

Low rate of cetuximab hypersensitivity reactions in Northeast Tennessee: An Appalachian effect?

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Abstract

Purpose: Cetuximab is a monoclonal antibody with a known risk of hypersensitivity reactions. Early studies showed hypersensitivity reaction rates of 3%, but there appears to be a higher incidence in the southeastern United States. To confirm the findings from nearby institutions that cetuximab-associated hypersensitivity reactions occur in approximately 20% of patients in the southeastern United States.

Methods: A retrospective chart review was conducted at Johnson City Medical Center in Johnson City, Tennessee. Each patient's first infusion was analyzed for hypersensitivity reaction, as well as for demographic information such as allergy and smoking history, pre-medications, and malignancy type.

Results: Data from the first infusion of cetuximab were collected for a total of 71 patients with various malignancies. The overall rate of grade 3 or higher hypersensitivity reaction was 1.4%, and total rate of hypersensitivity reaction was 8.5%. These findings more closely correlate to the early clinical trials and package insert. Both severe ($p = 0.001$) and any-grade ($p = 0.002$) hypersensitivity reaction occurred less frequently in one Southeastern Appalachian medical center compared to academic medical centers directly to the east and west.

Conclusions: Patients in southern Appalachia may be less likely to develop cetuximab hypersensitivity reactions compared to surrounding areas in the Southeastern U.S. These results lend support to the theory that exposure to lone star ticks (*Amblyomma americanum*) may be responsible for the development of IgE antibodies to cetuximab that cause hypersensitivity reactions. The development of quick and reliable bedside predictors of cetuximab hypersensitivity reactions may aid clinicians considering the use of cetuximab.

Keywords

Cetuximab, hypersensitivity reaction, oncology

Introduction

Cetuximab (Erbix[®]) is a chimeric monoclonal antibody that competitively inhibits epidermal growth factor by binding to the epidermal growth factor receptor (EGFR). It was the first antibody targeting EGFR approved for use in colorectal and head and neck cancers. Overall, it is well tolerated with an acceptable toxicity profile that includes acneform rash, malaise, diarrhea, nausea, hypomagnesemia, and increased incidence of infections. In early clinical studies, cetuximab was shown to have hypersensitivity infusion reactions (HSRs) in approximately 3% of patients, 90% of which occurred during the first infusion.¹

Since its FDA approval, several studies have produced conflicting information concerning the numbers of patients experiencing HSRs, particularly in the southeastern United States. The first evidence of regional differences in cetuximab HSR rates stemmed from a

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study at the University of North Carolina at Chapel Hill (UNC), which also included data from patients of Vanderbilt Ingram Cancer Center (VICC) and Sarah Cannon Cancer Research Institute (SCCRI), both located in Nashville, TN. After a retrospective study of 88 patients, an overall rate of grade 3 or 4 HSRs between the infusions was 22%.² Shortly thereafter, a study from Duke University ($n=72$) demonstrated a 29% incidence of HSRs, 18% being grade 3 or 4.³ Recently, Keating et al.⁴ provided an updated analysis of an additional 125 patients from UNC where 24.8% experienced any HSR and 14.4% experienced a severe HSR (grade 3 or worse).⁴

Higher rates of cetuximab HSRs have also been reported from a Veteran's Affairs hospital ($n=51$) in Florida where 27% of patients receiving cetuximab experienced any grade of reaction.⁵ Eight patients (16%) experienced a grade 3 or 4 HSR, further supporting the body of evidence that severe HSRs associated with cetuximab occur more commonly in the southeastern United States. High rates of severe cetuximab HSRs have also been reported in Oklahoma (12.4%) and Missouri (24.6%).^{6,7}

Potential predictors of HSRs to cetuximab have been hypothesized. Duke University's experience found that patients with head and neck cancer were more likely to experience HSRs.³ A history of atopy has also been described as a risk factor.^{2,7} University of Oklahoma researchers identified male gender and current smokers to be risk factors.⁶ Other possible risk factors include tick bites, histoplasmosis, or a particular pollen found in trees or plants that may mimic the cetuximab antigen.^{2,3,8} Conversely, corticosteroid pretreatment may have a protective effect.⁴

