Anaphylactic Shock due to Isatuximab and Successful Desensitization

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Isatuximab is an IgG1 monoclonal antibody (mAb) that acts against CD38. It is indicated in combination with carfilzomib-dexamethasone for the treatment of adults with refractory multiple myeloma previously treated with another therapy line. It is administered intravenously at 10 mg/kg/wk for 4 weeks and every 2 weeks thereafter [1].

Most reactions to mAbs are type I and typically occur after consecutive exposures to an mAb, while infusional and cytokine release reactions can occur during both the first exposure to an mAb and desensitization procedures. The mAbs most frequently implicated in hypersensitivity reactions are rituximab, infliximab, cetuximab, and trastuzumab [2-4]. Skin tests with mAbs have not been validated for the allergology study; therefore, false-positive and false-negative results are possible [2].

When assessing hypersensitivity reactions to isatuximab, it is important to consider polysorbate (PS-20 and PS-80), an FDA-approved excipient used in multiple mAbs. Systemic administration of high doses of polysorbate can cause hypotension and tachycardia. Several studies have demonstrated in vitro generation of the anaphylatoxins C3a and C5a, suggesting that the immunogenicity of polysorbate is complement-driven [5].

Immediate hypersensitivity reactions to mAbs, whether IgE-mediated or not, have been treated with rapid drug desensitization (RDD), which has proven to be a safe and highly effective procedure [2,6].

We present the case of a 64-year-old man diagnosed with multiple myeloma in January 2022. His personal history included iron deficiency anemia and dyslipidemia. Initially, he received 3 cycles of lenalidomide and bortezomib ending in April 2022. Owing to lack of response, treatment was switched to 4 cycles of isatuximab-carfilzomib-dexamethasone (June to October 2022), and autologous hematopoietic stem cell transplant (aHSCT) was performed. After aHSCT, it was decided to administer consolidation treatment with the same regimen. In April 2023, the patient received the first cycle of retreatment (with a previous infusion of dexamethasone). Under normal conditions, the total dose of isatuximab in this case is 620 mg in 250 mL of normal saline for a total volume of 281 mL. After 9.3 mL (20.51 mg isatuximab), the patient suddenly developed facial flushing, palmar pruritus, exanthema, wheals on the forearms, and blurred vision. After discontinuation of the infusion and aspiration of the perfusion line, the patient's vital signs were taken (blood pressure, 74/33 mmHg; heart rate, 109 bpm; temperature 36ºC). The clinical condition began to worsen immediately, with shivering (no fever) and syncope. He was treated with hydrocortisone 100 mg, dexclorpheniramine 5 mg, intensive fluid therapy, oxygen, paracetamol 1 g, and pethidine 25 mg (administered by the Oncology Day Unit personnel). His condition resolved completely after a few minutes. The patient was not treated with adrenaline because of the rapid response. A blood sample was drawn 90 minutes later for assessment of tryptase and interleukin (IL) 6. Carfilzomib was not administered. He was admitted to the hematology ward. At discharge, he was referred to the allergy department. The patient gave his written consent for the use of his medical data in this report.

Owing to the lack of information on testing with isatuximab, we used dilutions based on publications examining other mAbs [7]. Three weeks after the reaction, prick testing (20 mg/mL), intradermal testing (concentrations 1/1000, 1/100, 1/10, and 1/1), and PS-80 testing yielded a positive intradermal test result for isatuximab at the 1/1 concentration. The results of the polysorbate skin tests were negative. No positive or irritative test results were recorded for a control patient receiving the same isatuximab treatment regimen.

Postreaction values were 22.3 µg/L for serum tryptase and 33.5 pg/mL for IL-6. Baseline levels of tryptase and IL-6 were 3.1 µg/L and 2.0 pg/mL. The Flow CAST basophil activation test (BAT) yielded negative results.

After risk stratification, the hematologist confirmed the need for isatuximab. Therefore a 16-step RDD protocol was performed, as described previously [8]. This protocol was modified using 4 dilutions (Table), and home premedication was indicated 48 hours before initiation (ebastine, acetylsalicylic acid, and famotidine).

The RDD was performed at the Oncology Day Unit after hospital premedication with dexchlorpheniramine 5 mg IV, paracetamol 1 g IV, and oral montelukast 10 mg (hematologists routinely prescribe montelukast alongside all anti-CD38 drugs), with a final infusion rate of 140 mL/h over a total of 5.25 hours.

Isatuximab was recently approved for the treatment of refractory multiple myeloma. Isabwe et al [3] reported positive skin test results and/or positive specific IgE in infusional reactions with biologics, as well as increased levels of tryptase, IL-1, IL-6, and TNF-α. Consequently, the probable mechanism

Table. Desensitization Protocol Based on 16 Steps Corresponding to 620 mg of Isatuximab (100% Dose Needed) Modified According to Sloane et al [8].

	Step	mL/h	Time, min	Total mL	mg passed
Solution 1					
100 mL					
1/1000 dilution (0.62 mg)	1	2	15	0.5	0.0031
0.0062 mg/mL	2	4	15	1	0.0062
		Total	30	1.5	0.093
Solution 2	3	0.8	15	0.2	0.012
100 mL	4	2	15	0.5	0.031
1/100 dilution (6.2 mg)	5	4	15	1	0.062
0.062 mg/mL	6	8	15	2	0.124
		Total	60	3.7	0.229
Solution 3	7	2	15	0.5	0.310
100 mL	8	4	15	1	0.620
1/10 dilution (62 mg)	9	8	15	2	1.240
0.62 mg/mL	10	16	15	4	2.480
		Total	60	7.5	4.650
Solution 4[a]	11 12	5 10	15 15	1.25 2.5	3.07 6.15
250 mL	13	20	15	5	12.30
1/1 dilution (615 mg)	14	40	15	10	24.60
2.46 mg/mL	15 16	50 140	15 90.5	20 211.25	49.20 519.67
		Total, min	315.5	250	615
		Total, h	5.25	Total, mg	620

[a]Milligrams administered from bags 1, 2, and 3 have been removed from the total dose in bag 4 (615 mg).

of this reaction is a type I IgE-mediated hypersensitivity reaction. A concomitant cytokine release reaction cannot be ruled out, even though it is improbable owing to the absence of fever and the slight increase in IL-6. In our experience, cytokine release reactions generate IL-6 values of around 1000 pg/mL. Therefore, we do not consider the IL-6 value to be relevant in this patient.

The BAT can be used to diagnose hypersensitivity reactions to biologics, particularly rituximab [3]. However, studies in larger series of patients are needed to confirm the findings and establish BAT as a diagnostic tool.

Desensitization protocols have proven to be safe and effective for patients who experience hypersensitivity reactions to mAbs. The procedure enables patients to maintain their most effective treatment [2] and has proven to be more cost-effective than standard administration [6,8].

Isabwe et al [3] recorded a 23% rate of disruptive reactions during RDD with mAbs. These were mainly Brown grade I and occurred commonly during the final step of the RDD protocol. Other groups have observed a shift from a type I to a cytokine release reaction [2].

To our knowledge, there are no previous reports on RDD with isatuximab. We present the first case of a patient with anaphylactic shock due to isatuximab (grade III/severe according to the EAACI classification) and positive biomarkers (tryptase and skin test) suggesting a type I hypersensitivity reaction treated with successful RDD. The patient successfully underwent a 16-step RDD protocol with 4 dilutions. No disruptive reactions were observed. The second, third, and fourth desensitizations were based on 3 dilutions without incident. The fifth and sixth desensitizations are expected to be performed with a single dilution.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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