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A Successful Shortening of Desensitization Protocol in a Patient with Cetuximab Anaphylaxis

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Abstract

Desensitization therapy can help overcome severe hypersensitivity reactions and allow continuing administration of the culprit agents. However, this is time-consuming and labor-intensive due to a prolonged infusion time and the serial adjustment of infusion rate at different periods. Therefore, simplified protocols using fewer steps have been tested, although currently there is no established standard strategy. Cetuximab plays an important role in the treatment of metastatic colorectal cancer. Although cetuximab is well tolerated, severe infusion reactions occur in 1.1% of patients, and most occur within 1 hour of receiving the first dose. Here, we report a recent attempt to shorten the steps of gradual cetuximab desensitization. A 57-year-old male patient diagnosed with obstructive sigmoid colon cancer received cetuximab chemotherapy and experienced immediate anaphylaxis in the first cycle. A one-bag, 17-step desensitization protocol was applied to cetuximab administration. After the first successful desensitization cycle, the process of desensitization was shortened by 1–2 step(s) per cycle, down to 2 steps, without a breakthrough reaction. The patient ultimately received regular infusions. Shortening of the rapid desensitization protocol can be considered if the previous cycle is well-tolerated, even in a patient who has suffered anaphylaxis due to cetuximab.

Keywords

Anaphylaxis
Cetuximab
Desensitization
Immunologic tolerance

1. Introduction

Cetuximab is a monoclonal IgG1 antibody that selectively binds to the epidermal growth factor receptor (EGFR) and is known to have anticancer effects on tumors of epithelial cell origin [1]. Hypersensitivity reactions to cetuximab are not

uncommon (1.1%) [2], and although the mechanisms are not fully understood, the prevailing view is that they are non-IgE-mediated, with more than 90% of severe hypersensitivity reactions to cetuximab occurring at the first dose [3]. However, there are reports that some patients have pre-existing IgE antibodies specific to the galactose-α-1,3-galactose (α-gal) site, resulting in severe hypersensitivity reactions to the first dose of cetuximab [4].

If hypersensitivity reactions occur, patients may be given a second-line drug instead, or a desensitization therapy can be attempted [5]. Although desensitization therapy has a good safety record, it requires multiple stages of sequential treatment, which requires additional medical staff, and may lead to a decrease in drug stability due to the longer duration of drug administration. Therefore, if a patient develops an intolerance to a chemotherapy drug, it is ideal to return to the recommended clinical trial-validated dose afterward, if possible. In addition, because people have different levels of drug sensitivity, there is insufficient evidence to suggest that the commonly used 12-step protocol [6] is necessary for all patients. It has been reported that in patients requiring chemotherapy desensitization, the next step can be shortened after no breakthrough reaction has occurred [7]. However, this protocol shortening is not uniform and has been reported to vary depending on agent type and severity of hypersensitivity [8].

Therefore, in this paper, we report our experience with sequentially shortening the steps of the protocol, starting with a 1-bag, 17-step desensitization protocol, in a patient who experienced cetuximab anaphylaxis.

2. Case

A 57-year-old male patient had hypotension and loss of consciousness after cetuximab administration. The patient was diagnosed with obstructive sigmoid colon cancer with liver metastases, cetuximab was administered after pretreatment with hydrocortisone 100 mg and chlorpheniramine 4 mg. Thirty minutes after the first dose of cetuximab, he developed facial flushing and neck and chest urticaria with severe pruritus. The infusion was immediately stopped and 4 mg chlorpheniramine and 100 mg hydrocortisone were administered intravenously, but he was found unconscious 10 minutes after going to the toilet with abdominal pain and loose stools. His blood pressure was not measured at the time and his oxygen saturation was 93%. Two intramuscular injections of 0.5 mg epinephrine and rapid intravenous fluid resuscitation restored his consciousness, with a blood pressure of 127/86 mmHg, pulse of 94 beats/min, respirations of 18 breaths/min, temperature of 36.5°C, and oxygen saturation of 99%. There was no facial edema and lip edema, but variable-sized redness was observed on the skin all over the body. Other physical examination findings were unremarkable.

Medical history: hypertension, diabetes, dyslipidemia, no allergy to red meat, no history of tick bites. Family history: unremarkable, no family history of red meat allergy. Laboratory findings: Peripheral blood test immediately after the onset of symptoms showed white blood cells 3,480/μL, hemoglobin 13.0 g/dL, platelets 172,000/μL, aspartate aminotransferase/alanine aminotransferase 32/46 U/L, alkaline phosphatase 133 U/L, total bilirubin 0. 8 mg/dL, blood urea nitrogen/creatinine 12/1.05 mg/dL, Na/K/Cl 139/4.2/105 mEq/L, CK-MB/Troponin I 0.4 /< 0.01 ng/mL, tryptase 13.4 μg/L. A cetuximab skin test performed 10 days after symptom onset was negative for both the terminal test (5 mg/mL) and intradermal test (0.5 mg/mL).

