

# Incidence and predictors of cetuximab hypersensitivity reactions in a North Carolina academic medical center

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**Objectives.** Previous research has indicated a high incidence of cetuximab hypersensitivity reactions in the southern US. This study documents the incidence of hypersensitivity reactions in North Carolina, and explores whether factors such as patient demographics, allergy history, premedications, and cancer type are potential predictors for cetuximab reactions.

**Methods.** This retrospective chart review consisted of 72 consecutively treated patients from Duke University's Morris Oncology treatment center between September 2005 and August 2007. Data regarding stage of malignancy, premedications, and hypersensitivity reactions were collected from electronic databases. The number and type of reactions were characterized. Patients with and without hypersensitivity reactions were compared using bivariate statistics and multivariate logistic regression.

**Results.** Of the 72 patients, 21 (29%) experienced hypersensitivity reactions. The majority of reactions (62%) were grades III or IV. Of the 21

patients having a reaction, 9 (43%) were sent to the emergency room and 5 (24%) had an overnight hospitalization. Three hospitalized patients were admitted to the intensive care unit. Both male gender ( $p = 0.039$ ) and head/neck cancer ( $p = 0.014$ ) were related to an increased likelihood of hypersensitivity reaction in bivariate analyses. In multivariate analyses, controlling for demographics, allergy history, premedications, and cancer type/stage, only type of cancer was predictive of hypersensitivity reaction (colon vs head/neck OR = 0.177; 95% CI 0.036–0.858).

**Conclusion.** This study confirms a high rate of cetuximab hypersensitivity reactions in a southern region of the US. Patients with head/neck cancers were significantly more likely to have hypersensitivity reactions than patients with colon cancers. *J Oncol Pharm Practice (2010) 0: 1–6.*

**Key words:** cetuximab; hypersensitivity; predictors; observational

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## INTRODUCTION

Cetuximab (Erbix<sup>®</sup>, ImClone Systems Incorporated, Branchburg, NJ, USA) was the first monoclonal antibody approved by the US Food and Drug Administration for treatment in patients with advanced colorectal cancer and squamous cell head and neck cancer. Cetuximab is given in combination with radiation therapy for head and neck cancers, and in combination with chemotherapy for colorectal cancer. The benefits, risks, and costs of cetuximab are particularly important to treatment decisions. Although some studies indicate that cetuximab can improve overall survival in patients for whom other treatments have failed,<sup>1-4</sup> costs and potential risks associated with cetuximab may alter treatment decisions, especially given marginal improvements in survival. For example, the cost of cetuximab for 8 weeks is more than \$30,000 per patient.<sup>5,6</sup>

Although effectiveness and costs are important considerations with cetuximab, adverse events are a growing concern. One of the most serious adverse events involves hypersensitivity reactions. Cetuximab's product label indicates that hypersensitivity reactions occur in 3% of patients. However, higher percentages of reactions have been reported in states of North Carolina, Arkansas, Missouri, Virginia, and Tennessee.<sup>2,5,7-9</sup> A recent study showed that 22% of patients who were treated with cetuximab in North Carolina and Tennessee had severe hypersensitivity reactions.<sup>9</sup> Results of another study at a Florida Veterans Affairs facility indicated that 27% of the patients experienced grades II to IV hypersensitivity reaction. These patients had no differences in age, race, diagnosis, stage, or allergic history, and there were no known identifiable risk factors that predicted hypersensitivity reaction severity.<sup>10</sup> Around 90% of these hypersensitivity reactions occur within minutes of exposure to the drug and can be extremely detrimental to the patient's health. A treatment-related death due to hypersensitivity reaction in a patient was reported in 2004 during a clinical trial.<sup>11</sup>

Increases in reported incidence and the potential severity of hypersensitivity reactions has provoked the question of whether patient, disease, or treatment characteristics might be used to predict which patients are most susceptible to reactions. Existing data in this regard are limited as of now. One previous study found that an atopic history was a strong predictor of hypersensitivity reactions.<sup>9</sup> Another study suggested that IgE antibodies specific for

galactose- $\alpha$ -1,3-galactose could serve as an indicator for possible hypersensitivity reactions.<sup>8</sup>

The objectives of this study were (1) to document the incidence of cetuximab hypersensitivity reactions at our institution, which is located just a short distance from an institution (University of North Carolina) that previously documented high rates of hypersensitivity reactions, and (2) to explore whether observable factors could be used to predict who is most likely to have an allergic reaction with cetuximab. Allergic histories, other medications, demographic characteristics, and type of cancer were examined as potential predictors of severe reaction with cetuximab. In this manner, we hoped to find some markers that could help to differentiate patients who may be predisposed to a severe drug reaction with cetuximab.

