

High Incidence of Cetuximab-Related Infusion Reactions in Tennessee and North Carolina and the Association With Atopic History

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ABSTRACT

Purpose

To confirm the anecdotal observation that patients in North Carolina (NC) and Tennessee (TN) treated with cetuximab experience hypersensitivity reactions (HSR) at a much higher rate than are reported nationally and internationally ($\leq 3\%$).

Patients and Methods

Data from patients treated with cetuximab on clinical trials ($n = 88$) at three research sites were analyzed for grade 3 or 4 HSR. Additional information was obtained from medical records for patients treated with cetuximab at the University of North Carolina (Chapel Hill, NC) to determine whether history of other significant allergy was a risk factor for HSR to cetuximab.

Results

Data for 88 patients on clinical trials and an additional 55 patients treated outside of trials were included in this analysis. Patients had a variety of tumor types. For the clinical trial group ($n = 88$), the overall rate of grade 3 to 4 HSR was 22%, significantly higher than the rate noted in any large published trial. All HSRs occurred during the first dose. There was a strong relationship between prior allergy history and chance of HSR.

Conclusion

At the sites in neighboring NC and TN studied, HSR was far more common than reported in national studies. History of prior allergy is a strong predictor of HSR. Further investigation of more specific predictors of HSR in the US middle south region is warranted, and patients being treated with cetuximab in this area should be observed particularly closely during their first infusion.

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INTRODUCTION

Anaphylactic reactions or hypersensitivity reactions (HSR), defined by a constellation of symptoms including laryngeal edema, bronchospasm, or hypotension that occur soon after administration of a therapeutic agent, are potentially life-threatening adverse effects related to therapeutic antibody administration.¹ Cetuximab is a human-murine chimerized immunoglobulin G1 monoclonal antibody that is directed at the extracellular ligand-binding domain of the epidermal growth factor receptor (EGFR).² The EGFR signaling pathway appears to be aberrantly active in a number of malignancies. Cetuximab was the first antibody targeting EGFR approved by the US Food and Drug Administration for cancer therapy, and is now either approved or in phase III trials for multiple common tumor types.² Cetuximab has a favorable safety profile with the exception of relatively uncommon HSR. The most

common nonserious adverse effect of cetuximab is acneiform rash, which is likely related to the presence of EGFR in the skin and hair follicles, and is not indicative of hypersensitivity in any way. Rash is interesting in that its presence has been correlated with response and even survival in several tumor types.³

In a pivotal randomized phase II trial of cetuximab (with or without irinotecan) for patients with refractory metastatic colorectal cancer performed in Europe,⁴ 329 patients were randomly assigned to cetuximab plus irinotecan or cetuximab alone. To our knowledge, this is largest published cetuximab study to date. Only four of the 329 patients (1.2%) experienced grade 3 or 4 HSR, all of whom were in the single-agent cetuximab group. Patients in the monotherapy arm received only a dose of an antihistamine (H1) antagonist as premedication, whereas patients in the combined therapy arm were more likely to receive a corticosteroid as premedication for

nausea prophylaxis. Other studies have confirmed the relatively low rate of hypersensitivity reactions noted in the pivotal European cetuximab phase II trial. For example, in a recent US multicenter phase II study of 80 patients with colorectal cancer conducted primarily in the US northeast and far west, no patients experienced a grade 3 or greater infusion reaction.⁵ More recently, safety data from a large (800 patients; half randomly assigned to receive cetuximab), ongoing colorectal cancer study were presented.⁶ In this trial, the rates of any infusion reaction were 4%, and grade 3 or 4 reactions were reported in only 0.5% of patients receiving cetuximab.

In contrast to these results, the experience at several southeastern US medical centers has been anecdotally different, with investigators at several sites reporting significantly more reactions than would be expected based on the aforementioned percentages. This included experience at the University of North Carolina at Chapel Hill (UNC), in which the first three patients treated with cetuximab all experienced early infusion-related HSR requiring subcutaneous epinephrine administration and hospital admission for observation. Thorough investigation of these reactions conducted by UNC and Bristol-Myers Squibb personnel revealed no problem with the drug itself (all patients received drug from different production batches), no problem with premedication administration, and no problem with drug delivery (eg, rate, mixing). Subsequent experience upheld our suspicion that the rate of HSR being experienced at UNC to cetuximab was different than that reported at other sites. This experience was shared by investigators in neighboring states, particularly Tennessee, where a number of patients were treated with cetuximab on clinical trials, and the impression of the investigators was similar to our own.

