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Case Report

Successful rapid desensitization to zoledronic acid in a multiple myeloma patient

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Abstract

Background Multiple myeloma (MM) is a malignancy characterized by the proliferation of abnormal plasma cells in the bone marrow, leading to osteolytic lesions. This condition is accompanied by a serum accumulation of monoclonal immunoglobulin. Zoledronic acid (ZA) is a new-generation bisphosphonate commonly used to prevent bone complications. However, allergic reactions can pose challenges, potentially leading to ZA discontinuation. Thus, rapid desensitization (RD) has been proposed as a solution to continue treatment in patients with severe HR. RD consists in the induction of a temporary state of tolerance by administering increasing doses of the offending medication.

Methods We present the case of a 57-year-old woman with MM who developed face angioedema, flushing with itching, dizziness and fever to ZA. Thus, an allergy work-up with skin prick test and intradermal test (IDT) with ZA were performed. Subsequently, considering the necessity of maintaining ZA treatment, a 3-dilution, 12-step RD infusion protocol was implemented. Skin tests were also repeated after three RD infusions.

Results Skin tests showed positive IDT reactions to ZA confirming the hypersensitivity state of the patient to the medication. Then, the patient underwent RD procedures without any HR. Skin tests performed after three RD procedures were deemed negative.

Conclusions Here, we demonstrate successful management with RD in an MM patient with HR to ZA, providing a valuable therapeutic option for patients experiencing such reactions. The effectiveness of RD to ZA was confirmed by the negative response to skin tests after 3 RD procedures. Nevertheless, further research is needed to refine RD protocols and establish their safety and efficacy for patients with HR to ZA. Standardized in vitro testing may also improve the diagnosis and management of ZA hypersensitivity.

Keywords Drug allergy · Multiple myeloma · Rapid desensitization · Zoledronic acid

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1 Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by the accumulation of monoclonal immunoglobulin within the bone marrow, with an incidence of 86'000 new cases annually worldwide [1, 2]. Moreover, clinical signs are osteolytic lesions, renal dysfunction, hypercalcemia, anemia, and raised monoclonal paraprotein. Bone lesions develop from an impairment of normal bone remodeling, resulting in cancer-induced bone damage [3].

In the bone microenvironment, MM cells, osteocytes and stromal cells release factors such as RANKL, MIP-1α, IL-3, HB-EGF and IL-6, which increase osteoclast function and activity and mediate drug resistance [1, 2]. Conversely, DKK-1, SFRP2 and sclerostin inhibit osteoblast function. This process leads to bone resorption and decreased bone formation activity resulting in lytic bone lesions and hypercalcemia [4, 5].

Zoledronic acid (ZA) is a new-generation bisphosphonate widely used in adult patients to prevent bone complications in malignancies and bone metastases originating from both known and unknown primary to reduce the total amount of calcium in the blood due to the bone tumor [6]. Evidence showed that ZA directly inhibits the adhesion between tumor cells and mineralized bone and reduces both invasion and proliferation of tumor cells in a wide variety of malignancy types such as multiple myeloma, leukemia, breast and prostate cancers [6, 7]. Despite its efficacy, hypersensitivity reactions (HR) such as urticaria, angioedema, flushing, wheezing, hypotension or anaphylactic shock are rare but pose challenges, potentially leading to ZA discontinuation. Unfortunately, the exact frequency of hypersensitivity reactions to zoledronic acid is not specified in the literature. However, the drug's leaflet indicates that such reactions are classified as "Uncommon," meaning they may affect up to 1 in 100 people [8]. Generally, different possible mechanisms of HR may include IgE-mediated reactions, reactions due to cytokine release, and reactions due to complement activation. Positive skin testing may suggest the presence of a possible drug-specific IgE (Type I mechanism of Gell and Coombs classification) and stratify the risk of HR.