Application of desensitization therapy: An aqueous solution of cetuximab 2.84 mg/mL concentration (985 mg/347 mL) was prepared, and 1.38 mg ketotifen, 20 mg famotidine, and 10 mg montelukast were administered orally before starting therapy. The first bolus of desensitization therapy was started at a rate of 0.1 mL/hr and increased at 20-minute intervals to a final bolus rate of 225 mL/hr over 17 boluses, with the

Table 1. Desensitization protocol for cetuximab-induced anaphylaxis (17-step protocol)

Step	Rate (mL/hr)	Time (min)	Administered dose (mg)	Administered volume (mL)	Cumulative dose (mg)
1	0.1	20	0.0946	0.033	0.033
2	0.2	20	0.1892	0.070	0.100
3	0.3	20	0.2839	0.100	0.200
4	0.5	20	0.4731	0.170	0.367
5	0.8	20	0.7570	0.300	0.633
6	1.3	20	1.2301	0.430	1.067
7	2.1	20	1.9870	0.700	1.767
8	3.4	20	3.2171	1.130	2.900
9	5.5	20	5.2041	1.830	4.733
10	8.9	20	8.4212	3.000	7.700
11	14.4	20	13.6254	4.800	12.500
12	23.4	20	22.1412	7.800	20.300
13	38.2	20	36.1451	12.700	33.033
14	62.4	20	59.0432	20.800	53.833
15	95	20	89.8895	31.700	85.500
16	145	20	137.1998	48.300	133.833
17	225	56.8	605.0985	213.200	347.000

The 2.84 mg/mL solution was prepared by reconstituting cetuximab 985 mg in 150 mL of 0.9% normal saline.

infusion completed in 377 minutes without any symptoms (Table 1). Cetuximab was administered with desensitization therapy every 3–4 weeks between chemotherapy cycles. The principle was to shorten the desensitization phase in the absence of an adverse reaction, and the incremental rate of administration between phases was gradually increased, starting at 1.6-fold and reaching 5-fold. The desensitization regimen was tapered by 1–2 steps each time, leading to regular dosing. Each step of the first and second desensitization regimens was kept at 20 minutes, and from the third desensitization regimen onwards, each step was kept at 15 minutes. Despite this progressive reduction, cetuximab could be administered without significant adverse events (Table 2). The 2.84 mg/mL solution was prepared by reconstituting cetuximab 985 mg in 150 mL of 0.9% normal saline.

3. Case review

This case demonstrates that initial successful rapid desensitization in a patient with cetuximab anaphylaxis can be followed by progressively shorter steps during subsequent desensitization, minimizing the time and effort required for desensitization while still allowing safe administration of the offending drug.

In the event of a hypersensitivity reaction to an anti-cancer drug, the drug is discontinued and the patient is switched to the next best anti-cancer therapy, which may result in a reduced anti-cancer effect and shorter survival. Pretreatment with antihistamines and high-dose steroids can be used to manage the adverse reactions caused by chemotherapy, but it is not a perfect alternative, as previous adverse reactions may recur in 1% of patients after pretreatment with antihistamines and high-dose steroids [9], and there is a risk of adverse effects from repeated administration of high-dose steroids [10]. Therefore, in this case, desensitization of the causative agent can be used to safely maintain optimal chemotherapy, which may result in a better clinical outcome [11].

Desensitization involves the introduction of a very small amount of the antigen responsible for the adverse event, starting at a low concentration and gradually increasing to the target dose, to avoid the host's immune

Table 2. Serial shortening of desensitization protocol

Cycles of desensitization (time for each step)	Proceeding of flow rate in each cycle (mL/hr)	Time (min)
1st 17 steps (20 min)	0.1→0.2→0.3→0.4→0.8→1.3→2.1→3.4→5.5→8.9→14.4→23.4→38.2→62.4→95→145→225	377
2nd 15 steps (20 min)	0.1→0.2→0.3→0.5→0.9→1.6→2.9→5.2→9.4→17.0→30.6→55.1→99.2→175→280	326
3rd 13 steps (15 min)	0.1→0.2→0.4→0.8→1.6→3.2→6.4→12.8→25.6→50→90→160→280	236
4th 12 steps (15 min)	0.1→0.2→0.5→1.2→2.5→5.0→12.5→25→50→90→160→280	221
5th 10 steps (15 min)	0.1→0.2→0.5→1.2→3.0→7.5→18.8→47→118→280	199
6th 9 steps (15 min)	0.1→0.3→0.9→2.7→8.1→24→65→180→280	180
7th 7 steps (15 min)	0.1→0.4→1.6→6.4→24→90→280	158
8th 6 steps (15 min)	0.1→0.5→2.5→12.5→62.5→280	146
9th 5 steps (15 min)	0.5→2.5→12.5→62.6→280	131
10th 4 steps (15 min)	2.5→12.5→62.5→280	114
11th 3 steps (15 min)	12.5→62.5→280	99
12th 2 steps (15 min)	62.5→280	85