One death has occurred at one of the sites, and additionally these reactions have resulted in treatment discontinuation for the involved patients and treatment delays for other patients in clinic that day. In addition, these reactions are quite traumatic for the patients, family members, nursing staff, and physicians involved in managing these events. We therefore developed this study to quantify the rate of hypersensitivity reactions and to begin to define a clinical profile of patients who are more likely to experience HSR at our site. In doing so, we have demonstrated a strong association between an atopic history and chance of experiencing a HSR to cetuximab.

METHODS

Records of all patients treated with cetuximab (up to a cutoff date of November 15, 2006) at UNC were reviewed under an institutional review board–approved protocol. Patients were identified via a central pharmacy database. Documentation of hypersensitivity reactions in patients on cetuximab-containing clinical trials was obtained from UNC, along with the Sarah Cannon Cancer Research Institute (SCCRI) and the Vanderbilt Ingram Cancer Center (VICC), both in neighboring Tennessee. Details of premedications given were either determined from the chart (UNC patients only), or from examining the study protocol for patients on clinical trials at the two other sites. History of allergy was assigned as positive if the patient had any of the following documented in the medical record: history of drug allergy producing rash or anaphylactic/anaphylactoid symptoms (excluding narcotic allergies regardless of description), history of bee sting allergy, history of allergic asthma or eczema, or presence of a nonsedating antihistamine on the patient's medication list.

Statistical Methods

Fisher's exact test was used to test for differences in proportions (or percentages) between those who had any HSR, or those who experienced grade

1 or 2 HSR, or those who experienced grade 3 or 4 HSR, versus those who did not. Exact 95% confidence limits have been calculated for the reported binomial proportions (percentages). For the continuous variable of age, the Wilcoxon rank sum test (using Van der Waerden normal scores) was used for two-group comparisons. For more than two groups, the Kruskal-Wallis test (using Van der Waerden normal scores) was used. Statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Ninety sequential patients whose records clearly indicated that cetuximab was administered were identified in a UNC hospital pharmacy database. Table 1 details demographic information for the patients treated at UNC. In addition, 53 patients were treated with cetuximab on clinical trials at the VICC and the SCCRI (26 and 27 patients, respectively). Tumor type and the medications delivered before antibody infusion specified by each study protocol are described in Table 2. Of the 90 patients identified at UNC, 35 were treated on clinical trials. When restricting analysis to the trial-treated patients at all three sites (where grading was prospectively assessed consistent with National Cancer Institute Common Toxicity Criteria for Adverse Events Version 2.0 or 3.0 [varied by protocol]), 19 of 88 (22%; exact binomial 95% CI, 13.5% to 32%) experienced first infusion grade 3 to 5 HSR. Seventeen of these 19 reactions (89%; exact binomial 95% CI, 67% to 99%) were grade 3. None of the patients included in the study died as a result of an HSR event. The 22% of patients experiencing grade 3 to 4 HSR at UNC is significantly larger than the published percentage

Table 1. UNC Patient Characteristics (N = 90)

Characteristic	No.	%
Age, years		
Median	60	
Range	26-84	
Sex		
Male	48	53
Race		
White	71	79
Black	17	19
Hispanic	2	2
Primary tumor site		
Breast	4	4
Colorectal	33	37
NSCLC	21	23
Ovarian	7	8
SCCHN	19	21
Other	6	7
Premeds		
H1	8	9
H1, D	61	68
H1, D, H2	21	23
Clinical trial		
Yes	35	39
No	55	61

NOTE. Includes trial-treated and off-study treated patients.

Abbreviations: UNC, University of North Carolina, Chapel Hill, NC; NSCLC, non-small-cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; H1, antihistamine; D, dexamethasone; H2, receptor blocker.