In patients who experienced severe HR to a specific medication and have no other therapeutic options, rapid desensitization (RD) can be a valid approach to avoiding its discontinuation. RD procedures consist of the induction of a temporary tolerance to the medication responsible for HR by administering the offending drug with increasing dosages over a longer period compared with standard infusion schedule, up until the full cumulative therapeutic dose is given and tolerated. Classic RD protocols last about 6 h and include 12 consecutive steps using three bags of solutions with increasing drug concentrations. Except for the last step (step 12), which takes around 3 h, each step lasts 15 min with a twofold increase in the rate of drug administration [9]. On the other hand, this procedure is not indicated in patients who experienced life-threatening immunocytotoxic reactions, vasculitis, or severe cutaneous reactions (SJS/TEN, DIHS, DRESS).

Evidence on the mechanism of rapid RD is limited but the hypothesis is that increasing sub-therapeutics doses of the drug bind to IgE anchored to the surface FcεRI receptors and the cross-linking does not occur with subsequent mast cell and basophil unresponsiveness [9].

In this study, we report on a MM patient who developed HR to ZA infusion and subsequently underwent RD successfully. To our knowledge, this is the first case of RD to ZA.

2 Methods

2.1 Case presentation

A 57-year-old woman was diagnosed with IgA-l MM in 2017. She started VTD (bortezomib-thalidomide-dexamethasone) scheme with limb paresthesia and dizziness occurrence after 2 cycles. Then, treatment was switched to cyclophosphamide-thalidomide-dexamethasone for 3 cycles and the patient was subjected to autologous stem cell collection in 2018. However, the bone marrow biopsy showed 75% of plasma cell infiltration, hence stem cell autologous transplant was not performed. Thus, daratumumab-lenalidomide-dexamethasone schedule was started and suspended in April 2023, when she obtained a very good partial response.

In January 2024, given the presence of osteolytic lesions, the patient was a candidate for ZA administration. Thus, ZA 4 mg/5 ml (Zometa®) was diluted in 100 ml of saline solution and administered in about 20 min according to the leaflet's infusion schedule. However, after 30 min of the first ZA infusion, the patient presented face and hands angioedema, flushing with itching, dizziness, fever (38.5 °C) and headache. The HR resolved spontaneously after 3 days.

2.2 Zoledronic acid

Zoledronic acid (Zometa®) 4 mg/5 ml, manufactured by Sanochemia Pharmazeutika GmbH Landegger-Straße 7, 2491 Neufeld an der Leitha, Burgenland, Austria, was used both for the RD protocol and for performing skin tests [8].

2.3 Skin tests

An allergy workup with skin tests was implemented. A skin prick test (SPT) and intradermal test (IDT) were performed: SPT by full-strength ZA solution (concentration: 0.8 mg/ml); IDT, by increasing ZA concentrations, i.e., i) IDT 1:100 and ii) IDT 1:10, that consisted of the full-strength ZA solution diluted 100-fold (0.008 mg/ml), or tenfold (0.08 mg/ml) with saline. Histamine (10 mg/ml for SPT and 0.002 mg/ml for IDT) and saline were used as the positive and the negative controls, respectively. The skin test has been repeated after the third RD protocol.

2.4 Rapid desensitization schedule

Given the need of continuing ZA treatment, due to the patient's significant bone pain and its rapid onset of action compared to alternative bisphosphonates, in consideration of the clinical history and the results of the skin tests, we devised and implemented a 3-bag, 12-step protocol of rapid desensitization. The target dose was 4 mg, i.v. Thus, we prepared three ZA dilutions/bags for i.v. administration: i) 1/1 dilution (0.016 mg/ml): 4 mg of ZA in 250 ml of saline; ii) 1/10 dilution (0.0016 mg/ml): 10 ml of 1/1 dilution in 90 ml of saline; iii) 1/100 dilution (0.00016 mg/ml): 10 ml of 1/10 dilution in 90 ml of saline. The protocol begins with the 1/100 solution and continues the subsequent steps of the 1/10 and 1/1 solutions. Premedication included chlorphenamine 10 mg i.v. and 1 g paracetamol orally administered 30 min before the infusion. The RD procedure had 12 sequential stages with increasing speeds and dosages at each dilution/bag. Each stage lasted 15 min, except for step 12, which lasted around 82 min. The drug infusion lasted almost 4 h. The RD protocol is reported in Table 1.

