

Rapid desensitization and rush immunotherapy to trastuzumab (Herceptin)

To the Editor:

Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody directed against the proto-oncogene HER2/neu. It contains small amounts of murine Fab peptide sequences. Trastuzumab therapy has been shown to improve survival and to cause tumor regression in selected patients with metastatic breast cancer.¹

Severe hypersensitivity reactions, including respiratory distress, angioedema, and anaphylactoid symptoms, has been reported in 2.5 % of patients treated with trastuzumab.²

We here report 2 cases of rapid desensitization and rush immunotherapy to trastuzumab.

Patient 1 was a 39-year-old woman with a history of metastatic breast cancer expressing HER2/neu. She failed to respond to chemotherapy with Adriamycin and Taxotere. Trastuzumab 4 mg/kg and Taxotere therapy was instituted on a weekly basis. Mild urticaria with itching of the palms was noted after the third infusion of 2 mg/kg of trastuzumab and Taxotere. A week later, after 5 mg of trastuzumab was administered intravenously, she developed flushing, severe vaginal itching, nausea, vomiting, rigors, and angioedema of the face, lips, and tongue. The infusion was stopped and the patient was treated intravenously with 100 mg of hydrocortisone, Demerol 25 mg, Zofran 8 mg, and Benadryl 50 mg.

Patient 2 was a 48-year-old woman with a history of hormone receptor–negative metastatic breast cancer expressing HER2/neu. In October 2000 she was treated with vinorelbine, docetaxel, paclitaxel, and trastuzumab. Because of cardiac and neurotoxicity, she remained on trastuzumab alone, and her disease went into remission. Infusions were tolerated until July 2001, when she began to have diffuse pruritis that was treated with diphenhydramine and H2 blockers. In August 2001 she experienced throat tightening less than 1 minute after an infusion was started. Pretreatment with cortico-steroids did not prevent these reactions.

In patient 1, the result of allergy skin prick testing with 0.5 mg/mL of trastuzumab was negative; however, a 7-mm wheal and 15-mm flare was noted on intradermal testing at 0.5 mg/mL. In patient 2 and in 2 control subjects, trastuzumab failed to elicit a reaction on intradermal testing at 5 mg/mL.

After written informed consent was obtained, each of the 2 patients underwent a modified rapid desensitization protocol³(Table 1).

Table I. Rapid intravenous trastuzumab desensitization protocol

Dose	Amount injected	Time (h)
20.0 µg	2.0 mL (10 µg/mL)	0
40.0 µg	4.0 mL (10 µg/mL)	0.25
60.0 µg	6.0 mL (10 µg/mL)	0.50
125.0 µg	12.5 mL (10 µg/mL)	0.75
250.0 µg	25.0 mL (10 µg/mL)	1.00
500.0 µg	0.5 mL (1 mg/mL)	1.25
1.0 mg	1.0 mL (1 mg/mL)	1.50
2.5 mg	2.5 mL (1 mg/mL)	1.75
5.0 mg	5.0 mL (1 mg/mL)	2.00
7.5 mg	7.5 mL (1 mg/mL)	2.25
10.0 mg	10.0 mL (1 mg/mL)	2.50
15.0 mg	15.0 mL (1 mg/mL)	2.75
17.5 mg	17.5 mL (1 mg/mL)	3.00
25.0 mg	25.0 mL (1 mg/mL)	3.25
40.0 mg	40.0 mL (1 mg/mL)	3.50

Diphenhydramine 50 mg and ranitidine 150 mg were administered orally 1 hour before the procedures. Patient 1 developed an episode of angioedema of the tongue and urticaria at 5 mg that was treated with epinephrine administered intramuscularly, but she completed the protocol without further reaction.

Patient 2 developed diffuse pruritis after the 125 µg dose; she responded to diphenhydramine 50 mg administered intravenously. At the 7.5-mg dose the patient developed rigors and an elevated blood pressure requiring treatment with meperidine and sublingual nitroglycerin. She subsequently tolerated the rest of the desensitization without reaction.

Subcutaneous immunotherapy with trastuzumab (Table II) was interspersed with weekly therapeutic intravenous infusions of 2 mg/kg.

Table II. Rush immunotherapy protocol

Week(s)	Amount administered subcutaneously (mg)	Frequency
1	15	Daily
2	15	3 Times/wk
3-10	20	2 Times/wk
11 and ongoing	20	Weekly

The diphenhydramine/ranitidine pretreatment regimen was repeated before each infusion.

Postinfusion reactions occurred for several months in patient 1; these were characterized by rigors, chills, and occasional hives. After 3 years, this patient continues to receive weekly trastuzumab infusions; she has had no further allergic symptoms. Intradermal retesting at 11 months was negative at 5 mg/mL and subcutaneous immunotherapy was discontinued.

Patient 2 tolerated subcutaneous immunotherapy without adverse effects; however, after her second and third infusions she developed severe hypertension that necessitated discontinuation of trastuzumab. She was restarted on vinorelbine, docetaxel, and paclitaxel in November 2001 but had to discontinue this regimen again because of neurotoxicity.

Human antimouse and human antihuman antibodies were not detectable in either patient's serum.

This is the first report that we are aware of describing the combination of rapid desensitization and rush immunotherapy protocols to prevent anaphylaxis to monoclonal antibodies and allow maintenance of monoclonal immunotherapy. This protocol might be useful in treating patients who are experiencing anaphylaxis after therapy with other recombinant humanized monoclonal antibodies.

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