16 mg/mL) and experiencing a small volume extravasation immediately after the cisplatin infusion was started. Three days later, pain and erythema developed ultimately resulting in a 5 × 7 cm lesion with a necrotic center requiring radical debridement. In addition, skin grafting was performed 2 months later, resulting in eventual healing of the area [11]. The second report describes a 62-year-old male treated with cisplatin 75 mg/m² diluted <0.04 mg/mL in combination with docetaxel. 12 days post-infusion, the patient experienced pain, and blisters appeared around the area of the infusion. Treatment with saline washes, topical hydrocortisone, and antibiotic-based ointment relieved the symptoms [12]. The authors describe this as docetaxel extravasation, but since the symptoms developed multiple days after treatment, a definite conclusion on the contribution of either of the administered drugs, cannot be drawn. The third report describes a 70-year-old man receiving cisplatin (110 mg in 250 mL glucose 5% = 0.21 mg/mL) in combination with gemcitabine. During infusion, pain and redness were observed which were immediately treated with topical steroids and topical cooling. Nonetheless, 2 weeks later, the area had turned yellow, and histopathology showed skin necrosis of the entire dermis layer [13]. Again, in this case report, distinguishing between both agents or establishing the contribution of each, was not possible.

To ensure that the most appropriate measures are taken as soon as possible after the extravasation of a cytotoxic drug, sufficient knowledge on the potential late effects, are essential. For cisplatin, the literature provides guidelines with conflicting recommendations and has proven insufficient in our patients. One could argue that if platinum is not easily resorbed from an extravasation site, not only the concentration but also the total amount of extravasated platinum could be a predictor of the severity of late effects [10]. In our patient, the concentration of cisplatin was lower than the 0.4 or 0.5 mg/mL described as a threshold in the literature, but the volume of fluid that was infused outside of the vein was quite high, estimated at 40–50 mL. However, this hypothesis is contradicted by the case report of Bairey et al. [11] where only a small volume of highly diluted cisplatin already led to necrosis. Thus, we propose that more precautionary management procedures, possibly also the use of sodium thiosulfate or injecting hyaluronidase around the extravasation area, should be included in the guidelines for the management of cisplatin extravasation, irrespective of the infusion concentration.

In conclusion, our case demonstrates that cisplatin can cause severe necrosis even at a low concentration of 0.3 mg/mL. This finding is substantiated by one confirmed and two possible previous cases [11–13]. We recommend that the guidelines that classify cisplatin as a vesicant only at concentrations of 0.4 mg/mL or higher, incorporate this information in their recommendations. This will enable the use of more extensive measures to prohibit necrosis following cisplatin extravasation.

Statement of Ethics

Written informed consent was obtained from the patient to permit publication of the details of their medical case and any accompanying images. Ethical approval is not required for this case report in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have reported no potential conflicts of interest.

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Author Contributions

Mariëlle Wondergem was the principal consultant for this patient. Anouk M. Braam and Mirjam Crul performed the background literature review. Anouk M. Braam wrote the paper. Mariëlle Wondergem and Mirjam Crul read and approved the final manuscript.

Data Availability Statement

All data generated are included in this article. Further inquiries can be directed to the corresponding author.

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