

Increased rates of cetuximab reactions in tick prevalent regions and a proposed protocol for risk mitigation

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Abstract

Background: Cetuximab is an anti-epidermal growth factor receptor mouse-human chimeric monoclonal antibody used to treat advanced colorectal cancers. Initial data suggest that severe infusion reactions occurred in 4.5%, many on first exposure. The majority of those with anaphylactic reactions possess predeveloped IgE antibodies to galactose-alpha-1,3-galactose. It is thought that the vector for preexposure to alpha-gal is antigen inoculation via tick bites. This retrospective study reviews the experience of two community cancer centers in high tick exposure areas in Sydney with cetuximab anaphylaxis and proposes a protocol to avoid this.

Method: Severe cetuximab infusion reactions occurring in the Northern Cancer Institute Frenchs Forest and St Leonards clinics, Sydney, from May 2014 to February 2019 were recorded. Area of residence was then compared to areas of known high tick prevalence.

Results: A total of 87 patients received cetuximab in this period. Six patients (6.9%) experienced at least a grade 3 reaction, three females, age range 41–72 years (median 57.5 years). All were receiving cetuximab for metastatic colorectal cancer and their anaphylaxis occurred with the first infusion in all cases.

Conclusion: These cases support the existing theory of increased rates of cetuximab anaphylaxis in areas of high tick prevalence. Given this, we recommend the following protocol for patients being considered for cetuximab therapy: known mammalian meat allergy as an absolute contraindication; all patients receiving cetuximab should have RAST (ImmunoCAP®) testing for alpha-gal specific-IgE-specific antibodies before first infusion and those who test positive to be considered alternate therapy.

KEYWORDS

3-galactose, alpha-gal, anaphylaxis, Cetuximab, galactose-alpha-1, protocol, risk reduction

1 | INTRODUCTION

Cetuximab is an anti-EGFR mouse–human chimeric monoclonal antibody used to treat head and neck and advanced colorectal cancers.^{1,2} The chimeric nature of the antibody increases exposure to antigenic

nonhuman proteins. Initial trials suggested the incidence of severe adverse drug reactions to be around 4.5%.² Most severe reactions occurred on first exposure.² The majority of those with severe reactions possess predeveloped IgE antibodies to galactose-alpha-1,3-galactose (alpha-gal).³ Alpha-gal is an oligo-saccharide ubiquitous in



Map adapted from Roberts FHS (1970) *Australian Ticks*. Yeerongpilly, QLD, Australia by TAGS Inc., Bill Conroy & Norbert Fischer.

FIGURE 1 Map demonstrating areas of high tick prevalence (green) in Eastern Australia, which includes Sydney and its surrounding areas [Colour figure can be viewed at wileyonlinelibrary.com]

nonprimate mammalian tissue and is present on the murine heavy chain portion of the cetuximab antibody.³ Prior exposure to this antigen is believed to be responsible for the high incidence of reactions during the first infusion of the drug,^{3,4} in one study 17 out of 21 patients with a severe cetuximab reaction had predeveloped IgE antibodies prior to their first infusion.³

The relationship between tick bite and the development of mammalian red meat allergy was first described in 2009 by van Nunen et al.⁵ It is thought that the vector for preexposure to alpha-gal in Australia is antigen inoculation via tick bites from the Australian Paralysis Tick (*Ixodes holocyclus*).^{3,5} *I. holocyclus* inoculates human hosts with alpha-gal antigens. This hypothesis correlates with increased cetuximab reactions occurring in areas with regions of known high tick prevalence.^{3,4,6} Due to varying rates of tick exposure, it is difficult to define the variation in anaphylaxis rates between areas of high and low tick prevalence. However, it is believed that rates can be as high as 22% in areas of high tick prevalence.^{4,5} This is over a five-fold increase from initial global trials.

