







CLINICAL CASE REPORT ARTICLE

TRASTUZUMAB EMTANSINE EXTRAVASATION: MANAGEMENT IN CANCER PATIENTS EXTRAVASAMENTO DE TRASTUZUMAB EMTANSINA: MANEJO EM PACIENTE ONCOLÓGICO EXTRAVASACIÓN DE TRASTUZUMAB EMTANSINE: MANEJO EN PACIENTES ONCOLÓGICOS

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ABSTRACT







Objective: to describe the management of trastuzumab emtansine extravasation in a patient with invasive ductal breast carcinoma. **Method:** this is a qualitative, descriptive, clinical case report type, in a cancer treatment clinic. Data was collected through information in the medical records and images taken by the multi-professional team. The information was consolidated and the data were interpreted and analyzed after the description of the information. **Results:** extravasation was managed based on the institutional protocol with the patient being discharged on the same day, and this evolved with the appearance of an intense inflammatory reaction with the presence of edema, blisters and vesicles after the episode. Full recovery occurred 54 days after the event. **Conclusion:** it was concluded that a continuous qualification of the team is necessary, based on updated scientific evidence, so that it can intervene in situations of chemotherapy extravasation in an appropriate way. **Descriptors:** Drug Therapy; Extravasation of Diagnostic and Therapeutic Materials; Drug-Related Side Effects and Adverse Reactions; Antineoplastic Agents; Breast Neoplasms; Medical Oncology.

RESUMO

Objetivo: descrever o manejo do extravasamento de trastuzumabe emtansina em uma paciente com carcinoma ductal invasivo da mama. **Método:** trata-se de um estudo qualitativo, descritivo, do tipo relato de caso clínico, num ambulatório de tratamento de câncer. Coletaram-se os dados por meio de informações nos prontuários e imagens realizadas pela equipe multiprofissional. Consolidaram-se as informações e os dados foram interpretados e analisados após a descrição das informações. **Resultados:** manejou-se o extravasamento com base no protocolo institucional com a paciente recebendo alta no mesmo dia, e esta evoluiu com o surgimento de uma reação inflamatória intensa com a presença de edema, bolhas e vesículas após o episódio. Ocorreu-se a recuperação total após 54 dias do ocorrido. **Conclusão:** concluiu-se que é necessária uma qualificação contínua da equipe, com base em evidências científicas atualizadas, para que ela possa intervir em situações de extravasamento quimioterápico de forma adequada. **Descritores:** Tratamento Farmacológico; Extravasamento de Materiais Terapêuticos e Diagnósticos; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Antineoplásicos; Neoplasias da Mama; Oncologia.

RESUMEN

Objetivo: describir el manejo de la extravasación de trastuzumab emtansine en una paciente con carcinoma ductal de mama invasivo. **Método:** este es un tipo de informe de caso clínico cualitativo, descriptivo, en una clínica de tratamiento del cáncer. Los datos fueron recolectados a través de información en los registros médicos e imágenes tomadas por el equipo multiprofesional. La información se consolidó y los datos se interpretaron y analizaron después de la descripción de las informaciones. **Resultados:** la extravasación se manejó según el protocolo institucional con el alta del paciente el mismo día, que evolucionó con la aparición de una reacción inflamatoria intensa con la presencia de edema, ampollas y vesículas después del episodio. La recuperación completa ocurrió 54 días después del evento. **Conclusión:** se concluyó que es necesaria una calificación continua del equipo, basada en evidencia científica actualizada, para que pueda intervenir en situaciones de extravasación de quimioterapia de manera adecuada. **Descriptor:** Quimioterapia; Extravasación de Materiales Terapéuticos y Diagnósticos; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Antineoplásicos; Neoplasias de la Mama; Oncología Médica.

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How to cite this article

Amorim BF, Kameo SY, Silva GM, Hardman GL, Costa JS, Ramos MJO. Extravasation of trastuzumab emtansine: management in cancer patients. J Nurs UFPE on line. 2020;14:e244241
DOI: <https://doi.org/10.5205/1981-8963.2020.e244241>

INTRODUCTION

It is known that breast cancer is the second most frequent type of cancer in the world, being one of the main causes of death in women worldwide.¹⁻² It is estimated, in Brazil, that the incidence, for 2020, is 66,280 new cases, with an estimated risk of 61.61 cases for every 100 thousand women.³