Table 1 Rapid desensitization schedule for zoledronic acid (target dose: 4 mg)

Step	Dilution	Infusion rate (ml/h)	Time (minutes)	Volume administered (ml)	Dose administered (mg)
1	1/100	4	15	1.25	0.00016
2	1/100	10	15	2.5	0.0004
3	1/100	20	15	5	0.00081
4	1/100	40	15	10	0.0016
5	1/10	10	15	2.5	0.004
6	1/10	20	15	5	0.008
7	1/10	40	15	10	0.016
8	1/10	80	15	20	0.032
9	1/1	20	15	5	0.08
10	1/1	40	15	10	0.16
11	1/1	80	15	20	0.32
12	1/1	150	82	205	3.28
total			247		3.903

Dilution 1/1: 4 mg of ZA in 250 ml saline [0.016 mg/dl]

Dilution 1/10: 10 ml of 1/1 dilution in 90 ml of saline [0.0016 mg/dl]

Dilution 1/100: 10 ml of 1/10 dilution in 90 ml of saline [0.00016 mg/dl]

3 Results

3.1 Skin test result

While SPT and IDT 1/100 produced no reaction, the IDT 1:10 ZA concentration yielded a wheal of 6 mm (average diameter) after 4 h, deemed as positive (see Fig. 1).

Skin tests were also performed after 3 RD infusions and were deemed negative.

3.2 Rapid desensitization result

The RD protocol was performed two consecutive times (every 4 weeks), and the target dose was administered without any HR occurrence. Successively, we progressively removed a dilution with each subsequent infusion: firstly the 1/100 dilution and then the 1/10 dilution. No HR occurred.

To date, the patient is receiving ZA, every 4 weeks, for about 2 h with an infusion schedule consisting of 4 mg of ZA in 250 ml of saline given in 4 steps (infusion rates): 20 ml/h, 40 ml/h, 80 ml/h, 150 ml/h.

4 Discussion

MM represents an intricate and heterogeneous plasma cell malignancy with variable life expectancy (Terpos et al. [3]). Patients could suffer from a variety of signs and symptoms of osteolytic lesions and their complications [7]. Thus, bisphosphonates such as ZA are indicated to prevent bone complications such as hypercalcemia and fractures (Terpos et al. [3]). ZA is a new generation bisphosphonate administered usually every 3 or 4 weeks intravenously in at least 20 min. HR including urticaria, angioedema, wheezing and anaphylaxis to ZA are rare but they could lead to drug discontinuation. Slowing the infusion rate or increasing premedication is not always effective in preventing these reactions. Then, an allergy work-up and a RD procedure must be considered to avoid drug discontinuation. Evidence about RD efficacy is obtained from chemotherapy, antibiotics and recombinant enzyme studies [10–14].

This case report is the first to our knowledge on ZA desensitization in a 57-year-old woman affected by IgA-l MM. She experienced a significant immediate HR characterized by angioedema, flushing, fever, and headache after ZA infusion.