While regional differences in cetuximab-associated HSRs are not fully understood, the mechanism of such reactions with the first dose is likely caused by preformed IgE antibodies.⁷ These antibodies are specific to galactose- α -1,3-galactose, an oligosaccharide of cetuximab. This IgE antibody assay displayed a sensitivity of 68% and specificity of 98% for developing cetuximab-associated HSRs.⁷ An enzyme-linked immunosorbent assay (ELISA) developed by Mariotte et al.⁹ for detecting anti-cetuximab IgE immunoglobulins has been described in the literature and displayed a sensitivity of 87.5% and a specificity 82.1% for predicting grade 3 + HSRs. However, commercially available assays (ImmunoCAP Allergen c360 Cetuximab, Phadia) to predict cetuximab HSRs have been disappointing.¹⁰

Nashville, TN (home of VICC and SCCRI) is located approximately 285 miles west, while the medical centers of UNC and Duke University are located approximately 220 miles east of Johnson City Medical Center. Thus, Johnson City's location is ideally situated

to confirm the high rate of cetuximab HSRs reported by institutions in the southeastern U.S.

Methods

Study design

A retrospective chart review was conducted of patients treated with cetuximab at Johnson City Medical Center with the primary objective of this study was to compare the rate of cetuximab HSRs at our community medical center with the rates of nearby academic medical centers. Patients were identified by a central pharmacy database and electronic medical records. This study was approved by East Tennessee State University and Mountain States Health Alliance Institutional Review Board.

Participants and setting

Johnson City Medical Center is a 488-bed community hospital and level 1 trauma center and the flagship hospital for the Mountain States Health Alliance (MSHA). Multiple teaching services associated with the Quillen College of Medicine at East Tennessee State University round in the hospital along with other community providers. The MSHA Regional Cancer Center includes a 21-bed outpatient infusion suite and physician clinics. Patient records from JCMC and the Regional Cancer Center were reviewed to identify those over the age of 18, cetuximab naïve, and treated between the dates of 1 January 2005 and 31 October 2013. This date range coincides with institution's adoption of electronic medical record, which would allow for efficient data collection. Patients without available records for their first infusion, patients who received first infusion elsewhere, or who refused cetuximab were excluded.

Data collection

Information regarding each patient's allergy history, premedications for cetuximab treatment, type and stage of malignancy, demographics, tobacco use history, and treatment regimen (monotherapy or in combination with either chemotherapy or radiation therapy) were recorded. Similar to previous studies, an allergy to an opioid was not considered part of the patient's allergy history. Records such as nursing notes during infusion, blood pressure during infusion, medication administration records, or progress notes demonstrating treatment of HSRs were reviewed to ascertain the incidence of HSRs.

In the case of each hypersensitivity reaction, a grade of 1 to 5 based upon the Common Terminology Criteria for Adverse Events version 3.0 was given to

the patient's reaction.¹¹ Version 3.0 was used for consistency, given previous studies used the same version as well.^{2,3}

Data analysis

Chi-squared test was used to compare categorical the incidence of HSRs to previously published data unless expected group frequencies were < 10%, in which case Fisher's exact test would be used. Descriptive statistics were performed for baseline demographics, and odds ratios were calculated for possible risk factors for cetuximab HSRs (tobacco use, allergy history, and malignancy type). All statistically analyses were calculated using PASW Statistics 18 (SPSS, Chicago, IL, USA).