There is mounting evidence that risk stratification can be used to identify those at high risk of cetuximab anaphylaxis.^{8,9} Various

methods have been described, including Cetuximab enzyme-linked immunosorbent assay and ImmunoCAP[®] assays directed to common red meats and cat and dog dander. However, the most effective method appears to be measuring alpha-gal antibodies using the ImmunoCAP[®] assay in those known to live in areas of high tick prevalence.⁷

This retrospective study reviews the experience of two community cancer centers in high tick exposure areas in Sydney¹⁰ with severe cetuximab infusion reactions and proposes a protocol based on alpha-gal immunoCAP[®] assays to risk stratify patients prior to the commencement of cetuximab.

2 | METHODS

Human Research Ethics approval for this study was gained following review by the relevant committee for the involved centers (Northern Cancer Institute St Leonards and Northern Cancer Institute Frenchs Forrest). Severe cetuximab infusions occurring from May 2014 to February 2019 in these two private medical oncology treatment

TABLE 1 Clinical outcomes of the seven patients initially identified as having a potential severe reaction to cetuximab

Case number	Age	Gender	Residence in area of high tick prevalence?	History of allergy?	Cycle in which reaction occurred	Grade of reaction	Symptoms of reaction	Was patient rechallenged?
1	71	Male	Y	N	1	4	Rigors, respiratory distress, chest tightness	N
2	41	Female	Y	N	1	3	Flushing, chest tightness	N
3	51	Female	Y	N	1	4	Respiratory distress, chest tightness, whole body pain	N
4	70	Female	Y	Y- Penicillin	1	3	Flushing, rigors, mid back pain	N
5 Excluded	72	Female	Y	N	1	2	Flushing, generalized pruritus	Y- 36 additional cycles of cetuximab given
6	43	Male	Y	Y- Sulphur	1	3	Throat tightness, flushing, rash	Y- 1 additional cycle of cetuximab given
7	64	Male	Y	N	1	4	Hypoxemia, flushing and hypotension	N

centers in Sydney, Australia, were reviewed. Cases were initially retrieved based on activation and reporting of medical review, thus limiting the case finding to severe reactions. Severe infusion reactions were those that fulfilled the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5 for grade 3–4 reactions. Demographic and clinical features, as well as allergy history were recorded.

Correlation of residential status to known areas of high tick prevalence was based on patient's registered post code (see Figure 1). Oncological history collected included cancer type and stage and any concurrent treatment. Reaction details recorded included symptoms of reaction, cycle in which reaction occurred, if a rechallenge with cetuximab was undertaken and its outcome.

3 | RESULTS

From May 2014 to February 2019, 87 patients received cetuximab. All patients had a registered post code in an area of high tick prevalence, determined by previously published data.¹⁰ Seven patients were identified as having a severe reaction. The clinical outcomes of the patients identified as having a severe reaction are summarized in Table 1. One patient (case 5) was excluded as review of their reaction found it to be a grade 2.

Out of the remaining six patients (6.9%) who met the CTCAE criteria for severe reactions, the age range was 41–71 years (median 57.5 years); half were female. All patients were receiving cetuximab for metastatic colorectal cancer. All received cetuximab with first line FOLFOX chemotherapy and all developed their reaction on the first dose. Two patients had true prior documented medication allergies, one to penicillin (case 4) and one to sulfur (case 5), but no patient had a documented mammalian meat allergy. One patient (case 6) was chal-

lenged with cetuximab, but developed a further reaction and the treatment was discontinued. The remaining patients were transitioned to the alternative anti-EGFR therapy panitumumab.

4 | DISCUSSION

These cases support the existing theory of increased rates of cetuximab anaphylaxis in areas of high tick prevalence. However, the retrospective nature of this study leads to some limitations with a number of assumptions made on cause and effect. In particular, alpha-gal levels were not obtained from the six patients with anaphylaxis as it was not yet routine practice at either of the study centers. Alpha-gal positivity was assumed based on the observation of higher rates of alpha-gal antibodies in patients living in areas of high tick prevalence.^{3,5,11} We assumed residence in areas of high tick exposure based on post code of current address, but duration of exposure and time spent in other areas of tick prevalence cannot be quantified. Furthermore, history of known tick bites cannot be determined and can only assumed.