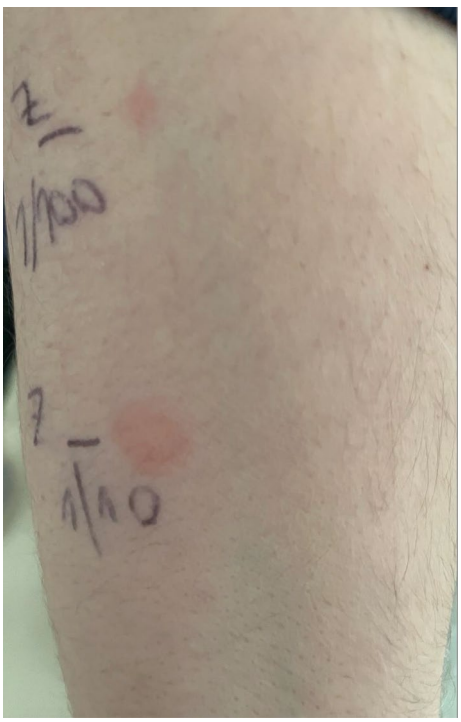

Fig. 1 Positive skin test to zoledronic acid. Positive intradermal skin test to 1:10 dilution of ZA

Allergy workup with skin tests revealed a positive intradermal test (IDT) reaction to ZA, confirming a hypersensitivity reaction. The possibility of an allergic reaction to excipients in Zometa®, such as mannitol, was deemed unlikely since the patient had previously received Darzalex® (daratumumab), which also contains mannitol, without experiencing any adverse reactions. This finding posed a dilemma of whether to suspend ZA treatment and change the drug. Thus, a 3-bag, 12-step RD approach was considered and implemented to induce a temporary tolerance to ZA. The patient tolerated the whole target dose of 4 mg without any HR. The mechanism underlying RD remains incompletely understood. However, the hypothesis implicates the gradual exposure of sub-therapeutic doses of the drug to desensitize mast cells and basophils, preventing anaphylactic reactions. Skin tests with the culprit drug may suggest the underlying mechanism of HR: i) IgE-mediated in positive skin tests; ii) MRXGPRX2 activation or complement activation with anaphylatoxins (C3a and C5a) production with mast cell/basophils activation. Our case showed a positive response to the skin test after 4 h which could suggest a delayed reaction. Nevertheless, RD can be performed in both immediate IgE-mediated or non-IgE-mediated HR and mild delayed HR [9]. After 3 RD infusions, we performed skin tests again that were deemed as negative, supporting the new evidence of the immunologic modification induced by RD that consists of the increase of regulatory cytokines (IL-10, IL-35), produced by the T-regulatory cells, that suppress the allergic response [15]. Indeed, the RD protocol for ZA was progressively shortened due to the excellent tolerance obtained.

On the other hand, skin tests for ZA are not standardized nor validated since a low sensitivity and false negatives may occur. The authors acknowledge standardized in vitro testing such as ZA-specific IgE or basophil activation test would be helpful. Nevertheless, the innovative desensitization protocol within an underexplored field of application paves the way for broader implementation in drug hypersensitivity management. Further research is essential to validate these findings and optimize desensitization protocols for clinical use.

Notably, based on our findings, we can assume that RD protocol guaranteed a safe and effective administration of ZA in our MM patient. However, further studies are warranted to elucidate the mechanism of hypersensitivity to ZA and establish the efficacy and safety of RD.

5 Conclusions

The presented case demonstrates the successful management with RD in a MM patient who developed HR to ZA. This approach provides a valuable therapeutic option for oncology patients experiencing HR to ZA, ensuring continued treatment efficacy and improving clinical outcomes. Further research is needed to refine RD protocols and establish their safety and efficacy for oncology patients who experienced HR to ZA.

Author contributions FS and AGS wrote the manuscript; FS performed the allergic workup and carried out the desensitization procedure; VD, AV and RR provided ideas and critical reading of the manuscript; FS conceived the desensitization approach; AGS, VD, AV and RR corrected the manuscript and secured financial support. All authors have read and approved the manuscript.

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Data availability The data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethical Committee of Bari University Hospital (reference number 1300, 21.12.2023). Informed consent was obtained from the patient to participate in the study. The participant was aware of the purpose of the procedure, its risks, and its benefits.

Consent for publication Informed consent was obtained from the patient for the publication of identifying information and images.

Competing interests The authors declare no competing interests.

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