Results

A total of 83 patients were identified via the pharmacy database, 12 of which were excluded from statistical analysis. Reasons for exclusion included receiving first dose of cetuximab at an outside facility (three patients), incomplete medical records for assessment (seven patients), and refusing to receive a dose of cetuximab (two patients). Gender distribution of the population was approximately equal and primarily Caucasian, except for three patients whose race was not recorded. The mean age of the population was 61 years ranging from 36 to 86 years. Twenty-four (34%) patients reported to have a previous allergy to non-opioid medications. Most patients (92%) received histamine 1 receptor antagonists (H1RA), many (46%) received dexamethasone, and some (25%) received histamine 2 receptor antagonists (H2RA) as premedication.

Six (8.5%) experienced hypersensitivity reactions of any grade, while one (3.4%) patient had a grade 3 or higher reaction. The rates of any ($p = 0.001$) and severe

hypersensitivity reactions ($p = 0.001$) were significantly lower than previously reported at surrounding academic medical centers²⁻⁴ (Table 1). Baseline demographics are presented for those with no HSR, any HSR, and severe HSR (Table 2). No risk factors (e.g. allergy history) or protective factors (e.g. dexamethasone pretreatment) were identified (Table 3).

Table 2. Baseline demographics.

Characteristic	No HSR (n = 65)	HSR (n = 6)
Male, n (%)	36 (55)	1 (17)
Female, n (%)	29 (45)	5 (83)
Age, mean (years)	60	70
Caucasian, n (%)	62 (95)	6 (100)
Malignancy, n (%)	25 (38)	2 (33)
Colorectal	32 (49)	4 (67)
Head and neck	8 (12)	0 (0)
Lung		
Chemotherapy, n (%)	30 (46)	2 (33)
Cetuximab monotherapy	35 (54)	4 (67%)
Combination therapy		
Tobacco use, n (%)	36 (55)	3 (50%)
Allergy history, n (%)	23 (35)	1 (17%)
Premedication, n (%)	59 (91)	6 (100)
H1RA	17 (26)	2 (33)
H2RA	31 (48)	2 (33)
Dexamethasone		
	No severe HSR (n = 70)	Severe HSR (n = 1)
Male, n (%)	41 (59)	1 (100)
Female, n (%)	29 (41)	0 (0)
Age, mean (years)	60	73
Caucasian, n (%)	67 (96)	1 (100)
Malignancy, n (%)	27 (39)	1 (100)
Colorectal	35 (50)	0 (0)
Head and neck	8 (11)	0 (0)
Lung		
Chemotherapy, n (%)	39 (56)	1 (100)
Cetuximab monotherapy	31 (44)	0 (0)
Combination therapy		
Tobacco use, n (%)	37 (53)	1 (100)
Allergy history, n (%)	24 (34)	0 (0)
Premedication, n (%)	64 (91)	1 (100)
H1RA	17 (24)	1 (100)
H2RA	31 (44)	0 (0)
Dexamethasone		

Table 1. HSR rates to cetuximab in Tennessee and North Carolina.

Medical center(s)	No HSR	Any HSR	P
JCMC	65 (91.5%)	6 (8.5%)	0.002
UNC/SCCRI/Duke ^a	208 (72.3%)	77 (27%)	
	No severe HSR	Severe (grade +) HSR	p
JCMC	70 (98.6%)	1 (1.4%)	0.001
UNC/SCCRI/Duke ^a	235 (82.5%)	50 (17.5%)	

HSR: hypersensitivity reaction; JCMC: Johnson City Medical Center; UNC: University of North Carolina; SCCRI: Sarah Cannon Cancer Research Institute.

^aPooled Data from references 2, 3, and 4.

HSR: hypersensitivity reaction; H1: histamine one receptor antagonist; H2: histamine two receptor antagonist.

Note: percentages may not add to 100 due to rounding.

Discussion

While Johnson City, TN is approximately the midpoint between Nashville and Durham/Chapel Hill, NC, the geography differs significantly. Johnson City is nestled in the Appalachian Mountains, resulting in a higher elevation, and a climate and ecosystem that likely vary

Table 3. Correlation between possible risk factors and any HSR.