It is reported that one of the treatments proposed for advanced cases of metastatic breast carcinoma is the use of trastuzumab emtansine, an antineoplastic agent, antibody-drug conjugate, which has the Human Epidermal Growth Factor Receptor type 2 (HER2) as its target and contains type 1 immunoglobulin G (IgG)1 anti-HER2 humanized, trastuzumab, covalently linked with the synthetic phenolate microtubule inhibitory drug (DM1) (a maytansine derivative) via the stable thioether ligand 4- [N-maleimidomethyl] cyclohexane-1-carboxylate (MCC).⁴

Entansine is said to refer to the MCC-DM1 complex and, on average, 3.5 molecules of DM1 are conjugated to each molecule of trastuzumab. Through the conjugation of DM1 to trastuzumab, selectivity of the cytotoxic agent for tumor cells that overexpress HER2, thus increasing the intracellular delivery of DM1 directly to malignant cells. It is detailed that, with binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in the release of cytotoxic catabolites containing DM1 (mainly lysine-MCC-DM1).⁴

The mechanism of action, as in trastuzumab, is linked to subdomain IV of the extracellular domain HER2 (DEC), as well as to Fcγ receptors and C1q complement; in addition, as trastuzumab, it inhibits the dispersion of HER2 DEC, inhibits signaling via the phosphatidylinositol 3-kinase (PI3-K) pathway and mediates cellular cytotoxicity by means of antibodies (ADCC) in cancer cells human breast that overexpress HER2.⁴

DM1, the cytotoxic component of this drug, is bound to tubulin by inhibiting tubulin polymerization, and both DM1 and trastuzumab emtansine cause cells to stop at the G2 / M phase of the cell cycle, ultimately leading to cell apoptosis. The results of in vitro cytotoxicity tests show that DM1 is 20 to 200 times more potent than the taxanes and vinca alkaloids. The MCC ligand is designed to limit systemic release and increase and target the delivery of DM1, as demonstrated by the detection of very low levels of free DM1 in plasma.⁴

It is administered intravenously every three weeks, the elimination is 0.68 L / day and the elimination half-life (t₁ / 2) is approximately four days.⁴

The injury resulting from the extravasation of antineoplastic drugs (EAD) constitutes one of the main adverse effects that demand greater care rigor on the part of nurses, being considered an oncological emergency due to the morbidity it can cause. It is pointed out, given the above, that the prevention of this complication is an important measure, since the EAD is a serious complication that generates stress in the Nursing team and can cause irreparable damage to the patient.⁵

It is explained that extravasation is the escape of drugs from the blood vessel to the surrounding tissues, and their local toxic effects vary, which may cause pain, tissue necrosis or flaking of the tissue. It depends on the morbidity of the type of the drug, the amount leaked, its concentration, the location of the leak, the patient's condition and the interval between the fact, its recognition and the treatment.⁵

It is clarified that vesicating agents are responsible for the most serious and exuberant reactions, as they cause severe irritation with formation of vesicles and tissue destruction when infiltrated outside the blood vessel. Less intense skin reactions, such as pain and burning, are caused by irritating agents when they leak, without tissue necrosis or vesicle formation.⁵

It is hoped, by this study, to disseminate knowledge about the conduct in cases of extravasation of trastuzumab emtansine, an antineoplastic agent, indicated as monotherapy for the treatment of patients with non-resectable metastatic or locally advanced HER2-positive breast cancer who have received previous treatment with trastuzumab and a taxane. It is concluded, then, since it is an antineoplastic agent recently approved, in 2014 by ANVISA in Brazil, where the multi-professional team is a protagonist in the administration and care during the treatment with this medication, that their knowledge is relevant in the team practice health, in addition to the spread of knowledge.

OBJECTIVE

- To describe the management of trastuzumab emtansine extravasation in a patient with invasive ductal breast carcinoma.

METHOD

This is a qualitative, descriptive, clinical case report type, based on the experience of the care team that works in an oncology treatment outpatient clinic in the city of Aracaju (SE), Brazil. It is known that the case study is an empirical investigation and comprises a comprehensive method, with the logic of planning, data collection and analysis.

It should be added that the case study does not accept a rigid script for its delimitation, but it is

possible to define four phases of its delineation: 1) delimitation of the case; 2) data collection; 3) data selection, analysis and interpretation; 4) preparation of the report.⁶

The project was submitted, in order to have access to the patient's medical record, to the Ethics and Research Committee of the Federal University of Sergipe Foundation, approving it with opinion number 2.244.176, and the signing of the Free and Informed Consent Term was also obtained. (FICT).

