Kadcyla and Extravasation

This letter responds to your request for information on Kadcyla® (trastuzumab emtansine) and extravasation. This response was developed according to the principles of evidence-based medicine and includes data from Phase 3 studies, case studies and published clinical guidelines.

In brief

- Systemic anti-cancer therapies may be classified as vesicants, irritants, or non-irritants, based on their potential to cause tissue damage if extravasation occurs.
- Reactions secondary to Kadcyla extravasation have occurred. Kadcyla has been classified as an irritant by the UK National Health Service (NHS) and the Cancer Institute of NSW's eviQ.
- No specific treatment for epidermal necrosis following Kadcyla extravasation is known or recommended. Resources for the management of extravasation with chemotherapeutic agents have been published.
- Case reports on reactions following Kadcyla extravasation are available.

Extravasation classifications

Systemic anti-cancer therapies may be classified based on the potential to cause tissue damage if extravasation occurs, as described in Table 1.[1-3]

Table 1. Extravasation classification of systemic anti-cancer therapies[1-3]

Classification	Definition
Vesicant	A drug or solution that is capable of causing necrosis of local skin and underlying structures when it extravasates. They can be classified into: • DNA-binding vesicants, or • non-DNA binding vesicants.
Irritant with vesicant properties	A drug or solution that is difficult to classify, but is capable of causing tissue damage and ulceration, proportionate to the concentration and the amount extravasated.
Irritant	A drug or solution that may cause pain, inflammation, irritation, and phlebitis, but rarely necrosis when extravasated.
Non-irritant (neutrals)	Inert or neutral compounds that may cause pain but not inflammation or damage.

It should be noted that any chemotherapeutic agent has the potential to cause significant symptoms and tissue damage if the volume or concentration of the drug that extravasated is high.[1]

Classification of Kadcyla

Kadcyla is an antibody-drug-conjugate (ADC) comprised of an anti-human epidermal growth factor receptor 2 monoclonal antibody (IgG1) covalently linked to the microtubule inhibitory drug DM1 via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate).[4]

Monoclonal antibodies are typically classified as non-irritants, however there is limited evidence to classify ADCs.[2,5] Roche does not provide an extravasation classification for Kadcyla.[4]

Reactions secondary to extravasation have been observed in Kadcyla clinical studies.[4] Kadcyla has been classified as an irritant by the UK NHS and the Cancer Institute of NSW's eviQ.[1,6]

Extravasation reactions

Extravasation reactions in Kadcyla clinical studies

In Kadcyla clinical studies, reactions secondary to extravasation have been observed.[4] These reactions were observed most frequently within 24 hours of infusion, were usually mild and comprised of the following signs at the infusion site:

- erythema
- tenderness
- skin irritation
- pain, and
- swelling.

Extravasation reactions in the post-marketing setting

In the post-marketing setting, very rare cases of epidermal injury or necrosis following extravasation have been observed, including delayed reactions.[4,7]

Recommendations for the management of extravasation

Roche does not have specific recommendations for the treatment of Kadcyla extravasation.[4]

During Kadcyla administration, the infusion site should be closely monitored for possible subcutaneous infiltration.[4] If extravasation occurs, the infusion should be terminated immediately and the patient should be examined regularly as necrosis may occur within days to weeks after infusion.[7]

No specific treatment for epidermal necrosis following Kadcyla extravasation is known or recommended.[4] Case resolution has occurred in majority of cases with general clinical practice measures.[8]

Clinical guidelines

Resources for the management of extravasation with chemotherapeutic agents have been published.[1-3,5,6] Examples include but are not limited to clinical practice guidelines published by the European Society for Medical Oncology (ESMO), the NHS and eviQ. The interested clinician is directed to the full guidelines for further information.

- ESMO - Management of Chemotherapy Extravasation.[5] ESMO Clinical Practice Guidelines may be accessed at: www.esmo.org/guidelines/supportive-and-palliative-care/chemotherapy-extravasation

- NHS - West Midlands Expert Advisory Group for Systemic Anti-Cancer Therapy (SACT).[1] Network Guidelines for the Management of Extravasation of a SACT Including Cytotoxic Agents may be accessed at: www.england.nhs.uk/mids-east/cancer-expert-advisory-groups/systemic-anti-cancer-therapy/

- eviQ - Cancer Institute of NSW.[9] Algorithm - extravasation management of intravenous anti-cancer therapies may be accessed at: www.eviq.org.au/clinical-resources/extravasation/1078-extravasation-management-immediate-manageme

Extravasation experience from case reports

Sibaud et al. reported a patient with diffuse, painful erythema that occurred 1 day after infusion of Kadcyla.[10] The erythema progressed over 6 days, followed by spontaneous improvement of symptoms after 15 days and no permanent damage. The authors suggested that this was a tissue irritant reaction.

Shafaee et al. described a patient who developed swelling 9 hours after the completion of the Kadcyla infusion.[11] Blisters developed within 2 days, and the patient was treated with opioids for pain control. After 4 weeks, the site had healed with residual hyperpigmentation.

Sallevelt et al. reported a patient who was found to have erythematous painless swelling upon completion of the Kadcyla infusion.[12] Based on the extent of the swelling, it was likely that the entire infusion volume was administered subcutaneously. The patient was initially observed and treated with acetaminophen for pain control. Blistering of the skin occurred approximately 11 days after infusion. The blisters were surgically removed, followed by local treatment with silver sulphadiazine for infection prophylaxis. At 6 weeks after extravasation, the skin had healed, with residual hyperpigmentation of the skin still present.

References

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