Variable	Odds ratio (95% CI)	p
Allergy history	0.36 (0.04 to 3.32)	0.37
Tobacco use	0.81 (0.15 to 4.29)	0.80
Head and neck cancer	2.06 (0.35 to 12.06)	0.42
Colorectal cancer	0.80 (0.13 to 4.69)	0.80
Male gender	0.16 (0.12 to 1.46)	0.10
Dexamethasone pretreatment	0.55 (0.09 to 3.21)	0.50

from the more populous cities of Nashville and Durham/Chapel Hill. One theory that may explain the higher HSR rate to cetuximab in the Southeastern U.S. centers on exposure to the lonestar tick (*Amblyomma americanum*), which has been shown to induce production of IgE antibodies specific to cetuximab.¹² Keating et al.⁴ presented geographic data describing a possible overlap in cetuximab HSR rates and prevalence of lonestar ticks in North Carolina counties. This geographic data also suggest the lonestar tick may be less prevalent in western North Carolina counties in Appalachia. However, it should be noted this geographic data are based on submission of tick specimens, which may be influenced by population.

In 2012, reported cases of *Ehrlichiosis chaffeensis*, a tick-borne pathogen also transmitted by the lonestar tick, occur in a similar geographic distribution¹³ (Figure 1). Counties of central North Carolina and Tennessee reported cases of Ehrlichiosis more frequently than the counties of Northeast Tennessee, where no cases were reported. Additionally, clusters

