

Desensitization Protocol 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.

Corresponding author:

Cindy Elizabeth de Lira-Quezada

Gonzalitos y Madero s/n Colonia Mitras Centro Monterrey, NL, México CP. 64460

E-mail: ce.dlira@gmail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0558

Key words: Trastuzumab, Desensitization, Anaphylaxis, Biologic therapy

Palabras clave: Trastuzumab, Desensibilización, Anafilaxia, Biológicos

A surge in hypersensitivity reactions (HSRs) to monoclonal antibodies (mAb) has been observed, 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 reducing recurrence and death by increasing 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 allergic to their oncology treatment [1]. Allergic patients can receive their 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, and so many physicians might be unaware of this option and thus decide to stop first line treatment when is still effective.

A 50 year old female patient was diagnosed with stage IV Her2- positive breast cancer on October 2018 with metastasis to bone, liver and lungs. The oncology service indicated the first cycle of treatment with trastuzumab (6 mg/kg), docetaxel

(75 mg/m²) and zoledronic acid (4mg) with administration every 3 weeks. Twenty minutes after initiating the second cycle of trastuzumab the patient presented 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 with resolution of anaphylaxis and referred to our allergy service for further evaluation. Skin tests were performed to docetaxel (1mg/1mL) with negative result. The following administration of docetaxel was treated as a high-risk drug provocation test, and this was negative, so hypersensitivity to docetaxel was ruled out [5]. Zoledronic acid had not been yet administered in the cycle so it was not tested. Trastuzumab skin prick test (21 mg/mL) and intradermal tests (0.21 mg/mL) were applied [6], resulting positive the latter one with a 12x10 mm wheal, 12x12 mm erythema and negative control wheal and erythema of 3x4 mm, confirming immediate hypersensitivity. Histamine (10 mg/ml) and saline solution were used as the positive and the negative control, respectively. Due to the need of a specific antibody for HER-2 treatment, desensitization 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 with a 6.67 hour duration. The patient was premedicated with clorpheniramine (10 mg) and methylprednisolone (40 mg) [8]. Corticosteroids can decrease the intensity of symptoms but do not protect from severe reactions [8]. Ondansetron (8mg) was used to prevent nausea induced by chemotherapy. After tolerating 9 more cycles of the 4-bag 16 step protocol, a 3-bag 12 step protocol with a 5.67 hour duration was

initiated using 0.0176, 0.176 and 1.746 mg/mL (table 1). We administered saline solution at 100 mL/hour throughout the first 11 steps with an increase to 250 mL/hour after step 12. The procedure was well tolerated and up to date after 20 RDD, the patient continues with no hypersensitivity reactions to trastuzumab.

Trastuzumab is known to induce HSRs in 16% of patients, including anaphylaxis in 2% of cases [9]. When a patient presents with 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 this patient the culprit drug was essential.

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

We have reported a series of successful and uneventful RDDs to trastuzumab in a high-risk patient (anaphylaxis as initial reaction and positive skin tests). The literature shows how assessment and management by an expert team of allergists is a guarantee for the success of RDD. Thanks to this procedure, the patient could continue with a life-saving treatment that would have otherwise been stopped. Data on RDD to mAb such as trastuzumab is still very limited, so reports such as this on

the successful use of this technique are extremely promising for the future of these patients.

Consent for publication

Written and informed consent for publication was obtained from the patient. The patient was informed that de-identified data would be used in the scientific research and publications.

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 presentation in 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* 2019; <https://doi.org/10.18176/jiaci.0425>. [epub ahead of print]
- [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):331-33

[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.

Table 1. 3-bag 12 step desensitization protocol to trastuzumab

Step	Solution (Bag)	Infusion (mL/hr)	Time (minutes)	Infused Volume	Dose administered	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

Adapted from Hong et al [7].