The case was delimited at first, starting with the reading of the patient's medical record and then with the collection of data; in the second moment, data collection related to socioeconomic, clinical and extravasation episode data was carried out; in the third moment, the analysis and interpretation of the data of the Nursing diagnoses elaborated by the nurses and the respective Nursing interventions was proceeded, and in the fourth moment, the process of elaboration of the report occurred, that is, the evaluation of the results achieved and the new affected basic human needs identified, from which new Nursing diagnoses and interventions have emerged.

The data was analyzed using the Reflection-Synthesis Analysis method, after the exercise of analytical and intuitive reading of the records obtained from the medical record associated with the reflection of the clinical manifestations of breast cancer and adverse reactions of chemotherapy. Through this process, it was possible to understand the studied reaction through socioeconomic, clinical data and the extravasation of chemotherapy and its recurrence during treatment.

RESULTS

The case of patient O.R.S, 72 years old, woman, married and born in Paripiranga - BA, but resident in Lagarto - SE, was raised. She was consulted in October 2014, presenting a lesion in her right breast that had existed for more than four years, and was referred for a mammogram that injured her nipple. She was later diagnosed by the mastologist with infiltrating ductal carcinoma (ICD) in the right breast (breast D) locally advanced and in liver metastasis, stage T4NxM1. On occasion, the CLEOPATRA protocol was carried out, being positive for HER-2. Treatment with chemotherapy started, receiving eight cycles of Taxotere, together with Herceptin and Perjeta, presenting complications due to the treatment. They became the most significant: alopecia; diarrhea; lipothymia; nausea; emesis; dark and stiff affected breast; ulcerated and bleeding.

This was followed by maintenance treatment, with Herceptin + Perjeta for, on average, 20

cycles, for the surgical procedure of Mastectomy D on November 9, 2015, with removal of a 10 cm tumor, pT4d classification, presence of GH3 and GN3, additional to the infiltration of the dermis, remaining in medical care after manifestation of thrombocytopenia and dermatitis in the abdominal region. It is added that she received guidance on the protocol of postoperative treatment, with the administration of five additional cycles of Perjeta + Herceptin.

On November 15, 2016 (Day 1 - Cycle 1), the Kadcylla protocol, which uses the chemotherapy trastuzumab emtansine, began. The patient was instructed on the duration and interval between cycles (21 days), possible adverse reactions, complete blood count with creatinine, general and home care. It is reported that the patient, on December 5, 2016 (Day 1 - Cycle 2), attended the service without side effects during the QT interval, however, maintaining leukocytosis and an ulcerated lesion in breast D, evaluated in consultation days before, a central venous access puncture was performed in the left subclavian region for administration, with no reflux and fixation with micropore tape.

It is described that the Kadcylla infusion procedure occurred uneventfully and as prescribed, however, during hydration with 0.9% SF, the patient reported burning sensation in the catheter region, where the needle was outside the insertion, showing thus, the extravasation of the medication to the left breast (breast E), with the presence of edema measuring 10x8 cm and erythema, with no possibility of aspiration of the extravasated content (Figure 1). When contacting the doctor on duty, the institutional protocol for extravasation began, which presents, as Nursing interventions based on the Nursing Intervention Classification (NIC), skin care through the application of topical Dexamethasone (3584) and heat with a warm compress (1380) for 15 minutes and, after one hour, the procedure is repeated, however, with a cold compress. It is detailed that the patient was discharged after being observed by the Nursing team, with normalized vital signs, and was instructed to return the next day to assess the location, according to the protocol.



Figure 1. Record made on the day of the extravasation episode of antineoplastic drugs, showing sero-sanguinolent secretion at the puncture site. Aracaju (SE), Brazil, 2019.

The patient was reassessed on December 6, 2016, as scheduled, instructing her to apply cold compresses of chamomile tea to reduce local

edema, until the next appointment date, on December 12.



Figure 2. Day 3, after the extravasation of antineoplastic drugs, with extensive erythema and edema in the left hemithorax region. Aracaju (SE), Brazil, 2019.

In the following days, contact was made with family members to collect information about the situation, which were positive for the improvement of the consequences of the overflow of the chemotherapy (Figure 2), however, on December 10, there was an aggravation wound, with hyperemic skin, blisters, pain and heat, requiring the patient to be admitted to an

emergency hospital (Figures 3 and 4). Oral antibiotics and anti-inflammatory drugs were prescribed for treatment for seven days. Starting from D12, maintenance of the lesion in breast E began, concomitant with the maintenance of the cancer lesion, with the cleaning of both with 0.9% SF and coverings of Silver Alginate, Jelonet and Melolin for the lesion E and Hydrogel for breast D.



Figure 3. Day 8, after the extravasation of antineoplastic drugs, with extensive erythema and edema and vesicles in the left hemithorax region. Aracaju (SE), Brazil, 2019.