Table 2. Cetuximab Clinical Trials at All Three Study Sites

Table 2. Continued: Clinical Trials at Four Sites Study Sites					
Site and Study	Cancer Type	No. of Patients	HSR Grade		Premedication
			1-2	3-4	
UNC					
CALGB 80405	Colorectal	3	0	2	H1, D
NCCTG N0147	Colorectal	2	0	0	H1, D
LCCC 0503	NSCLC	6	1	1	H1, D
CA225058	NSCLC	2	0	1	H1
CA225081	NSCLC	13	2	4	H1, H2, D
LCCC 0421	HCC	5	0	1	H1, D
LCCC 0403	Breast	4	0	0	H1
Total		35	3	9	
SCCRI					
GI 46	Colorectal	14	1	2	H1, D
LUN 92	NSCLC	12	0	4	H1, D
Total		26	1	6	
VICC					
GI 0466	Pancreatic	5	1	1	H1
GI 0410	Colorectal	17	1	3	H1
GI 0602	Menetriers	5	0	0	H1
Total		27	2	4	
Overall total		88	6	19	

Abbreviations: HSR, hypersensitivity reaction; UNC, University of North Carolina; CALGB, Cancer and Leukemia Group B; NCCTG, North Central Cancer Treatment Group; LCCC, Lineberger Comprehensive Cancer Center; SCCRI, Sarah Cannon Cancer Research Institute; GI 46, gastrointestinal trial 46; LUN 92, lung trial 92; VICC, Vanderbilt Ingram Cancer Center; NSCLC, non-small-cell lung cancer; HCC, hepatocellular carcinoma; H1, diphenhydramine; D, dexamethasone; H2, receptor blocker.

from the study by Cunningham et al⁴ of 1.2% (for 4 of 329; exact binomial 95% CI, 0.3% to 3%; $P < .0001$).

The HSR rates among the cetuximab clinical trials at the three study sites of interest were similar (Table 2). For HSR grade 1 or 2, UNC had three of 35 or 9% (95% CI, 2% to 23%), SCCRI had one of 26 or 4% (95% CI, 0.1% to 20%), and VICC had two of 27 or 7% (95% CI, 0.9% to 24%). For the three sites combined, the rate was six of 88 or 7% (95% CI, 3% to 14%). For HSR grade 3 or 4, UNC had nine of 35 or 26% (95% CI, 12% to 43%), SCCRI had six of 26 or 23% (95% CI, 9% to 44%), and VICC had four of 27 or 15% (95% CI, 4% to 34%). For the three sites combined, the grade 3 to 4 rate was 19 of 88 or 22% (95% CI, 14% to 32%).

Among the 90 patients treated at UNC (both on- and off-study), the reaction rate was similar to the three-site, trial-treated group. Eighteen of 90 or 20% (95% CI, 12% to 43%) patients had any HSR, and 13 of 90 or 14% (95% CI, 8% to 23%) had a grade 3 or 4 HSR. It is possible that the number of grade 1 or 2 reactions were underestimated for patients treated outside of trials because of differences in documentation for patients not being observed in a study.

All patients (trial and nontrial) were treated with a prophylactic dose of H1 antagonist. Fifty-seven of 88 (65%) of trial-treated (all sites) patients additionally received a glucocorticoid, almost always dexamethasone, as a premedication either for the cetuximab itself or as an antiemetic for chemotherapy given the same day. There was no apparent protection from hypersensitivity afforded by per-protocol glucocorticoid premedication ($P = .27$); however, we were not able to confirm whether dexamethasone was actually given before cetuximab for patients at SCCRI and VICC. In the UNC patient cohort, 81 (90%) of 90 patients were pretreated with a glucocorticoid on the day of cetuximab administration. We were able to confirm that glucocorticoid was given before cetuximab in 66 (81%) of 81 of patients. The

grade 3 to 4 HSR rate in those premedicated with dexamethasone was 11 (16.7%) of 66. This number was not statistically different than the reaction rate for the entire group. Twenty-one patients treated at UNC received a prophylactic receptor blocker (H2) antagonist, with no evidence of protection from any HSR ($P = .21$) or grade 3 or 4 HSR ($P = .49$).

