

Letter to the Editor

A desensitization protocol for the mAb cetuximab

To the Editor:

Cetuximab, an antiepidermal growth factor receptor mAb, is currently approved for the treatment of metastatic colorectal cancer¹ and squamous cell head and neck cancer.² As with any biologic agent, cetuximab infusion can be associated with adverse events. Original data suggested that infusion reactions could occur in up to 20% of cetuximab infusions,³ with approximately 3% of these being anaphylactic or anaphylactoid in nature.⁴ Interestingly, an even higher incidence of hypersensitivity reactions has been reported (approximately 20%), particularly in the south-eastern United States, since the original US Food and Drug

Administration approval.⁵ Recently, it was reported that most of these reactions occur in patients who have preformed IgE antibodies to the galactose- α -1,3-galactose portion of the cetuximab molecule.⁶ Although avoiding a rechallenge with cetuximab after a severe infusion reaction is preferable, this might not be an option if other chemotherapy regimens have been exhausted. We report the first successful case of a desensitization regimen for cetuximab in a patient with an IgE-mediated hypersensitivity reaction who required continuation of treatment.

Our patient was a 60-year-old woman with a history of metastatic breast cancer and documented progression of disease despite various chemotherapy regimens. She was undergoing her first infusion with carboplatin and cetuximab (400 mg/m²) as a salvage regimen. The patient had received premedication with

TABLE I. Cetuximab desensitization protocol

Bag 1: 0.0002 mg/mL cetuximab

Dose no.	Cumulative dose (after receiving each dose)	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	0.001	0.001	5	1
2	0.003	0.002	10	2
3	0.007	0.004	20	4
4	0.015	0.008	40	8

Bag 2: 0.002 mg/mL cetuximab

Dose no.	Cumulative dose (after receiving each dose)	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	0.03	0.015	7.5	1.5
2	0.06	0.03	15	3
3	0.12	0.06	30	6
4	0.25	0.13	65	13

Bag 3: 0.02 mg/mL cetuximab

Dose no.	Cumulative dose (after receiving each dose)	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	0.5	0.25	12.5	2.5
2	1	0.5	25	5
3	2	1	50	10
4	4	2	100	20

Bag 4: 0.2 mg/mL cetuximab

Dose no.	Cumulative dose (after receiving each dose)	Dose of cetuximab (mg)	Volume of infusion (mL)	Time of infusion (min)
1	8	4	20	4
2	16	8	40	8
3	32	16	80	16
4	64	32	160	32

Bag 5: 2 mg/mL cetuximab

Dose no.	Cumulative dose (after receiving each dose)	Dose of cetuximab (mg)	Volume of infusion (mL)	Original proposed time of infusion (min)	Actual time of infusion* (min)
1	129	65	32.5	6.5	6.5 + 30-min wait period
2	259	130	65	13	13 + 30-min wait period
3	519	260	130	26	60 (infusion rate 2.5 mL/min)
4	844	325	162	32.5	60 (infusion rate 2.5 mL/min)

Premedication

Prednisone, 20 mg, 12 hours before desensitization

Prednisone, 20 mg, 1 hour before desensitization

Diphenhydramine, 25 mg administered intravenously, 30 minutes before desensitization

Infusion rate of 5 mL/min unless otherwise specified.

Successive doses are 15 minutes apart unless otherwise specified.

*Doses were prolonged in bag 5 (2 mg/mL) because of a pruritic maculopapular rash on the torso. Diphenhydramine, famotidine, and solumedrol were administered at doses 1 and 2 in bag 5 for cutaneous symptom relief.

