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Fatal Infusion Reactions to Cetuximab: Role of Immunoglobulin E–Mediated Anaphylaxis

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To the Editor

In *Journal of Clinical Oncology*, Tronconi et al[1] report a fatal hypersensitivity reaction to cetuximab in a 63-year-old patient with metastatic colon cancer and outlined a 0.1% incidence of death in the literature. We greatly acknowledge the authors' desire to communicate the risk of fatal anaphylactic reaction with cetuximab. Over the past 2 years in our center in Tours, France, four instances of grade 4 anaphylactic reactions occurred in patients treated for head and neck cancer (locally advanced or metastatic), with one immediately fatal; another patient died within 5 days (unpublished data). Seven lethal anaphylactic reactions were registered in a pharmacovigilance survey in France, based on spontaneous declarations (Grandvuillemin et al, manuscript in preparation). Anaphylaxis to cetuximab is a problem that merits serious clinical attention.

In the authors' words, "the pathogenic mechanisms underlying the development of this phenomenon remain to be elucidated."[1] They raise the hypothesis of immunoglobulin E (IgE)–independent mechanisms, even in the context of a paradoxic atopic history. Moreover, Tronconi et al suggest that the field "search for reliable risk factors that can facilitate the safe selection of patients as candidates for cetuximab-based treatment."[1]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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These comments are quite surprising, because they do not integrate major contributions that have been previously published. Indeed, it has been known for 3 years that anaphylaxis to cetuximab is the result of antidrug IgE antibodies present in patient serum before therapy.[2] These IgE antibodies are directed against galactose-α-1, 3-galactose (α3Gal) residues, present in the Fab portion of this monoclonal antibody.[3] Because humans do not express this glycan, anti-α3Gal IgM and IgG antibodies spontaneously develop, whereas the appearance of IgE is only occasional. The observation that most of the patients developed reactions to cetuximab during their first infusion supports this hypothesis and is consistent with an IgE-mediated event. Environmental factors, such as bites by ectoparasitic ticks, probably explain the heterogeneous proportion of individuals displaying anti-α3Gal IgE and the heterogeneous incidence of anaphylactic reactions to cetuximab among studies and geographic areas. [2,4–6] History of atopy, age, race, additional therapy (ie, chemotherapy or radiotherapy), sex, and head and neck cancer (rather than colorectal cancer) have also been proposed as factors favoring anaphylaxis to cetuximab, but they remain controversial.[2,4,5]

Therefore, instead of searching for reliable risk factors, it seems more straightforward to detect the presence of anti-α3Gal IgE before treatment. Since the first studies, several academic groups and companies around the world have developed such assays (Pointreau et al, manuscript in preparation),[2,7] and the recent international congress held in Tours dedicated to anaphylaxis to cetuximab provided us with the opportunity to discuss this relevant strategy.[8]

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