The retrospective chart review limits the ability to confirm true anaphylaxis in the cases reported. Although two patients had features of a non-immune-mediated infusion reaction (case 1 had rigors and case 4 had rigors and back pain), it is likely the remainder had a true allergic reaction. However, the only way to confirm anaphylaxis over a non-anaphylactic infusion reaction is with a rise in tryptase levels which was not available for these cases.

Anaphylactoid reactions can also be misinterpreted as a cetuximab allergic reaction. This is due to the preservative, polysorbate 80, a known potent inducer of the anaphylactoid response.¹² There are also reports of allergic reactions to polysorbate 80.^{13,14} Therefore, the presence of polysorbate 80 in cetuximab preparation is a confounder in the identification of true cetuximab allergic reactions.

TABLE 2 Time line of the alpha-gal and cetuximab story

Year	Development
1936	Lancaster et al. identified all humans had IgG to a protein from nonprimate mammals identified as alpha-gal ²⁰
1987	van Nunen presents the first case of mammalian meat anaphylaxis in a tick bitten individual to the New South Wales Allergy meeting
1991	Dr Deutsch and Mrs Sandra Latimer present 10 cases of red meat allergy associated with tick bites to the Georgia Allergy Society
2004	ImClone and BMS investigate cetuximab in clinical trials ²¹
2006	O'Neil et al published data demonstrating high incidence of cetuximab hypersensitivity in areas of the United States not noticed elsewhere. An ImmunoCAP® assay was developed to detected antibodies to cetuximab The assay is used by an investigation team lead by Dr Chung, Dr Mirakhur and Dr Hicklin, who identify that patients who had a cetuximab reaction have the antibody prior to infusion. It is concluded that there is an unknown epitope on the cetuximab antibody patients are exposed to elsewhere. ⁷
2007	Qian et al describe the molecular structure of cetuximab and in doing so identify the epitope to the cetuximab antibodies is alpha-gal ²¹
2007	van Nunen et al. describe the association between red meat allergy and prior tick bites in 25 patients
2008	Chung et al publish their findings implicating alpha-gal as the missing epitope responsible for the increased rates of cetuximab anaphylaxis ³
2009	van Nunen et al. Further describe the association between a history of tick bites and red meat allergy in Australia ⁵ Commings et al. describes a similar association between tick bite and red meat allergy in America and demonstrates an association with alpha-gal antibodies ¹⁰
2011	Distribution of the tick spread disease, Rocky Mountain Spotted Fever, and cetuximab and red meat allergy noted to overlap. Further supporting the link between tick bites and cetuximab and alpha-gal allergies ¹¹
2013	Rispens et al. describe the shift in IgG2 anti-bodies to IgE and IgG1 antibodies, following exposure to alpha-ga ²²
2017	Weis et al. demonstrate the use of alpha-gal antibody assays to mitigate the risk of cetuximab anaphylaxis ¹⁵

Despite these limitations, this study still demonstrates a higher than predicted incidence of infusion reactions, with almost double the rate of that seen in initial studies. Given the demonstrated association between alpha-gal exposure, cetuximab reactions and areas of high tick exposure, it is not unreasonable to assume a similar phenomenon is at play in this population. The timeline for the discovery of these associations is recorded in Table 2.

Based on this, we recommend the following protocol for patients considered for cetuximab therapy (Figure 2):

- Known mammalian meat allergy is an absolute contraindication.
- Those who test positive for alpha-gal specific-IgE-specific antibodies on the ImmunoCAP® should be given alternative therapy or considered for desensitization in consultation with an allergy specialist.