Figure 4. Day 9, after the extravasation of antineoplastic drugs, showing erythema, edema, vesicles and bleeding in the left hemithorax region. Aracaju (SE), Brazil, 2019.

At D19, during the dressing change, on inspection, it was noticed the rupture of vesicles in the lower left quadrant of breast E, with the release of liquid (Figure 5); effective healing process in upper 2/3 of the right lesion and lower 1/3 with active granulation tissue in the left lesion

and decreased fibrin and exudate in the right lesion. By medical decision, the beginning of the next chemotherapy cycle scheduled for the following week, scheduled for January 2, 2017, was postponed in order to favor the healing process.



Figure 5. Day 19, after the extravasation of antineoplastic drugs, with erythema, crusts and granulation tissue in the lower breast region in the left hemithorax. Aracaju (SE), Brazil, 2019.

The Kadcylla protocol for peripheral venous access started again at D29 for the patient, as she still had hyperemia and a slight induration in the

left breast, but at D54 she no longer had symptoms due to extravasation, but only sequelae of left breast dermatitis (Figure 6).



Figure 6. Day 54, after the extravasation episode of antineoplastic drugs, with sequelae of dermatitis in the left breast. Aracaju (SE), Brazil, 2019.

DISCUSSION

It is noted that the intravenous infusion of chemotherapeutic agents occurs through peripheral or central venous catheters. Leakage in peripheral infusion catheters is generally related to endothelial dysfunctions caused either by disease or by old age, impaired blood flow, obesity, previous radiotherapy, small veins, disseminated skin disease, multiple anterior punctures, and movement during the infusion and inexperience of the team. It is described that, in the Central Venous Catheters (CVC), although they are considered safer, extravasations can occur due

to curves and ruptures in their extension and tip, the poor positioning of the catheter, the formation of thrombi in its extremity and the dispositioning CVC.⁷

Extravasation is characterized by infiltration of the antineoplastic agent in extra-luminal tissue into blood vessels. It is reported that the signs of extravasation, in addition to the earlier ones, such as paralysis or decreased infusion flow and venous return, are the sensation of pain and burning at the puncture site and surrounding tissue, local redness, edema in case of irritating substances, and / or tissue destruction, formation of vesicles,

ulceration and necrosis in case of more aggressive substances such as vesicants.⁸

As side effects, Kadcyła (trastuzumab emtansine) appears as side effects, reactions that are considered mild, such as redness and local pain, skin irritation and pinprick or prickly pain and swelling at the infusion site, however, in its package insert, the classification of this drug as an irritating or vesicant substance.⁴ However, it is revealed that, although monoclonal antibodies such as trastuzumab, generally do not produce irritation or tissue damage, their association with cytotoxic drugs with anti-microtubule action such as entasin, forming an antibody-drug complex, makes -the capable of producing tissue damage and necrosis. In a review study for the formulation of an institutional guideline by a group at the University of Illinois Hospital and Health Sciences System, antibody-drug conjugates as irritants that may have vesicating properties, however, there is still a need to more data and studies to support the classification of these new compounds used in the treatment of oncological diseases.⁹

In the episode of extravasation with trastuzumab emtansine reported in this study, initially, the patient had a burning sensation at the puncture site, edema and local hyperemia. It appears that six days after the episode, there were the appearance of new symptoms, such as increased hyperemia, the presence of blisters, pain and heat, which were managed in another health service through antibiotic treatment with ciprofloxacin 500mg. The patient had a complete remission of the symptoms and consequences from the overflow occurring 54 days after the episode.

It consists of the immediate conduct to be performed in the suspicion of EAD, supported by the scientific literature, in the immediate interruption of the medication infusion without the removal of the intravenous device, identification of the substance and measurement of the extravasated amount, trying to aspirate the extravasated content to the maximum by through the device still implanted, drugs whose intravenous antidotes are available must be administered by the same device and later it must be removed. If a limb has been affected, it must be maintained in an elevated position in relation to the body. It is also necessary to photograph the puncture site with the authorization of the patient and family, as well as its evolution over the management of injuries caused by extravasation, and all procedures and procedures performed must be described in detail in the patient's medical record.⁸⁻⁹

It was mentioned, in a study of eight patients carried out in Austria, very positive results regarding prevention of tissue necrosis by using the technique Subcutaneous Wash-Out Procedure (SWOP) after the immediate withdrawal of the

CVC in cases whose detection of extravasation it was early. It is this technique consists in the subcutaneous administration of saline solution for local rinsing and removal of leaked substance, however, requires staff training to be carried out.⁷

