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Case Report About Fatal or Near-Fatal Hypersensitivity Reactions to Cetuximab: Anticetuximab IgE as a Valuable Screening Test

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ABSTRACT: Hypersensitivity reactions are a classic side effect of cetuximab. We report the cases of three patients who developed life-threatening hypersensitivity to cetuximab, which could have been predicted by assessing the concentration of serum anticetuximab immunoglobulin (Ig)E. The anti-cetuximab IgE concentration could be an interesting test to predict which patients are at risk of experiencing severe hypersensitivity reactions to cetuximab.

KEYWORDS: hypersensitivity, anaphylaxis, cetuximab, antidrug IgE, neoplasms

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Introduction

Hypersensitivity reactions are a classic side effect of cetuximab. The frequency of severe reactions varies from 1.2%–22%.[1–6] No clinical criteria (previously reported to be associated with a risk of hypersensitivity to cetuximab) is so strong that it can predict patients at risk of hypersensitivity reaction.[4,7] However, a strong correlation between the occurrence of hypersensitivity reactions to cetuximab and the presence of anticetuximab immunoglobulin (Ig)E in the sera of patients before an initial injection of cetuximab has been demonstrated.[8,9] The anti-cetuximab IgE concentration could be an interesting test to predict which patients are at risk of severe hypersensitivity reactions to cetuximab. We have previously developed a reliable and reproducible anticetuximab IgE assay using enzyme-linked immunosorbent assay (ELISA).[9]

We report the cases of patients living in Normandy (France) who developed life-threatening hypersensitivity to cetuximab, which could have been predicted by assessing the concentration of serum anticetuximab IgE.

Materials and Methods

Anti-cetuximab IgEs were measured using an enzyme-linked immunosorbent assay (ELISA). Polystyrene microtiter plates (Maxisorp Nunc, Roskilde, Denmark) were coated with 100 µL of a 0.5 µg/L cetuximab solution (Erbitux® , Merck Serrano) in phosphate buffered saline (PBS), overnight at 4 °C. After three washes with PBS containing Tween-20 (0.1%), plates were saturated with a solution of human albumin (0.1%) for 2 h at 37 °C. Duplicate serum samples (diluted 1/25) were added and incubated overnight at 4 °C. Bound anti-cetuximab IgE antibodies were detected using a biotinylated rat monoclonal anti-human-IgE (LO-HE-17, P.A.R.I.S, Compiègne, France), allowed to react for 1.5 h at 37 °C. Streptavidin-alkaline phosphatase Beckman Coulter, Fullerton, USA,

1/2,000 dilution, was added, followed by 1 mg/mL paranitrophenyl phosphate solution (PNPP, Interchim, Montluçon, France). Positive samples were titrated after serial dilutions from 1/50 to 1/200 or more as appropriate. Optical density (OD) was measured at 450 nm (Elx808, KC4 software, Bio-Tek) and the mean of duplicates was calculated. Results were expressed in arbitrary units of IgE (AU) using a positive serum sample from a healthy donor as a standard.

To assess the specificity of the detection, a competition ELISA was performed on sera diluted 1/25 using an excess of cetuximab or an IgG1 isotype control (rituximab, Mabthera®) or a G1 m3 allotype control (basiliximab, Simulect®), at 1.1 mg/mL final concentration.

Case Report

Case 1. A male patient in his 60s was treated in our institution for metastatic rectal cancer. The patient was in good condition otherwise and had no known allergies – in particular, no food allergies. It was decided that a combined therapy of irinotecan (180 mg/m^2 intravenously [IV] over 90 minutes) and cetuximab (400 mg/m^2 IV with the first dose over 180 minutes) against the metastasis be used.