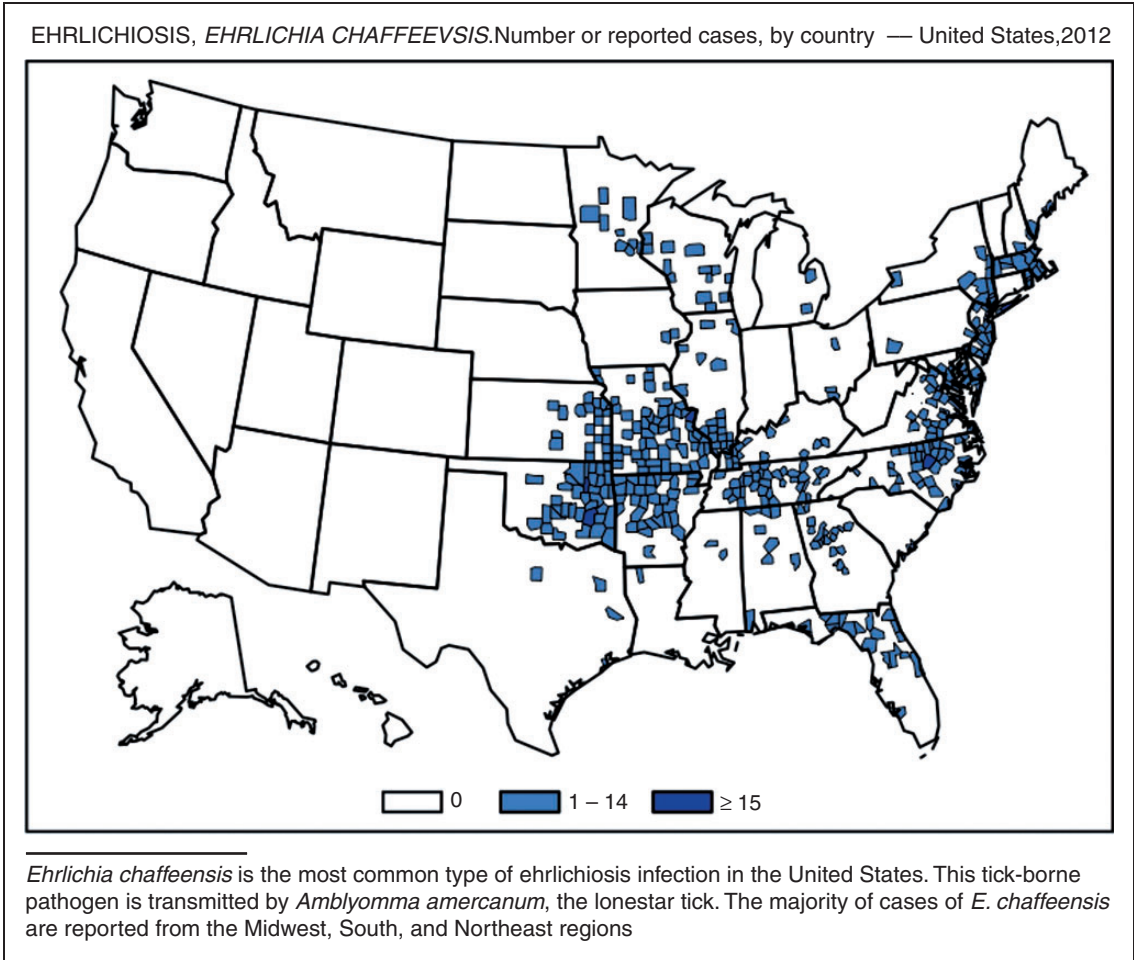


Figure 1. Centers for Disease Control and Prevention-reported Ehrlichiosis cases.

of Ehrlichiosis cases appear in Florida, Missouri, and Oklahoma where higher rates of cetuximab HSR have been reported.^{5–7} This geographic overlap of reported Ehrlichiosis cases and higher published rates of cetuximab HSR in Missouri, Oklahoma, Florida, North Carolina, and Tennessee is compelling, but not definitive. There may be other factors contributing to the increased cetuximab HSR in these areas, but intraregional differences and varying methodology in data collected from previously published studies limit the ability to study all possible risk factors.

A protective Appalachian effect that prevents lone-star tick activity may explain the surprisingly low rates of cetuximab HSRs at our center. Lone-star tick activity and survival have been shown to be seasonal and correlate with relative humidity since tick survival is dependent on moisture retention.^{14,15} Thus, it is plausible the higher elevation and corresponding lower absolute humidity of Appalachia mitigate Lone-star tick activity. The geographic distribution of Ehrlichiosis is also present along most of the eastern coast of the U.S. As high rates of cetuximab HSRs have not been described in this heavily populated area, and it seems there may be other factors than lone-star tick exposure involved in the regional differences in hypersensitivity.

In contrast to the UNC and VICC/SCCRI experience, none of the patients in our study were enrolled in clinical trials. Clinical trial enrolment may provide extra watchfulness and recordkeeping that our patients may not have received in the community setting. Even in the cases of the most minor reactions, the physician may have chosen the safest route (i.e. hospitalization) to ensure that the patient did not experience complications from a severe HSR. Hospitalization would be classified as a grade 3 adverse event.⁶

Limitations of our study include the small sample size (n=71) and its retrospective nature. Data were recorded only from one medical center. Our small sample size and low rate of HSRs likely prevented any meaningful evaluation of possible risk factors for cetuximab HSRs. Also suboptimal documentation in the medical record may have affected our results. For example, race was not recorded in the medical record for 3 patients in our study.

Our data suggest patients in southern Appalachia may experience a lower risk of cetuximab HSRs than surrounding areas in the Southeastern U.S. There appears to be a geographic association between reported cases of lone-star tick activity and the incidence of cetuximab HSRs. This hypothesis-generating conclusion requires prospective validation by other Southern Appalachian medical centers with populated areas such as Asheville, NC, Charleston, WV, and Roanoke, VA as ideal study locations. Despite multiple single-center studies of the incidence and risk factors for cetuximab

HSRs, conflicting results present a cloudy picture when it comes to identifying risk factors. Given cetuximab's utility in several malignancies and the desire to individualize care at a molecular level, reliable bedside predictors of cetuximab hypersensitivity are needed. Collaborative practice based-research networks should be considered a possible avenue to better address this concern.

Declaration of conflicting interests

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