Desensitization Protocol to Atezolizumab and Bevacizumab after Severe Anaphylaxis in the Treatment of Lung Adenocarcinoma

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Lung cancer is the most common cancer in the world, accounting for 19% of all cancer-related deaths [1].Monoclonal antibodies (mAbs) transformed the treatment of multiple diseases, including lung cancer [2] inducing humoral and cellular immune responses, and subsequent hypersensitivity reactions (HSR) and infusion reactions (IR). These reactions range from mild cutaneous manifestations to life-threatening anaphylaxis with hypotension, oxygen desaturation, cardiovascular collapse, and death [3].

Antineoplastic agents are the third leading cause of fatal drug-induced anaphylaxis in the United States. Severe HSRs threaten first-line treatments and affect survival prognosis, so proper management of this problem is essential [4].

A 64-year-old male with no allergic history, bladder cancer in 2017 in treatment with platinum salts with complete resolution, was diagnosed with poorly differentiated lung adenocarcinoma with metastases to the adrenal glands and mediastinum,T4N3M1 (classification TNM) in March 2020. The oncologist indicated atezolizumab (1,200 mg), bevacizumab (600 mg), carboplatin (4 AUC) and paclitaxel (180 mg/m^2) every 3 weeks for 4 cycles; the first cycle of treatment was administered without hypersensitivity reactions. Thirty minutes after starting the second cycle of atezolizumab, he presented chest pain, hypotension, diaphoresis and dizziness, the infusion was suspended and intravenous hydrocortisone and diphenhydramine were administered, resolving the symptoms. Two days later the second cycle of bevacizumab was administered and 20 minutes later he

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presented hypotension, diaphoresis, cyanosis, hypoxia, and syncope (anaphylaxis grade 3); which was successfully controlled with 0.5 mg of intramuscular epinephrine, corticosteroids and antihistamines.

Skin prick test at concentration of 60 mg/mL of atezolizumab and 25 mg/mL of bevacizumab were negative. The intradermal skin tests at concentration of 0.6 mg/mL and of 0.25 mg/mL were positive with a 10 x 10 mm and 13 x 11 mm wheal respectively, compared to the negative control (glycerinated solution) 3 x 3 mm wheal. Due to the severity of the symptoms and need for treatment, desensitization protocols were performed 24 hours apart each. He was premedicated with intravenous chlorpheniramine (10 mg), methylprednisolone (60 mg) to decrease the intensity of symptoms and ondansetron (8 mg) 1 hour prior to the infusion of the mAbs.

A total of 1,200 mg of atezolizumab and 600 mg of bevacizumab were given in separate days with 4 bags – 16 steps protocols (initial concentration 1:1,000 of the total dose) (Table 1) with increasing rate and concentration every 15 minutes without presenting hypersensitivity reactions. Fluids with normal saline solution at 100 mL/hour throughout the first 15 steps with an increase to 250 mL/hour after step 16 were administered.Due to the tolerance of the protocol without presenting HRS, it was decided to perform a 3 bag - 12step protocol (initial concentration 1: 100 of the total dose) every 3 weeks, which was successfully tolerated for 2 cycles. This protocol will be carried out for 1 year by indication of the oncologist as the first line of treatment.

Atezolizumab is a humanized immunoglobulin (Ig) G-1 class antibody that binds to programmed death ligand 1 (PD-L1) approved for bladder, breast, and lung cancer. In 2016 the FDA reported severe IR at 1.3-1.7% and HSR in ≤1% of cases [2].

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Bevacizumab is a humanized IgG-1monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), which is essential for normal and tumor angiogenesis, and is considered first-line therapy for non-small cell lung cancer.HSR to bevacizumab has been reported in 0.3 – 6.1% of cases, manifested with dyspnea, erythema, hypotension, oxygen desaturation, chest pain and nausea/vomiting [2].

HSRs are classified according to the time of onset and the mechanism involved, as immediate (<1 hour) or late (>1 hour) and allergic or non-allergic. Immediate ones include IR, IgE-mediated cytokine release syndrome, and HSR. They can be clinically indistinguishable from each other and mixed-type reactions can be observed [5].

IRs are "any signs or symptoms experienced during the infusion of pharmacological or biological agents or any event that occurs on the first day of administration of the drug." Reactions to mAbs appear most frequently from 10 minutes to 4 hours after starting administration. Although there is a lot of similarity with anaphylaxis symptoms, IR can be caused by multiple mechanisms, while anaphylaxis is an IgE-mediated reaction [6].

Brown and colleagues classify grade 1 anaphylaxis as skin symptoms, grade 2 involves systemic symptoms, and grade 3 presents with severe symptoms such as syncope, incontinence, hypotension, or hypoxia. Standardized skin tests for mAbs have not been established. The recommendation is to wait 2 to 4 weeks after the reaction, to avoid false negatives after anaphylaxis. Positive skin tests will indicate an IgE-mediated immune mechanism, so the patient will be a candidate for a desensitization protocol [7].

In vitro and in vivo models propose that in desensitization, mast cells and basophils can be induced to inhibitory pathways by small increased doses of antigen, disabling signal

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transduction and mediator release. In severe anaphylaxis, starting at 1/1000 of the target dose, delivering them with an interval of time sufficient to avoid mast cell degranulation; it inhibits the acute release of beta-hexosaminidase, prevents the generation of arachidonic acid and products such as leukotrienes and prostaglandins, as well as the late generation of inflammatory cytokines. Furthermore, the entry of calcium is eliminated, and the polymerization of actin is altered, which provides stability to the intracellular granules in an antigen-specific manner, inducing a temporary tolerance that protects from anaphylaxis [3].

The safest option for HSR to a drug is to avoid it, but in patients with malignancies, switching to a second-line agent negatively affects quality of life and expectancy. Patients with type I and cytokine-release reactions to mAbs are thought to be candidates for desensitization [8].

In terms of safety and efficacy, desensitization is highly effective and provides patients first-line therapy, better clinical results and fewer complications, which reduces mortality, morbidity and expense in medical care [9, 10].

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Conflicts of interest

The authors declare that they have no competing interests.

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Table 1. 4bags - 16 steps desensitization protocols to atezolizumab and bevacizumab.

Steps	Solution	Rate (ml/h)	Time (min)	Volume per step (ml)	Administered dose (mg)	Cumulative dose (mg)	Administered dose (mg)	Cumulative dose (mg)
					Atezolizumabprotocol		Bevacizumabprotocol	
1	1	2.5	15	0.625	0.003	0.003	0.0015	0.0015
2	1	5	15	1.25	0.006	0.009	0.003	0.0045
3	1	10	15	2.5	0.012	0.021	0.006	0.0105
4	1	20	15	5	0.024	0.045	0.012	0.0225
5	2	2.5	15	0.625	0.03	0.075	0.015	0.038
6	2	5	15	1.25	0.06	0.135	0.03	0.068
7	2	10	15	2.5	0.12	0.255	0.06	0.128
8	2	20	15	5	0.24	0.5	0.12	0.248
9	3	5	15	1.25	0.6	1.1	0.3	0.55
10	3	10	15	2.5	1.2	2.3	0.6	1.15
11	3	20	15	5	2.4	4.7	1.2	2.35
12	3	40.	15	10	4.8	9.5	2.4	4.75
13	4	10	15	2.5	11.9	21.4	5.95	10.7
14	4	20	15	5	23.8	45.2	11.9	22.6
15	4	40	15	10	47.6	92.8	23.8	46.4
16	4	80	174.4	232.5	1,107.2	**1,200**	553.6	**600**