Initial studies for alpha-gal testing used a cut off for alpha-gal specific-IgE-specific antibodies of 0.35 kU/L.¹⁵ However, there has been evidence that a level of 0.1 kU/L may be more appropriate.⁷ Namba et al. demonstrated that a cut off level 0.35 kU/L identified 40% of those who had cetuximab anaphylaxis, however, if the cut off level of 0.10 kU/L is used then 80% of anaphylaxis cases could be predicted.⁸ The importance of having appropriate cut-off levels for alpha-gal specific-IgE-specific antibodies as highlighted in a recently published case of cetuximab anaphylaxis where retrospective pre-infusion serum showed near undetectable levels of alpha-gal (0.19 kUA/L).¹⁶

The finding of low levels of alpha-gal antibodies may be explained by the intravenous delivery of the antigen. This results in much higher and more sudden systemic antigen exposure leading to direct basophil acti-

vation. It has also been shown that alpha-gal levels decrease over time, with a significant reduction in level occurring over 18–24 months.¹⁷ However alpha-gal antibody levels will increase significantly (up to 20-fold in some studies) following a further tick bite,^{5,7} causing an allergic reaction. This phenomenon has been demonstrated in patients with red meat allergy, a reaction also mediated by alpha-gal sensitivity.¹⁸

There is evidence that dexamethasone and anti-histamines should be given to all patients from high tick prevalence areas, irrespective of their alpha-gal status, prior to cetuximab infusion. One study demonstrated the addition of a steroid to the preinfusional anti-histamine reduced all grades of infusion reactions from a 22% incidence to 7% and grade 3–4 from 4.7% to 1%.¹⁹ Therefore, preinfusion anti-histamine and steroids are recommended for all patients, particularly if previously or currently residing in high tick prevalent areas.

It has been demonstrated that following a tick bite, there is a recharging effect on previous alpha-gal antibody levels, which therefore increases the risk of anaphylaxis after subsequent tick bites.¹⁸ Therefore, the proposed protocol requires reassessment of alpha-gal in the event of a recent tick bite during cetuximab treatment.

5 | CONCLUSION

Cetuximab is an EGFR-targeted agent widely used as part of cancer therapy with proven benefit in patients with head and neck and metastatic colorectal cancers. Its most serious toxicity risk is anaphylaxis, especially on initial exposure. The association between infusion reactions and tick exposure and predeveloped alpha-gal antibodies allows risk stratification of patients in order to minimize the likelihood

Risk of alpha-gal sensitization:

- Has patient had prior histamine mediated/anaphylactic reaction to cetuximab?
- Does the patient have a known red meat allergy?
- Does the patient have a history of histamine release symptoms related to ingestion of red meat ingestion?

YES

Use alternative anti-EGFR antibody- panitumumab or consult an allergy specialist for consideration of desensitisation

NO**Perform alpha-gal IgE ImmunoCAP:**

- Level greater than 0.1kUA/L? (levels based on ImmunoCAP® assay)

NO

Proceed with cetuximab
- With pre-infusional steroid and anti-histamine

YES

Use alternative anti-EGFR antibody- panitumumab or consult an allergy specialist for consideration of desensitisation.

If patient receives a tick bite at any point during treatment then repeat alpha-gal IgE ImmunoCAP

FIGURE 2 Proposed protocol for selection of patients for cetuximab therapy

of such reactions. Our protocol offers a practical approach to reducing the risk of serious cetuximab infusion reactions, based on patient history of tick bites and mammalian meat allergy, and alpha-gal specific-IgE-specific antibody testing.

DATA AVAILABILITY STATEMENT

The data that support the findings of the study are available from the corresponding author, AY, upon reasonable request.

FUNDING STATEMENT

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ETHICS APPROVAL STATEMENT

Ethics approval for this study was gained following review by the research committees for the involved centers (Northern Cancer Institute St Leonards and Northern Cancer Institute Frenchs Forrest)

PATIENT CONSENT STATEMENT

This study did not involve obtaining consent from participants. This retrospective analysis was deemed to have a low or negligible risk to patients. Furthermore, there is no therapeutic or invasive component involved.

In accordance with the National Statement, section 2.3.10, the size of the population and the proportion of patients who are likely to have moved or died would prevent a logistically appropriate method in obtaining informed consent from each individual. For this reason, a waiver of consent was agreed upon by the research committees.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

All material used in this paper is either original material for this study or is common property with appropriate attributions and acknowledgements included in the paper.

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