On the day of the first infusion of cetuximab, the patient remained in good condition. He was pretreated, as required, with dexchlorpheniramine (5 mg IV). However, at 1 minute after beginning the cetuximab infusion (after receiving ~2 mg of the drug), the patient developed a generalized rash and malaise, with loss of consciousness and hypotension, immediately followed by cardiorespiratory arrest. Cetuximab was immediately stopped and the patient was supported with fluid resuscitation, intubation, mechanical ventilation, and high-dose IV epinephrine (up to 15 mg/day). He was transferred to the intensive care unit (ICU). Despite an initial improvement, he died as a result of the reaction. High levels of tryptase and histamine (277 µg/L [normal value <12.5 µg/L] and 6,580 nmol/L [normal value <6 nmol/L], respectively) measured at 1 hour after the reaction confirmed allergic hypersensitivity. Retrospectively, we assayed for anticetuximab IgE in a serum sample taken from the patient before treatment with cetuximab and stored in a biobank. The assay was highly positive (3,300 arbitrary units [AU]: laboratory normal value <29 AU).[9]

Case 2. The second case was that of an 81-year-old man who was followed for locally advanced head and neck cancer. A history of asthma was noted without any other medical or allergy history. Combined treatment with cetuximab (400 mg/m^2 IV for the first dose) and radiotherapy was decided upon. As part of a research protocol (European Clinical Trials Database number: 2009–016968–37), we measured serum anti-cetuximab IgE, which was strongly increased (480 AU). As allowed under the protocol, and after multidisciplinary consultation, the referring physician decided to administer cetuximab under close monitoring in the presence of an intensivist and with resuscitation equipment on standby. The patient was pretreated with methylprednisolone (120 mg IV) and dexchlorpheniramine (10 mg IV). Cetuximab was infused at half the usual speed (100 mg/hour). Despite these precautions, after receiving approximately 13 mg of the drug, the patient developed dyspnea, loss of consciousness, and respiratory arrest. Cetuximab was immediately stopped and the patient was supported with epinephrine (1 mg IV), fluid resuscitation, and transient ventilatory support. The patient recovered all vital functions without subsequent complications. He was transferred to the ICU for 24 h of monitoring. The patient was allowed to return home the next day and could later resume radiotherapy without cetuximab. Plasma histamine concentration was increased (>100 nmol/L), as was tryptase (64 µg/L). These results and the clinical presentation confirmed the allergic nature of this reaction.

Case 3. In the third case report, a 50-year-old male patient was treated for recurrence of mouth cancer. A history of asthma was noted with no other medical history and without a food allergy past. The patient was in good condition. It was decided to give this patient a combined treatment of cisplatin (100 mg/m^2 IV over 60 minutes), 5-fluorouracil (1,000 mg/m^2 IV per day for 4 days), and cetuximab (400 mg/m^2 IV over 180 minutes). The anticetuximab IgE assay was strongly positive (490 AU). Thus, it was decided to maintain the prescription of cetuximab under close monitoring. After administration of 60 mg of cetuximab, the patient developed tachycardia of 120 bpm, oxygen desaturation of 89%, and tachypnea of 30 breaths/minutes with a bronchospasm. Cetuximab was immediately stopped, and the patient received methylprednisolone (60 mg IV) and dexchlorpheniramine (10 mg IV), as well as inhaled ipratropium, terbutaline, and oxygen. Recovery was immediate and complete.

Case 4. The fourth case report is of a 54-year-old male patient with no other medical history who was treated for locally advanced head and neck cancer. We planned to give a combined chemotherapy treatment that included cetuximab. However, the anticetuximab IgE level was very high (260 AU). Intradermal tests (IDTs) were performed with cetuximab at increasing concentrations, starting at 0.5 µg/mL. IDT became positive with cetuximab at 5 µg/mL. After multidisciplinary discussion, and as allowed by the protocol, we decided not to administer a cetuximab infusion given the high risk of an allergic reaction; instead, the patient was given an alternative therapy of cisplatin plus 5-fluorouracil.

Discussion

We reported on three patients who developed life-threatening hypersensitivity to cetuximab, which could have been predicted by assessing the concentration of serum anticetuximab IgE: Table 1 summarizes the different cases. Hypersensitivity reactions are a classic side effect of monoclonal antibodies.[10] The frequency of severe reactions to cetuximab varies in the literature from 1.2%–22%, depending on different areas of the world.[1–6,11] Fatal reactions, as in one of our cases, have been

Table 1. Case descriptions.

