Case Report

Successful rechallenge of cetuximab following severe infusion-related reactions: a case report

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Abstract: Cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, is associated with a risk of infusion reactions, similar to other infusional agents. Although avoiding a rechallenge with cetuximab following a severe infusion reaction is preferable, this may not be an option if few other reasonable alternatives exist. We report herein a successful case of cetuximab rechallenge, carried out by extending infusion times and using saline dilution in a patient who had severe infusion reactions twice and who required continuation of treatment. Cetuximab reintroduction with saline dilution and a slower infusion rate in an intensive care setting allowed safe continuation of therapy.

Keywords: Cetuximab; infusion reaction; colorectal cancer; rechallenge

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Introduction

Cetuximab, a chimeric mouse-human IgG_1 monoclonal antibody against the epidermal growth factor receptor (EGFR), is approved for use in metastatic colorectal cancer and squamous-cell carcinoma of the head and neck (1-3). As with any biologic agent, such as rituximab, trastuzumab, alemtuzumab, bevacizumab, panitumumab, etc, cetuximab infusion can be associated with adverse events. Infusion reactions to cetuximab can occur in up to 25 percent of patients, but only 3 to 4 percent are severe, as demonstrated in a number of phase III trials (1-3). The most common signs and symptoms are chills, fever, urticaria, hypotension, bronchospasm, and other respiratory conditions. For most patients, the reaction is reversible with the use of IV fluids, steroids, antihistamines, bronchodilators, and epinephrine. It was reported that most of these reactions occur in patients who have preformed IgE antibodies to the galactose-a-1,3-galactose portion of the cetuximab molecule (4). Most patients who experience a reaction, particularly when the symptoms are mild to moderate, can safely continue the treatment with proper medication and close monitoring (5,6). Following a severe infusion reaction, rechallenge is usually discouraged. Although avoiding a rechallenge with cetuximab after a severe infusion reaction is preferable, this may not be an option if the use of other chemotherapy regimens has been exhausted. We report herein a successful case of cetuximab rechallenge, carried out by extending infusion times and saline dilution in a patient who had a severe infusion reaction twice and who required continuation of treatment.

Case presentation

A 64-year-old male had undergone radical proctectomy and adjuvant chemoradiation for stage III (pathological stage: pT2N1, wild-type KRAS) rectal adenocarcinoma in 2008. Multiple lung metastases developed in August 2010 and he was then treated with a systemic combination of bevacizumab, irinotecan and 5-fluorouracil/leucovorin. Progression was detected in March 2011 and the patient was treated with a combination of oxaliplatin, 5-fluorouracil, and leucovorin (mFOLFOX6 regimen). In October 2011, liver and lung metastases also progressed, and a combination of cetuximab (loading dose 400 mg/m^2; afterwards, 250 mg/m^2 weekly intravenously) followed by irinotecan (180 mg/m^2 intravenously every 14 days), 5-fluorouracil (400 mg/m^2 bolus and 2,400 mg/m^2 in

46-h infusion intravenously every 14 days) and leucovorin (200 mg/m^2 intravenously every 14 days) was selected as third-line treatment. The dose administration of cetuximab was planned as a 2-hour infusion after premedication with diphenhydramine 30 mg and hydrocortisone 100 mg. He reported no history of allergic disorder.

The patient experienced shortness of breath ten min after start of cetuximab administration. Physical examination indicated flush face, severe diaphoresis, confused mental status, and low blood pressure (76/52 mmHg). The patient's oxygen saturation fell to 80% in ambient air, and a stridor breathing sound was detected on chest auscultation. Cetuximab was discontinued, and the patient was treated with intravenous hydrocortisone, diphenhydramine, volume expansion, oxygen, bronchodilator and epinephrine inhalation; the patient's blood pressure and mental status recovered after the treatment. Shortness of breath and the stridor breathing sound also subsided gradually. We administered cetuximab the next day, extending the infusion time up to six hours and maintaining surveillance in the intensive care unit without further anaphylaxis or infusion reaction after the patient agreed to receive the drug; the infusion time was extended taking into consideration both the patient's treatment benefits and administration safety. The subsequent infusion of cytotoxic drugs was without any additional side effects.

The second course of cetuximab infusion was arranged two weeks later. The dose administration of cetuximab was planned as a 6-hour infusion about ten min after premedication with diphenhydramine 30 mg and hydrocortisone 100 mg, based on the experience in the previous cycle. However, the patient again experienced shortness of breath immediately after cetuximab administration. The patient's blood pressure dropped to 90/75 mmHg, and physical examination indicated flush face, severe diaphoresis and a stridor breathing sound. Immediately after the discontinuation of cetuximab and the administration of hydrocortisone, diphenhydramine, nasal oxygen, volume expansion bronchodilator and epinephrine inhalation, the patient's symptoms and blood pressure improved. The situation was explained to the patient, and therapeutic options were discussed. The patient was willing to continue the therapy because the therapeutic options were limited. After the signs accompanying the infusion reaction had subsided, the rest of the cetuximab dose (around 300 mg) was diluted in 360 mL normal saline and administered in a 6-hour infusion (1 mg/mL at a rate of 1 mL/min) under surveillance in the intensive care unit the next day. There was no further anaphylaxis or infusion reaction related to cetuximab infusion. We arranged a further six cycles of cetuximab infusion without an infusion reaction by extending the infusion time and using a saline dilution (1 mg/mL at a rate of 1 mL/min). This patient experienced bone metastasis in April, 2012, but had the benefit of another seven months' progression-free survival as a result of the cetuximab treatment.

Discussion

The acute infusion reactions to cetuximab occur in up to 25 percent of patients, but only 3 to 4 percent are severe (7). Grade 1 (transient flushing or rash, no fever) or 2 (flushing, urticaria, rash, and fever up to ≥100.4 degrees F) reactions occur in approximately 20 percent of patients, typically during the first exposure. Severe reactions (grade 3 or 4) are characterized by the rapid onset of bronchospasm, stridor, hoarseness, nausea and vomiting, urticaria, and/or hypotension (8). These symptoms are consistent with anaphylaxis. In patients with a severe reaction or anaphylaxis, drug infusion should be discontinued immediately. Appropriate medical therapy during the reaction includes epinephrine, IV fluids, IV antihistamines, glucocorticoids, and if needed, bronchodilators and oxygen. Patients should be carefully observed until the resolution of all symptoms and signs. The manufacturer recommends that cetuximab be permanently discontinued if there is a severe infusion reaction (6,8).

When encountering an infusion reaction to this drug, the medical oncologist is faced with a difficult choice. If a patient is felt to be a candidate for continuation of therapy because of the potential for clinical benefit and no other reasonable alternatives exist, then rechallenge may be pursued. Previous reports showed that decrease infusion rate and pre-medications with steroid could be successful for patients who need re-treatment with cetuximab (9). Our patient suffered from severe infusion reactions twice, as described above, but rechallenge was successful due to extending the infusion time and using saline dilution under intensive monitoring after managing the side effects. As in the case presented here, the afflicted patient may have few therapeutic options left. This experience, although anecdotal, indicates that administration of cetuximab may be continued safely in patients after severe infusion reactions. In clinical trials of cetuximab alone or in combinations published so far, infusion reactions were rare, but cetuximab therapy was always discontinued. The patient presented

here derived some benefit (seven-month progression-free survival) from the therapy that would not have happened had the drug been interrupted. In our experience, cetuximab reintroduction with saline dilution and a slower infusion rate in an intensive care setting allowed safe continuation of therapy.

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