There appeared to be no significant association between HSR and the demographic covariates of age, sex, or race with any HSR (Table 3; $P = .36$, $P = .99$, and $P = .24$, respectively). There did, however, appear to be a significant association between HSR and type of cancer

Table 3. Associations Between Demographic Variables and HSR

		HSR Grade					
Demographic	No. of Patients	Any			3-4		
		No.	%	<i>P</i>	No.	%	<i>P</i>
Race							
Black	17	1	6		0		
Hispanic	2	0			0		
White	71	16	23		13	18	
Sex							
Female	42	8	19		7	17	
Male	48	9	19		6	13	
Cancer type							
Colon	30	3	10		3	10	
SCCHN	19	2	11		1	5	
NSCLC	21	9	43		6	29	
Other	20	3	15		3	15	

Abbreviations: HSR, hypersensitivity reaction; SCCHN, squamous cell carcinoma of the head and neck; NSCLC, non-small-cell lung cancer.

with the percentage of those with non-small-cell lung cancer (NSCLC) as the primary tumor type experiencing significantly higher rate of any HSR (nine of 21 or 43%; $P = .03$; Table 3). However, this association was not significant when considering only grade 3 or 4 HSR (six of 21 or 29%; 95% CI, 11% to 52%; $P = .21$).

We further examined the medical records of the group of 90 patients treated at UNC for an atopic history (see definition in Methods section). Types of allergies recorded are listed in Table 4. Patients with history of prior significant allergy history were significantly more likely to experience either any HSR (10 of 28 or 36% *v* seven of 62 or 11%; $P = .009$) and grade 3 or 4 HSR (eight of 28 or 29% *v* five of 62 or 8%; $P = .02$).

DISCUSSION

Our study revealed an alarming frequency of infusion-related HSR at the three sites examined, data that would call for a comprehensive survey of reactions in the middle southern US region that includes North and South Carolina, Tennessee, northern Georgia, and extends westward to Arkansas where HSR is also anecdotally problematic. The immediate and severe nature of these reactions suggests a pre-existing immunoglobulin E-based immune reaction directed at the antibody itself. In fact, an immunoglobulin E antibody directed against cetuximab has recently been identified in patients who experience HSR to cetuximab, and a study to determine the utility of this finding as a predictor of HSR is ongoing (Christine Chung, VCCCC, personal communication, May 2006). It has been speculated but not proven that such a crossreactive response could be caused by increased exposure to mouse antigens or another antigen mimic of cetuximab that is regionally based, such as a particular plant or tree pollen. It is worth noting that all reactions occurred with first dose, and therefore there is no reason for physicians in the region to consider discontinuation of therapy in a patient already tolerating the drug on the basis of this report.

As data mature for several completed trials of the efficacy of cetuximab in first- and second-line colorectal cancer therapy, NSCLC, and head and neck cancer, the indications for use of the drug may substantially increase. If a significant survival benefit is associated with the use of this drug in several common tumor types, cetuximab-related HSR could become a significant public health concern. To our

knowledge, there are no published studies addressing a desensitization protocol that have been successful. Experience with desensitization protocols for other drugs such as trastuzumab,⁷ carboplatin,⁸ paclitaxel,⁸ and even oxaliplatin⁹ have met with some success, and are being considered for cetuximab. However, the reactions to these other agents are different in that they generally occur after exposure to the drug, and may have a significantly different mechanism of occurrence.

A potential alternative to cetuximab for patients with HSR has recently become available, the fully human immunoglobulin G2 monoclonal antibody panitumumab.¹⁰ The three sites involved in this study have together treated approximately 100 patients with panitumumab, with no known severe (grade 3 or 4) HSR at any of our sites to date. Indications from a recently presented randomized study in colorectal cancer were that the rates of reaction were less than those seen for cetuximab; however, the nationwide and worldwide HSR rates to cetuximab are generally low as well. A current lack of data regarding the use of panitumumab in conjunction with chemotherapy makes it difficult to consider a wholesale switch to that drug at present (as the most effective use of anti-EGFR therapy in colorectal cancer currently appears to be in combination with irinotecan). In fact, a recent press release from Amgen reporting a planned interim analysis of their phase III trial of infusional plus bolus fluorouracil/leucovorin plus oxaliplatin with bevacizumab with or without panitumumab indicated that its use increased toxicity without adding activity.¹¹ In contrast, preliminary phase II data on the combination of cetuximab with chemotherapy has indicated some potential increase in activity with an acceptable toxicity profile for that combination¹² and phase III trials are underway and will soon be reported from these studies. To date, single-agent studies with the two drugs have shown relatively comparable efficacy.^{4,13}

