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CASE REPORT

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Extravasation of an antibody-drug conjugate: A case report of epidermal necrosis after trastuzumab-emtansine extravasation

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Abstract

What is known and objective: Trastuzumab-emtansine is an antibody-drug conjugate developed to decrease off-target toxicity. According to the product label, reactions secondary to extravasation are mild or moderate.

Case summary: We report on a 51-year-old woman who developed epidermal necrosis after extravasation of trastuzumab-emtansine, which required surgical intervention. Six weeks later, the lesions were healed with residual hyperpigmentation.

What is new and conclusion: We describe the course of a case of severe toxicity following trastuzumab-emtansine extravasation. We provide treatment recommendations and recommend amending the information on the product label on extravasation.

KEYWORDS

antibody-drug conjugate, chemotherapy, epidermal necrosis, extravasation, oncology, trastuzumab-emtansine

1 | WHAT IS KNOWN AND OBJECTIVES

Trastuzumab-emtansine is indicated for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane. Trastuzumab-emtansine is an antibody-drug conjugate (ADC) and consists of trastuzumab, a humanized IgG1-antibody linked with a covalent bond to a highly cytotoxic maytansine derivate (DM1), which disrupts microtubule function by binding near the vinca alkaloid binding side. The toxic agent DM1 is 20-200 times more potent compared with systemically administered taxanes and vinca alkaloids. As a result, parenteral administration of DM1 alone is restricted due to severe side effects and poor efficacy. Therefore, DM1 is only registered as an antibody-drug conjugate. The DM1-trastuzumab conjugate promotes selectivity of the cytotoxic agent for HER2-overexpressing tumour cells. This increases intracellular delivery of DM1 to malignant cells with HER2-overexpression and decreases off-target exposure. Upon binding to HER2, trastuzumab-emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in release of intracellular DM1-containing cytotoxic catabolites.[1]

Extravasation is an accidental leakage of intravenously administered drug into the tissue around the vein. Complications caused by extravasation depend on many factors such as the irritant or vesicant properties of the drug itself, composition of the drug formulation (eg pH, tonicity and emulsifiers), the pharmacological properties of the drug (eg vasoconstriction) and the volume of extravasation. The product label of trastuzumab-emtansine states that reactions secondary to extravasation observed in clinical studies were usually mild or moderate and comprised erythema, tenderness, skin irritation, pain or swelling at the infusion site. Furthermore, no specific treatment recommendations are mentioned for trastuzumab-emtansine extravasation.[1] Although the label does not warn for severe

toxic effects of extravasation, we report a case of a patient that developed severe epidermal necrosis after extravasation, which required surgical intervention.

2 | CASE DESCRIPTION

We report on a 51-year-old woman who was treated for oestrogen receptor (ER)-negative, progesterone receptor (PR)-negative and HER2 positive breast cancer. She was diagnosed with supraclavicular lymph metastasis for which she initially received a combination of docetaxel, carboplatin, trastuzumab and pertuzumab. After mastectomy, she continued with trastuzumab in combination with radiotherapy. Unfortunately, progression of disease with leptomeningeal metastasis was shown on MRI, and oral treatment with lapatinib and capecitabine was initiated. The patient discontinued oral treatment because of further progression and was switched to trastuzumab-emtansine infusions. Trastuzumab-emtansine was administered on day one of a 21-day cycle, as intravenous infusions via peripheral access. The weight-based dosage of 3.6 mg/kg was diluted with 250 mL of normal saline.

At the end of the infusion of the second cycle, extravasation of trastuzumab-emtansine was noticed by the oncology nurse while disconnecting the infusion line. As the infusion access was covered by the patient's clothes, the patient had not noticed the extravasation during infusion. At the time of discovery, the patient had a slightly erythematous, painless swelling. According to the size of the swelling, it was assumed that the total infusion volume had been administered subcutaneously. According to local protocol, the oncologist and hospital pharmacist were consulted to discuss whether supportive treatment was indicated.

It was decided to choose an observational approach, substantiated by statements in the product label about relatively mild reactions and a lack of (known) specific treatment strategies after trastuzumab-emtansine extravasations. However, one case of delayed epidermal necrosis after extravasation was reported, but no treatment strategies were provided.[2] Therefore, the patient was instructed to elevate the affected arm in order to prevent further swelling, was informed about a possible delayed response and was instructed to contact her oncologist as soon as cutaneous symptoms (swelling, erythema and pain) worsened.

