



Desensitization to Chemotherapeutic Agents

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Question:

I would like your help with a patient referred because of severe anaphylactic reaction to her chemotherapy. The patient had received ado-trastuzumabemtansine, which is a human epidermal growth factor receptor 2 (HER2) targeted antibody-drug conjugate. It contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative). The patient is a 64-year-old woman who had HER2⁺ metastatic breast cancer that was unresponsive to all medications, including trastuzumab alone. She was started on ado-trastuzumabemtansine, but the infusion had to be stopped due to a severe anaphylactic reaction. Approximately three-fourths of the way through her infusion, she developed severe breathing difficulty and became hypoxic. She also became hypotensive and almost lost consciousness. However, her tumors were responsive to even this first dose of the medication, and the patient begged to continue, despite her reaction. I am unsure of how to proceed with her desensitization, due to the severity of her reaction and the newness of this medication.

Response:

Your inquiry was sent to Mariana Castells, MD, PhD, who is an internationally known expert in desensitization procedures and who has published extensively in this area. Here is her response:

Thank you for your inquiry regarding a hypersensitivity reaction to ado-trastuzumabemtansine, a humanized IgG1 monoclonal antibody against HER2 (trastuzumab) linked to DM1. Ado-trastuzumabemtansine is used as a single agent for the treatment of patients with HER2⁺ metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination, and who developed disease recurrence during or within 6 months of completing adjuvant therapy.

Ado-trastuzumabemtansine toxicities include hepatic and cardiac toxicity as well as neuropathy and thrombocytopenia. In addition, interstitial lung disease and acute respiratory distress

syndrome have been documented. Infusion-related reactions (IRR) and hypersensitivity reactions are rare and, if severe, have prompted discontinuation of the medication.¹ Treatment with ado-trastuzumabemtansine has not been studied in patients who had trastuzumab permanently discontinued due to IRR and/or hypersensitivity, but treatment with ado-trastuzumabemtansine is currently not recommended for these patients.

IRR and hypersensitivity are characterized by one or more of the following symptoms: flushing, chills, fever, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia. In a randomized trial, the overall frequency of IRRs in patients treated with ado-trastuzumabemtansine was 1.4%.¹ In most patients, these reactions resolved over the course of several hours up to 24 hours after the infusion, and the recommendation is to interrupt treatment in patients with severe IRR or life-threatening IRR. Patients may present with reactions upon first exposure, or the reaction may relate to prior exposure and sensitization to trastuzumab. One case of a serious, allergic and/or anaphylactic-like reaction has been observed in clinical trials of ado-trastuzumabemtansine,² and 44 of 836 patients (5.3%) treated in 6 studies developed anti-therapeutic antibodies, which indicated that the medication is immunogenic,² although the clinical significance of these antibodies has not been studied. Hypersensitivity to trastuzumab has been well described, and, although anaphylactic reactions are rare, they can be severe and life threatening.

The mechanism of these reactions, as for other monoclonal antibodies, is consistent with 2 different patterns. Some patients react at the first or second exposure with chills; fever; hypotension or hypertension; and shortness of breath, wheezing, or acute respiratory failure, consistent with a cytokine storm and nonspecific activation of immune cells, such as macrophages and lymphocytes. These reactions respond to premedications such as adrenal corticosteroids and COX-1/COX-2 inhibitors if mild and have responded to desensitization if severe. A second pattern of presentation occurs in patients exposed to many courses of trastuzumab in which pruritus, flushing, hives, angioedema, shortness of breath and wheezing, nausea, vomiting, and diarrhea occur and progress to anaphylaxis with hypotension, cardiovascular collapse, and possibly death.

Your patient had a severe anaphylactic reaction, and she should have received epinephrine. Tryptase levels should have been measured and were likely elevated, as seen with other monoclonal antibody reactions. Evaluation of the patient requires skin testing to trastuzumab, the likely agent involved in the reaction. Positive skin testing to trastuzumab has been shown in patients with several exposures before the initial reaction. Despite the severity of the reaction, the patient is a likely candidate for rapid desensitization if ado-trastuzumabemtansine is considered first-line therapy. Premedication with steroids and antihistamines alone is not recommended as the only management plan because these medications do not provide protection against anaphylaxis due to the

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administration of chemotherapeutic agents. But premedication can be used during desensitization, which may include long- and short-acting H1 antihistamines, H2 antihistamines, leukotriene receptor blockers, and aspirin for prostaglandin blockade.

Due to the severity of the reaction, the patient needs admission to an intensive care setting for constant monitoring. The rapid desensitization protocol should include 4 intravenous infusion solution bags and 16 steps, and the first infusion bag should consist of 1/1000 dilution of the target infusion concentration. The infusion should proceed by doubling the dose at each step every 15 minutes until reaching the target dose. This protocol³ has been used in hundreds of patients with no deaths and in whom 94% of the patients had no or mild reactions during desensitization, and only 6% had moderate-to-severe reactions

that did not prevent the completion of the protocol. Because of the inherent risk for anaphylaxis during rapid desensitization, if the medication can be replaced by one that induces equal life expectancy or equal quality of life, rapid desensitization should not be attempted.

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