Successful Desensitization to Daratumumab after Severe Life-Threatening Reaction in A Patient with Refractory Multiple Myeloma.

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Multiple Myeloma (MM) is a clonal proliferation of malignant bone marrow plasma cells with high and uniform expression of CD38 [1]. Its survival has improved with autologous stem cell transplantation, proteasome inhibitors (Bortezomib and Carfilzomib) and inmunomoduladory drugs (Lenalidomide, Thalidomide and Pomalidomide). Nevertheless, most patients die from refractory disease despite the use of the first-line therapies previously mentioned. Humanized monoclonal antibodies (MoAb) represent a significant addition or even the only therapeutic option for the treatment of refractory MM. Daratumumab is an IgG1κ novel human monoclonal antibody that binds to CD38 and induces apoptosis [1]. It has been described that around 38,8 % of patients treated with Daratumumab present infusion related reactions (IRRs) after the administration of the first or second dose. They usually present with grade 1 or 2 IRRs consisting of symptoms of rhinitis, cough, dyspnea, bronchospasm, chills and nausea. Grade 3-4 IRRs are rare (3.8 %)[1].

A 66-year-old female with a history of refractory MM, started treatment with Daratumumab (final dose of 896 mg) due to disease progression. It included intravenous premedication with 5 mg dexchlorpheniramine, 1000 mg paracetamol and 20 mg dexamethasone administered 60 minutes prior to the infusion. Within 30 minutes of the

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start of Daratumumab, the patient developed flushing, oropharyngeal pruritus, bronchospasm and poor respiratory mechanic. Vital signs reported that Oxygen saturation was 85%, Blood Pressure 80/40 mmHg, Pulse 60 bpm and temperature 36.5 ºC.

The infusion was then interrupted and intravenous methylprednisolone (60 mg), hydrocortisone (200 mg) and dexchlorpheniramine (5 mg), as well as intramuscular epinephrine (0.5 mg), were administered. Nevertheless, the patient's symptoms progressed with right oculocephalic deviation, lack of glabellar and menace reflexes and hypercapnic respiratory acidosis, reason why she was admitted to the Intensive Care Unit, where invasive mechanical ventilation and norepinephrine perfusion was started. The patient was stabilized and was successfully extubated after two days without any neurological sequelae. No tryptase levels were measured. A grade 4 IRR[2] was diagnosed and referred to our Allergy department. Cutaneous tests with Daratumumab (Skin prick test at a concentration of 20 mg/ml; 2 mg/ml and 0.2 mg/ml. and intradermal test at a concentration of 2 mg/mL and 0.2 mg/mL) were performed 3 weeks after the reaction with negative results[3]. Baseline tryptase was measured to be 3.41 ng/mL (normal, <11.5 ng/mL). A basophil activation test (BAT) to Daratumumab was performed at different concentrations of 0,5 mg/mL, 1 mg/mL and 2 mg/mL using the two most common markers of activation/degranulation (CD203c and CD63)[4] with negative results for all concentrations tested. The referring physicians confirmed that Daratumumab was the mandatory treatment due to disease progression and failure of first line therapy. We assessed the management risks and informed consents were signed. Based on risk stratification for her severe reaction, a 4-bag, 14-step rapid drug desensitization protocol (RDD)[5], with additional premedication with montelukast and aspirin was administered without any breakthrough reactions (Table 1). Levels of IL-6

were measured using the high-sensitivity single molecule array (Simoa) technology[6], which have shown a reduction on IL-6 levels after desensitization (basal IL-6 21,85 pg/mL, after desensitization IL-6 < 2 pg/mL).To date the patient has tolerated 15 cycles without incident and excellent disease control.