PATIENTS	ANTICETUXIMAB IgE ASSAY (NORMAL VALUE <29 AU)	CETUXIMAB INFUSION PERFORMED	HYPERSENSITIVITY REACTION (GRADE*)	TRYPTASE (NORMAL VALUE <12.5 μg/L)	HISTAMINE (NORMAL VALUE <6 nmol/L)
1	3300 AU	Yes	Yes (5)	277 μg/L	6,580 nmol/L
2	480 AU	Yes	Yes (4)	64 μg/L	>100 nmol/L
3	490 AU	Yes	Yes (3)	–	–
4	260 AU	No	–	–	–

Notes: The results of anticetuximab IgE assay are expressed in Arbitrary Units (AU). *The grade of reactions was established according to NCI CTAE v4.0.

reported.[12–14] Clinicians often underestimate this complication until they themselves are confronted with such a case. It is now well documented that these hypersensitivity reactions are mediated by preexisting specific anticetuximab IgE.[8] However, the origin of these specific antibodies is still debated. A strong correlation between the occurrence of hypersensitivity reactions to cetuximab and the presence of anticetuximab IgE in the sera of patients before a first injection of cetuximab has been demonstrated.[8,9]

Several teams have attempted to determine the discriminating markers that enable the identification of subjects who are likely to develop a hypersensitivity reaction to cetuximab. An atopic history and Caucasian origin are significantly associated with this hypersensitivity, but these criteria are not sufficient to select patients at risk.[4,7] In this context, identifying specific IgE against cetuximab seems to be a good candidate. According to the study by Chung et al,[8] anticetuximab IgE assays have high sensitivity (92%) and specificity (90%) if used as a diagnostic test to identify patients who are likely to develop life-threatening reactions. The development of anticetuxmab IgE as a screening test for severe hypersensitivity reactions to cetuximab could be a major issue for patients from areas with a high incidence of hypersensitivity reactions to cetuximab or a high prevalence of IgE antibodies against cetuximab, such as in Tennessee or North Carolina, United States.[4,8]

Using this perspective, we have developed an ELISA assay for anticetuximab IgE.[9] As in Chung et al's study,[8] the detection of anticetuximab IgE is based on using cetuximab itself as a coating reagent to allow for binding of the specific IgE. This test probably prevented the death of the second patient described above.

Until now, no correlation between specific IgE levels and severity of allergic reactions to cetuximab has been shown.[8,9] The unexpected finding of a possible correlation between a very high level of specific IgE and a fatal or near-fatal allergic reaction has prompted us to report our experience. In our report, all the patients had very elevated values of anticetuximab IgE, exceeding 250 AU. In comparison, the mean value in a previously reported cohort was 5 AU.[9] Thus, highly increased values of anticetuximab IgE should be considered a possible contraindication for the use of cetuximab, as we did for the fourth patient described above. The precise cut-off point of anticetuximab IgE that defines this high-risk population remains to be determined. To date, with the cut-off value <29 AU established in the previous work that permitted us to develop the anticetuximab IgE assay, the test had a negative predictive value of 98.5% and a positive predictive value was of 33.3%.[9] The excellent negative predictive value suggests that when the test was negative, we can safely administer cetuximab. It was the priority of our team when we developed this test after the first case reported here. Given the positive predictive value for patients with a positive test, we can imagine performing another test such as an IDT with cetuximab, like in case 4, but this approach needs to be validated.

Conclusion

In the same way that screening for dihydropyrimidine dehydrogenase deficiency before using 5-fluorouracil has been recommended,[15] systematic screening for the risk of severe hypersensitivity to cetuximab should be considered before using this product. Although hypersensitivity reactions to cetuximab are infrequent, we believe that screening for anticetuximab IgE is necessary, considering the potential severity of these reactions.

Author Contributions

Conceived and designed the study: BD, DM, RG. Performed medical operations: DM, DL, MCV, CM. Analyzed the data: BD, JMG. Wrote the first draft of the manuscript: BD. Contributed to the writing of the manuscript: BD, DM, DL, RG. Agree with manuscript results and conclusions: BD, DM, DL, MCV, CM, RG. Jointly developed the structure and arguments for the paper: BD, DM, RG. Made critical revisions and approved final version: BD, DM, DL, RG. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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