dexamethasone (12 mg) 12 hours and 1 hour before the infusion and ranitidine (150 mg) and intravenous diphenhydramine (50 mg) 30 minutes before the infusion. Cetuximab was initiated at 25 mL/h and gradually increased every 3 minutes to achieve a final rate of 200 mL/h. Ten minutes into the infusion (28 mg of the expected 843-mg dose), the patient became warm and flushed. She was tachycardic (124 beats/min) and hypotensive (19 mm Hg decrease in systolic blood pressure), and her oxygen saturation decreased to 90% on room air. No urticaria was noted. The infusion was stopped, and the patient was given antihistamines and intravenous steroids and observed for several hours. Epinephrine was not administered at the discretion of the oncology infusion service. Carboplatin was then infused without incident, and the patient was discharged. Further laboratory investigation performed at the University of Virginia revealed that the patient had pre-existing detectable anti-cetuximab IgE antibodies (1.06 IU/mL, positive being >0.35 IU). Details regarding this assay have been published.⁶ Her systemic symptoms would be classified as a grade 3 reaction⁷ and, combined with the presence of IgE anti-cetuximab antibodies, were consistent with anaphylaxis. This patient had few other therapeutic alternatives and had progressed despite multiple chemotherapy and radiation regimens. Cetuximab desensitization was pursued after informed consent was obtained.

A desensitization protocol was designed based on the patient's known dosage of reaction and final dose to be achieved (Table I). Dose escalation occurred every 15 minutes, with each dose representing a doubling of the prior dose. Because the rate of infusion was constant at 5 mL/min, the time of infusion and concentration of the solution were the variables that were adjusted. The patient was admitted to the medical intensive care unit and premedicated with prednisone 12 hours and 1 hour before desensitization and diphenhydramine 30 minutes before desensitization. The patient tolerated the doses without any symptoms until a total of 64 mg of cetuximab was infused (completion of bag 4).

Soon after the first dose of the full-strength bag 5, she began to have an intensely pruritic maculopapular, nonraised, erythematous rash on her torso and extremities that was consistent with a non-IgE-mediated cutaneous reaction. She also complained of subjective shortness of breath, although oxygen saturation and pulmonary auscultation were normal, and she was not hypotensive. She received diphenhydramine, famotidine, and solumedrol. The desensitization continued without dose reduction or repetition after a 30-minute wait period because her cutaneous reaction was not urticaria and thus not thought to be IgE mediated. Similar cutaneous symptoms occurred with the second infusion, and therefore she was given the same medications and another 30-minute wait period before the next dose. The final 2 doses were infused at half the rate (taking approximately an hour each instead of the planned 26 and 32.5 minutes), and the patient tolerated them without any further symptoms. Through the entire desensitization, the patient's vital signs remained stable, and urticaria was not observed.

Because the half-life of cetuximab is approximately 4 days (compared with antibiotic half-lives of hours), it was assumed that the patient would remain desensitized through her next needed infusion. Thus 1 week later the patient was rechallenged with cetuximab administered at full strength with a graded increasing infusion rate, according to a published protocol.⁸ She tolerated her second dose without any difficulty, including an absence of rash. Unfortunately, she had progression of her metastatic disease, and further treatment was discontinued for lack of efficacy. The

patient died from refractory metastatic breast carcinoma 3 months later.

Clinical indications for biologic agents are ever expanding, and as a result, infusion reactions are being observed more frequently. Most hypothesize that these infusion reactions occur in response to soluble immune complexes (type III hypersensitivity reaction/serum sickness), autoantibody formation, or even neutralizing antibodies.⁹ Our patient had measurable IgE antibodies to cetuximab, supporting a true type I hypersensitivity reaction, which made it amenable to a desensitization protocol. Because our patient tolerated the desensitization with only a cutaneous reaction and then subsequently tolerated a regular dose of cetuximab, we propose that our protocol showed efficacy. Work by Chung et al⁶ has shown the presence of anti-cetuximab antibodies in up to 20% of patients from certain geographic pockets (suggesting a cross reactivity with an unknown environmental antigen), implying that a validated desensitization protocol for cetuximab might be useful to many patients. In consideration of this patient's cutaneous symptoms, we would recommend extending the infusion times of the final bag 5 (2 mg/mL) to 30 minutes for doses 1 and 2 and 1 hour for doses 3 and 4.

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