The use of hot or cold compresses varies according to the substance used, which may contribute to a better prognosis for the patient and his treatment, hence the importance of knowing the different classes of antineoplastic agents. Detail of the hot compresses for drugs such as vincristine, vinorelbine, vindesine, vinblastine, etoposide, teniposide and oxaliplatin because they act causing local vasodilation, allowing systemic absorption of these drugs, reducing local tissue damage reactions. Indicate it is already cold compresses to other chemotherapy and its local effect the reduction of symptoms, local vasoconstriction, thus limiting the diffusion of the drug to surrounding tissues, reducing the injured area.^{5,7-9} It is clear, however, that there is still no scientific evidence that cold compresses really help reduce the formation of lesions.⁵

It is noteworthy, in relation to the case exposed in this study, that the leakage identification occurred after the end of the medication infusion during irrigation with 0.9% saline, however, it was not described in the medical record if, during the medication infusion, there was a professional responsible for observing the procedure throughout the administration, as recommended in the package insert and in the scientific bibliography on the prevention and management of EAD.^{4-5,7-8} This extra care in infusion of chemotherapy is necessary, as the early identification of EAD definitely influences the amount of spilled content and, consequently, the size and importance of the injuries caused by this accident.

It is indicated, both in cases where the aspiration procedure failed, as reported in this study, and in those that were successful, the use of the SWOP technique, after CVC removal, in order to reduce the effects of extravasation and ensure a better prognosis for the patient and his treatment with antineoplastic drugs.⁷

The NIC-based institutional protocol established in this service consisted in the administration of topical Dexamethasone associated with warm compresses for 15 minutes and, after one hour; the procedure was repeated, however, with cold compresses. However, it is intended for the use of hot compresses for a limited number of chemotherapeutic agents, such as vinca alkaloids, etoposide, teniposide and oxaliplatin, with cold compresses being indicated for other chemotherapeutic agents, such as trastuzumab emtansine.^{5,7-9}

It is warned that the use of topical Dexamethasone and other corticosteroids (topical

or systemic) is not recommended for the management of EAD and, with regard to the extravasation of alkaloid from the vinca, its use has demonstrated an increase in the area of necrosis at the extravasation site.¹⁰ It is inferred, therefore, that there is no indication for its use in the extravasation of trastuzumab emtansine in the scientific literature, and the belief that its use would be beneficial due to the interruption of the acute inflammatory process is not justified in the management of EAD. An exception is made to this non-recommendation with regard to the extravasation of oxaliplatin in which there appears to be a positive impact on your administration of Dexamethasone 8mg oral or intravenous for up to 14 days.⁹

Chemotherapy treatment evolves in oncology, constantly changing, with the emergence of new drugs being frequent and, like the conjugate trastuzumab emtansine, there is little in the literature on the management of adverse reactions from complications from extravasation, being important, for the nursing professional, to know the different classes of chemotherapy and how to proceed in case of overflow of these drugs. It is essential, therefore, that the protocols established for the prevention and management of EAD are updated and built based on updated scientific evidence and the best clinical evidence available in the literature.^{5,7-8,10}

In Brazil, the nursing professional is assured, by the Resolutions of the Federal Nursing Council 210, of 1998, and 257, of 2011, the function of elaborating therapeutic protocols for prevention, treatment and minimization of side effects, in addition to preparing and administering antineoplastic chemotherapy.⁹ Thus, there is continuing education in health for this professional, which is of central importance in the quality of services provided in an oncology patient care unit, with several studies showing that more qualified professionals better recognize risk factors associated with EAD, prevention of extravasation and its most immediate signs, classifications of antineoplastic agents, immediate conduct and proper management of EAD.^{5,7-8,10}

CONCLUSION

It is known that chemotherapy can cause mild or severe adverse effects to patients. It is added that, with the overflow being an unusual reaction, liable to complications that interfere in the treatment and in the quality of life of the users, but that, when observed and managed early, provide a greater possibility of reversal, conduct consistent with updated scientific evidence and a team of professionals who supervise the moment of administration are necessary in order to recognize early reactions presented by patients.

It is inferred, however, that few studies make reference to this type of complications arising from extravasation, thus, it is essential that the Nursing professional knows the different classes of chemotherapy to proceed correctly in case of extravasation of these drugs, in addition to the installation of protocols with the objective of preventing and managing episodes of leakage constructed based on scientific evidence.

Thus, the need for continued qualification of the team to intervene in situations such as these in order to provide quality care is minimized, minimizing the suffering of cancer patients.

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Submission: 2019/02/12

Accepted: 2019/03/19

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