An alternative approach to using a different agent would be to screen patients for use of cetuximab based on allergy history, as would be suggested by our data. This approach would best be validated prospectively. Even in our patients with negative allergy history, the rate of grade 3 or 4 HSR was more than twice as high (8%) as that reported in other US or European trials; therefore this history alone may not be adequate to predict which patients should avoid cetuximab. Our plan going forward is to comprehensively assess patients for all allergies in hopes of refining a clinical profile of a potential HSR-prone patient, an endeavor that would benefit from being carried out at multiple centers. Also, as mentioned before, the recently noted presence of anticetuximab immunoglobulin E may be a predictor of HSR.

In addition to the association between atopic phenotype and HSR, we also noted a potential association between a diagnosis of NSCLC and chance of HSR that would be worthy of further exploration in a larger data set. We cannot exclude ascertainment bias by the individual investigators on NSCLC studies as the explanation for this finding, nor can we exclude the possibility that patients with NSCLC are more likely to experience dyspnea with a minor reaction due to underlying pulmonary disease that might have increased the grade of their HSR reaction artifactually. An association between NSCLC and HSR would be interesting because it could, for example, lead to investigation of exposure to tobacco byproducts as the exposure that leads to presensitization to cetuximab. Two recent and relatively large US studies of cetuximab for NSCLC have just completed accrual, with a noted HSR rate of only 3% in a study of 162 patients also receiving two different schedules of carboplatin and paclitaxel (M.A. Socinski,

Table 4. Number and Types of Prior Allergies in Patients Receiving Cetuximab at the University of North Carolina

Type of Allergy	No.
Any defined	28
Drug	30
Penicillin	17
Sulfa	8
IV contrast	3
Azithromycin	1
Tetanus vaccine	1
Asthma, allergic rhinitis, or eczema	11
Food (seafood, eggs, artificial sweetener)	2
Bee sting	3
Multiple	12

personal communication May 2007). A higher rate of 10.5% was observed in a smaller study of 57 patients also treated with carboplatin. The smaller study included research sites in North Carolina, Kentucky, Arkansas, and Georgia (M.A. Socinski, personal communication, May 2007). Interestingly, an Eastern Cooperative Oncology Group study of patients with head and neck cancer, a group with similar tobacco exposure as NSCLC patients, treated with cetuximab plus cisplatin also reported a higher HSR rate (6% grade 3 or 4) than was reported in colorectal cancer studies.¹⁷ The geographic distribution of reactions from this study was not available.

Reactions at our sites have resulted in several management practices regarding administration of cetuximab. At UNC, an advanced practitioner (physician, physician assistant, or nurse practitioner) is physically present in the infusion area during first 30 minutes of the first administration of cetuximab for any patient. At SCCRI, all cetuximab-containing studies were halted due to the number of HSRs.

If a reaction does occur, early administration of subcutaneous epinephrine (1:1000 dilution, 0.2 to 0.5 mg administered subcutaneously or intramuscularly) is critical in the case of airway compromise or hypotension, in addition to repeated dosing of a corticosteroid. Detailed guidelines for the management of anaphylaxis have been published by the Joint Council of Allergy, Asthma, and Immunology,¹⁸ and these guidelines should be available to practitioners who administer cetuximab or other agents that share this potential adverse reaction. While many patients in our study had received premedication with dexamethasone, an H2 agonist, or both (in addition to the recommended H1 antagonist), there was no evidence that these measures are protective. Mechanistically, one would not expect corticosteroids to provide protection from an immediate immunoglobulin E-mediated reaction.

In conclusion, cetuximab is a drug that is used safely in most of the country, but we have identified several sites in the US middle south that have reaction rates much higher than reported nationwide. Invest-

igation of the mechanism of this high rate of HSR is ongoing, but practitioners and patients in the region should be aware of the added risk of using cetuximab and take appropriate precautions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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