surveillance so that the drug can be administered without causing hypersensitivity reactions. Although the exact mechanisms of desensitization are not yet fully understood, it has been suggested that decreased reactivity of mast cells due to internalization of high-affinity IgE receptors such as FcεRI, production of antibodies that block drug-specific IgG4, alterations in the signaling system of mast cells and basophils, and decreased Ca^{2+} influx may be involved [12-13]. Despite desensitization therapy, some patients may develop anaphylactic reactions; a study of infusion reactions associated with four monoclonal antibodies – rituximab, cetuximab, infliximab, and trastuzumab – using 12-step rapid desensitization showed a 13.5% incidence of anaphylactic reactions, but these reactions were less severe than the initial hypersensitivity reactions before desensitization [14].

Cetuximab is a recombinant human/mouse chimeric monoclonal antibody that binds specifically to EGFR, and upon binding to EGFR, cetuximab inhibits its phosphorylation, thereby interfering with cancer cell growth and inducing apoptosis [15]. Most cetuximab hypersensitivity reactions are thought to be infusion-related, which occurs at the first dose, and the frequency of severe infusion-related reactions is reportedly 5% [16]. As such, cetuximab hypersensitivity reactions are generally considered to be non-IgE-mediated, although there are studies suggesting that they may be IgE-mediated. Immunological hypersensitivity reactions to the first dose of cetuximab may occur in patients who have developed specific IgE to α-gal contained in mammalian meat. However, these findings appear to be regional, with studies showing that in tick-bite-prone areas of the Rocky Mountains, exposure to mammalian α-gal following a bite from a lone star tick (Amblyomma americanum) that has fed on the blood of a mammalian animal results in the development of specific IgE antibodies to α-gal [17]. The patient in this case had anaphylaxis at the first dose and had a negative skin test, suggesting a non-IgE-mediated hypersensitivity reaction. In addition to skin testing, galactose-α-1,3-galactose-specific IgE can be measured to confirm the presence of cetuximab-specific IgE. However, in this case, due to the severity of the reaction and the focus on the successful administration of cetuximab, it was decided to continue chemotherapy with desensitization regardless of the mechanism of action, so galactose-α-1,3-galactose-specific IgE testing was not performed, limiting the ability to elucidate the mechanism of hypersensitivity.

In general, the 3-bag, 12-step desensitization protocol reported by Castells et al. [16] is widely used for desensitization, but the dilution of the agent is not necessary for successful desensitization. There have

been several recent reports of 1-bag desensitization without dilution [18-19]. In this case, we applied the 1-bag desensitization protocol, which was administered as a single concentration without dilution, to a variety of agents. This case was a classic case of anaphylactic shock with severe hypotension and elevated tryptase, which should be proceeded with great caution due to the risk of breakthrough reactions even with desensitization. Therefore, we applied desensitization therapy from the second dose of cetuximab, which is usually a 13-step protocol; but in this case, given that the first reaction was anaphylactic shock, we applied a 1-bag, 17-step protocol in which the desensitization therapy was increased to 17 steps, but each step was kept for 20 minutes, and if there was no breakthrough reaction, the steps were sequentially reduced in the next round of chemotherapy desensitization. As a result, the total time to perform the first 17 steps of desensitization was 377 minutes, but the time was gradually reduced with each subsequent step, and the thirteenth dose was completed without adverse events by switching to the original dosing protocol, which had caused hypersensitivity reactions prior to desensitization (Supplementary Figure 1).

The use of antihistamines as premedication during desensitization therapy may have contributed to the absence of hypersensitivity reactions in this case. However, given that anaphylaxis occurred with the first dose of cetuximab despite pretreatment with a combination of antihistamines and steroids, it is likely that the lack of anaphylaxis with the second dose of cetuximab was a result of successful desensitization rather than simply an effect of pretreatment. While pretreatment has the advantage of minimizing patient discomfort by mitigating or preventing adverse reactions that may occur during desensitization, there are concerns that it may only prevent mild symptoms but not severe reactions, resulting in missed early warning signs and putting patients at risk. Therefore, more objective evidence is needed on the need for pretreatment and the details of how it should be used in future desensitization.

This case confirms that even if cetuximab-induced anaphylaxis occurs, the drug can be safely administered by applying desensitization therapy; and that if desensitization therapy is successfully performed without an adverse reaction, the next step can be progressively shortened to reduce the manpower and time required for desensitization therapy, thereby lowering the barrier to implementing desensitization therapy. However, there is no standard protocol for shortening desensitization, so further research is needed.

Disclosure statement

The authors declare no conflict of interest.

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