Protocol for Desensitization to Trastuzumab in a Patient With Anaphylaxis and Stage IV Breast Cancer: A Case Report

de Lira-Quezada CE, Villarreal-González RV, González-Díaz SN, Acuña-Ortega N
Regional Center of Allergy and Clinical Immunology, University Hospital "Dr. José Eleuterio González", Faculty of Medicine, Autonomous University of Nuevo León, Monterrey, Mexico

J Investig Allergol Clin Immunol 2020; Vol. 30(5): 376-377
doi: 10.18176/jiaci.0558

Key words: Trastuzumab. Desensitization. Anaphylaxis. Biologic therapy.

Palabras clave: Trastuzumab. Desensibilización. Anafilaxia. Terapia biológica.

The frequency of hypersensitivity reactions (HSRs) to monoclonal antibodies has increased considerably, often preventing the use of first-line therapies for fear of inducing severe reactions [1]. Trastuzumab is approved for the treatment of metastatic breast cancer and has reduced the frequency of recurrence and death by increasing the pathological response rate and improving overall survival [2]. Rapid drug desensitization (RDD) is a safe and effective tool for the administration of first-line therapy to patients who are allergic to their cancer treatment [1]. Allergic patients can receive chemotherapy and biologics thanks to RDD, which ensures the same survival outcomes as standard first-line therapy [3] and is cost-effective [4]. We found that no allergy or oncology society has yet published a specific guideline on drug desensitization to chemotherapy. Therefore, many physicians might be unaware of this option and decide to stop first-line treatment when it is still effective.

A 50-year-old woman was diagnosed with stage IV *HER2*-positive breast cancer in October 2018, with metastasis to bone, liver, and lungs. The oncology service administered the first cycle of treatment with trastuzumab (6 mg/kg), docetaxel (75 mg/m^2), and zoledronic acid (4 mg) every 3 weeks. Twenty minutes after initiating the second cycle of trastuzumab, the patient developed dyspnea, facial and palmar erythema, angioedema, blurred vision, hypotension, hypoxia, and tachycardia. The infusion was suspended, and she was treated with intravenous norepinephrine in the emergency room. Anaphylaxis resolved, and she was referred to our allergy service for further evaluation. The results of skin tests performed with docetaxel (1 mg/1 mL) were negative. The following administration of docetaxel was treated as a high-risk drug provocation test, which was negative; therefore, hypersensitivity to docetaxel was ruled out [5]. Zoledronic acid was not tested since it had not yet been administered in the cycle. Trastuzumab was assessed with skin prick testing (21 mg/mL) and intradermal testing (0.21 mg/mL) [6], which proved positive, with a 12×10–mm wheal and 12×12–mm erythema and a negative control wheal and erythema of 3×4 mm, thus confirming immediate hypersensitivity. Histamine (10 mg/mL) and saline solution were used as the positive and the negative control, respectively. Given the need for a specific antibody for treatment of HER2-positive breast cancer, the desensitization protocol was adapted from Hong et al [7], with 4 bags and 16 steps, at increasing concentrations of 0.00188, 0.0188, 0.176, and 1.746 mg/mL (duration, 6.67 hours). The patient was premedicated with chlorpheniramine (10 mg) and methylprednisolone (40 mg) [8]. Corticosteroids can decrease the intensity of symptoms but do not protect from severe reactions [8]. Ondansetron (8 mg) was used to prevent the nausea induced by chemotherapy. After tolerating 9 more cycles of the 4-bag, 16-step protocol, the patient initiated a 3-bag, 12-step protocol based on concentrations of 0.0176, 0.176, and 1.746 mg/mL (duration, 5.67 hours) (Table). We administered saline solution at 100 mL/h throughout the first 11 steps, with an increase to 250 mL/h after step 12. The procedure was well tolerated, and, after 20 RDD procedures, the patient remains free of HSRs to trastuzumab.

Trastuzumab is known to induce HSRs in 16% of patients, and these take the form of anaphylaxis in 2% of cases [9]. When a patient presents with an HSR to biologics, doctors tend to administer an alternative treatment [4], thus compromising the patient's prognosis by avoiding the optimal first-line treatment [4]. In the case we report, the culprit drug was essential.