Hypersensitivity reactions to MoAb include infusion-related reactions, cytokine-release reactions (CRRs), type I (IgE/non-IgE), type III (immune complexes), and delayed type IV reactions[3]. IRRs and CRRs to MoAb can occur at first infusion. In most cases the difference between IRRs and CRRs is the self-limiting nature of IRRs on repeat exposure and the response to premedication [5]. Despite the fact our patient received premedication following Daratumumab's data sheet, she developed a severe life-threatening reaction. To date there are not known reported IgE-mediated hypersensitivity reactions due to Daratumumab. Polysorbate 20 and mannitol are excipients found in Daratumumab presentations. There are reported cases of anaphylaxis due to sensitization to mannitol and polysorbate (mainly polysorbate 80) [7,8]. Since no IgE-mediated mechanism was demonstrated in our patient following skin tests and BAT, and the fact that she developed a severe life-threatening reaction in spite of receiving adequate premedication following Daratumumab's data sheet, we considered a CRRs as a possible mechanism of the severe reaction, that could benefit of a RDD protocol for Daratumumab administration [3]. Due to negative skin testing to daratumumab further studies with mannitol and polysorbate 20 were not performed.

It is well known that desensitization by expert allergists has emerged as a powerful tool that is safe and effective to maintain treatment in reacting patients with monoclonal antibodies [3,9].It has been described that in case of CRRs endotype/phenotype a desensitization protocol could be consider as a method of drug re-introduction [3].

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The molecular mechanisms of CRRs are not completely understood. It has not been fully shown that mast cells play a key role in the underlying molecular mechanisms of CRRs, It is considered that T cell activation and the release of pro-inflammatory cytokines like IL-6 and TNF-a play a major role. Isabwe et al described 8 patients that reacted during desensitization that had elevation of IL-6 levels. This explains that elevation of IL-6 and probably other pro-inflammatory cytokines are responsible of the clinical picture of reacting patients in CRRs and can be an important biomarker to identify these symptoms. Sancho-Serra et al noted that desensitized cells had a diminished early and late IL-6 and TNF-a production compare to activated cells [10]

To our understanding there are no reports of IL-6 measurements in non-reacting patients before and after desensitization to MoAb, so we do not know how IL-6 levels may vary. We found a downregulation of IL-6 after desensitization that could explain the absence of symptoms in our patient. This is only a case report so further studies are needed to confirm this findings.

To our knowledge, we report the first successful desensitization, following a RDD protocol in a patient with severe life-threatening Cytokine release reaction to Daratumumab.

Conflicts of interest

Maria Pilar Berges Gimeno has the following conflict of interest to declare:

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Table 1. RCUH standard rapid desensitization protocol adapted for a total dose of 896 mg of Daratumumab diluted in a volume of 250 mL of saline solution 0.9%.

Total Dose	896 (mg)	Solution concentration (mg/mL)	Total dose in each solution (mg)	Drug
Solution A	250 (mL)	0.0072	1.8	Daratumumab
Solution B	250 (mL)	0.072	18	Daratumumab
Solution C	250 (mL)	0.716	179	Daratumumab
Solution D	250 (mL)	3.024	756	Daratumumab

Step	Solution	Administered volume (mL)	Rate (mL/h)	Time (min)	Administered dose (mg)	Fold increase per-step	Approximative cumulative dose infuse (mg)
1	A	22	88	15	0.0	NA	0.0
2	A	25	100	15	0.2	NA	0.2
3	A	50	200	15	0.4	x2	0.6
4	A	100	400	15	0.7	x2	1.3
5	B	22	88	15	0.0	NA	1.3
6	B	25	100	15	1.8	x2.5	3.1
7	B	50	200	15	3.6	x2	6.7
8	B	100	400	15	7.2	x2	13.9
9	C	22	88	15	0.0	NA	13.9
10	C	25	100	15	18	x2.5	31.9
11	C	50	200	15	36	x2	67.9
12	C	100	400	15	72	x2	139.9
13	D	22	88	15	0.0	NA	139.9
14	D	250	125	120	756	x2.6	896

Total infusion time: 315 minutes (5.2h)
NA, Not applicable

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