The next day, the patient experienced an increase in pain and erythema at the site of extravasation. There was no increase in swelling or skin temperature. Pain could be sufficiently managed with acetaminophen. We contacted the patient every other day to monitor the extravasation. After a week, the patient attended our oncology outpatient clinic. The erythema was expanded to a larger area. After consulting plastic surgery, watchful waiting was continued as the skin was intact and the extravasation was too long ago to consider other treatments (eg local hyaluronidase injection or liposuction). Four days later, the patient developed blisters and the skin turned somewhat darker. The blisters were removed, and the affected area was treated with silver sulphadiazine to prevent infection. The darker discoloration did not progress to full-thickness necrosis. Six weeks after the event,

FIGURE 1 Development of symptoms after extravasation of trastuzumab-emtansine over time from the start of infusion (day 1) until 6 wk after administration. [Colour figure can be viewed at wileyonlinelibrary.com]

the lesion healed with residual hyperpigmentation of skin. The development of cutaneous symptoms over time is presented in Figure 1.

3 | WHAT IS NEW AND CONCLUSION

To our knowledge, this is the first case report that describes a detailed course of cutaneous trastuzumab-emtansine extravasation over time—illustrated by photos—and provides recommendations for clinicians how to manage trastuzumab-emtansine extravasations.

Shafaee et al also reported a case of trastuzumab-emtansine extravasation. A 55-year-old woman developed similar symptoms.[2] In this patient, no pain or swelling was noted at the end of infusion. After 9 hours, a swelling and tenderness were present at the infusion site. Two days later, large clear fluid-filled blisters developed with eventual rupture and serosanguinous discharge. Treatment existed of pain control requiring opioids. The lesion slowly healed in 4 weeks with residual hyperpigmentation, but without permanent sensory changes. This only other case report confirms that the worst symptoms develop with a delay of several hours to days. However, no clear treatment recommendations for trastuzumab-emtansine extravasations were provided. These two cases illustrate that severe toxic reactions can develop after trastuzumab-emtansine extravasation.

There are theoretically three mechanisms that could contribute to local cytotoxicity after extravasation of trastuzumab-emtansine: (a) proteolysis by intracellular lysosomes after HER2-mediated internalization by cutaneous cells; (b) uptake by local cells of the reticuloendothelial system (RES-cells) followed by proteolysis; or (c) chemical degradation of the ADC in situ. According to literature, HER-2/neu protein is present on cell membranes of skin tissue, suggesting that internalization by cutaneous HER2 is possible.[3,4] In addition, RES cells such as macrophages are found in skin tissue and thus may attribute to local toxicity by facilitating proteolysis of trastuzumab-emtansine.[5] In situ chemical degradation of the non-cleavable, stable thioether bond between trastuzumab and DM1 seems to be very unlikely.[1]

In addition to general recommendations for drug extravasations such as liquid aspiration and the use of agent-specific antidotes (eg dexrazoxane for anthracyclines), treatment options can be roughly divided into a 'spread and dilute' or 'concentrate and condensate' approach. A warm compress, administration of subcutaneous hyaluronidase or vasodilatants (eg nitroglycerin and phentolamine) will promote agent dispersion, whereas cold dressings will decrease the spread into adjacent skin tissue by vasoconstriction.[6] For the treatment of trastuzumab-emtansine extravasation, no specific treatment recommendations are mentioned by the product label or in literature. Although the intracellular action of emtansine (DM1) is similar to vinca alkaloids, the treatment strategy for extravasation of vinca alkaloids with hyaluronidase[7] cannot be extrapolated to trastuzumab-emtansine as the pharmacokinetic profile is determined by trastuzumab pharmacokinetics. The pharmacokinetics of the trastuzumab-emtansine conjugate has only been studied as an intravenous infusion. However, trastuzumab as a monoclonal antibody is also available as a 600 mg subcutaneous injection. This subcutaneous formulation contains recombinant human hyaluronidase in order to facilitate distribution to plasma. Despite the use of co-formulated hyaluronidase in subcutaneous injections, it takes 3 days to reach peak plasma concentrations (Tmax) with a high inter-individual variation (1-14 days) due to transport via de lymphatic system.[8] Treatment with hyaluronidase after subcutaneous extravasation of trastuzumab-emtansine will therefore not be able to provide a distribution to plasma, but will likely promote spreading of the agent into adjacent cutaneous tissue. Dilution of emtansine over a larger area will not decrease its toxicity, because of the extremely high potency of the payload. As a result, concentrating the agent to minimize the affected area, for example with a cold compress, seems to be a safer strategy. If blisters develop, a plastic surgeon should be consulted to consider surgical removal and monitor for full-thickness necrosis and subsequent treatment if necessary.

In conclusion, we recommend a non-operative treatment after trastuzumab-emtansine extravasation, including pain control, elevation of the affected limb and close patient monitoring. Cooling may be considered to decrease the spread of fluid into adjacent skin tissue, thereby possibly reducing the size of the affected area. Due to the extravascular pharmacokinetics of trastuzumab and the cytotoxic potency of emtansine, administration of hyaluronidase is not expected to be helpful since it will only enlarge the affected cutaneous area.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Authorship eligibility is based on the four ICMJE authorship criteria. All authors certify that they have participated sufficiently in the work to take public responsibility for the content. We have not received substantial contributions from non-authors.

PATIENT CONSENT FOR PUBLICATION

Obtained.

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