Brennan et al [10] described RDD to trastuzumab in 3 patients with mild to moderate anaphylaxis who presented reactions in 29% of the procedures performed. RDD is a high-risk procedure that requires specific resources and trained staff and must be tailored to the patient's specific needs. Thus, RDD should only be performed by expert allergists who can assess the patient's risk and treat anaphylaxis if needed [10].

We report a series of successful and uneventful RDDs to trastuzumab in a high-risk patient (anaphylaxis as the

Table. Three-Bag, 12-Step Protocol for Desensitization to Trastuzumab[a]

Step	Solution (Bag)	Infusion, mL/h	Time, min	Infused Volume, mL	Dose Administered, mg	Cumulative Dose, mg
1	1	2.0	15	0.5	0.0088	0.0088
2	1	5	15	1.25	0.022	0.0308
3	1	10	15	2.5	0.044	0.0748
4	1	20	15	5	0.088	0.1628
5	2	5	15	1.25	0.22	0.3828
6	2	10	15	2.5	0.44	0.822
7	2	20	15	5	0.88	1.7028
8	2	40	15	10	1.76	3.4628
9	3	10	15	2.5	4.365	7.828
10	3	20	15	5	8.73	16.558
11	3	40	15	10	17.46	34.02
12	3	80	175	232.5	405.945	440

[a]Adapted from Hong et al [7].

initial reaction and positive skin test results). The literature shows how assessment and management by an expert team of allergists can guarantee the success of RDD. Thanks to this procedure, the patient was able to continue with a life-saving treatment that would have otherwise been stopped. Since data on RDD to monoclonal antibodies such as trastuzumab remain very limited, reports such as this one on the successful use of this technique are extremely promising for the future of these patients.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

The abstract "Trastuzumab Desensitization Protocol: A Therapeutic Challenge In A Patient With Metastatic Breast Cancer" was presented as an e-poster at the 2019 ACAAI Annual Meeting held on 11/08/2019 in Houston, Texas.

References

1. Kahn D. Hypersensitivity and immunologic reactions to biologics: opportunities for the allergist. Ann Allergy Asthma Immunol. 2016;117:115-20.
2. Isabwe G, Garcia Neuer M, de las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. J Allergy Clin Immunol. 2018;142:159-70.
3. Berges-Gimeno MP, Carpio-Escalona LV, Longo-Muñoz F, Bernal-Rubio L, Lopez-Gonzalez P, Gehlhaar P, et al. Does rapid drug desensitization to chemotherapy affect survival outcomes? J Investig Allergol Clin Immunol. 2020;30(4):254-63
4. Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, costs, and efficacy of rapid drug desensitization to chemotherapy and monoclonal antibodies. J Allergy Clin Immunol Pract. 2016;4:497-50.
5. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A large single hospital experience using drug provocation testing and rapid drug desensitization in hypersensitivity to antineoplastic and biological agents. J Allergy Clin Immunol Pract. 2019;7:618-3.
6. Castells M. Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic inflammatory Diseases: The Role of Desensitizations. Front Immunol. 2017:8;1472.
7. Hong DI, Bankova L, Cahill KN, Kyin T, Castells M. Allergy to monoclonal antibodies: cutting-edge desensitization methods for cutting-edge therapies. Expert Rev Clin Immunol. 2012;8(1):43-54.
8. Castells M. Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol. 2017;140:321-33.
9. Price L, Brunt AM. Trastuzumab infusion reactions in breast cancer. Should we routinely observe after the first dose? Eur J Hosp Pharm. 2018;25(6):331-3.
10. Brennan PJ, Rodriguez-Bouza T, Hsu FI, Sloane D, Castells M. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol. 2009;124:1259-66.

Manuscript received January 27, 2020; accepted for publication April 22, 2020.

Cindy Elizabeth de Lira-Quezada
Regional Center of Allergy and Clinical Immunology, University Hospital "Dr. José Eleuterio González", Faculty of Medicine, Autonomous University of Nuevo León
Gonzalitos y Madero s/n
Colonia Mitras Centro Monterrey, NL, México CP, 64460
E-mail: ce.dlira@gmail.com