## METHODS

### Study design

This was a retrospective chart review of patients consecutively treated with cetuximab at Duke University's Morris Oncology treatment center from September 1, 2005, through August 1, 2007. Data were extracted from the electronic medical record (ebrowser) and the pharmacy electronic database (Aria). The study was approved by the Duke University Institutional Review Board.

### Participants and setting

Duke University Medical Center's electronic pharmacy database was used to identify oncology patients who were  $\geq 18$  years old, cetuximab naïve, and treated with cetuximab between September 1, 2005, and August 1, 2007. All patients were treated at Morris Oncology Treatment center at Duke University Medical Center in Durham, NC. Morris is an outpatient oncology treatment center that serves approximately 90 oncology patients daily.

### Data collection

Subjects who received cetuximab at Morris Oncology Treatment center for the first time between September 1, 2005, and August 1, 2007, were identified via a computer generated list printed from the pharmacy dispensing database. 72 patients were identified and patient specific information was collected from electronic databases (ebrowser and Aria) and transcribed into the data collection sheets. Patient specific information included patient demographics, allergy history, malignancy type and stage of malignancy, premedications received prior to cetuximab

infusion, and cetuximab infusion specifics. These specifics included date of infusion, whether it was monotherapy or combination therapy, and if the patient experienced a hypersensitivity reaction. Grading of hypersensitivity reactions was according to National Cancer Institute guidelines.<sup>12</sup> Further information was collected from these patients such as amount of drug received prior to reaction, if the patient was rechallenged, and whether the patient was sent to the emergency room (ER) or hospitalized.

### Data analysis

To examine differences in demographic characteristics between patients with and without hypersensitivity reactions, bivariate analyses were employed using *t* tests for continuous variables (e.g., age), and chi-square tests for categorical variables (e.g., race and sex). Similarly, chi-square tests were also used to examine differences in patient specific information, including type of malignancy, stage of malignancy, allergy history, premedications received prior to cetuximab infusion, and monotherapy or combination with chemotherapies. Multivariate logistic regression was used to further assess risk factors of hypersensitivity reactions, with adjustment for patient's individual characteristics. All analyses were conducted using SAS version 9.1.3 (SAS, Cary, NC, USA).

## RESULTS

Out of the 72 patients that received cetuximab, 21 (29%) experienced a hypersensitivity reaction. Table 1 provides detailed demographic characteristics for the cetuximab-treated patients identified for this study. The majority of patients were Caucasian, which is otherwise representative of the patient population at this treatment center. Males comprised 63% of cetuximab-treated patients, which is generally consistent with national averages provided by the American Cancer Society, where considerably more males suffer from head/neck cancer and colon cancer than females.<sup>13,14</sup> Approximately 62% of the patients with hypersensitivity reactions were suffering from head/neck cancers, compared with 29% suffering from colon cancer. Most patients treated with cetuximab had stages III or IV malignancies. Among the patients that experienced hypersensitivity reactions, 62% had no allergy history, 86% were not allergic to any pain medication, and 76% were not allergic to any antibiotic. Also, all the patients received premedication as per protocol; 95%

received an H1 blocker, 29% received an H2 blocker, and 57% received a steroid as premedication. Around 57% of the patients with reactions were on a single chemotherapeutic agent (i.e., cetuximab), whereas 43% were on multiple chemotherapeutic agents.

The types of reactions that occurred among patients in this study are described in Table 2. Of the 21 patients having a reaction, 3 patients (14.3%) experienced grade I reactions, 5 patients (23.8%) experienced grade II reactions, 6 patients (28.6%) experienced grade III reactions, and 7 patients (33.3%) experienced grade IV reactions. Only five patients (24%) were restarted on cetuximab on the same day, whereas four patients (19%) restarted on a later date. The mean infusion volume administered was 66 mL with a standard deviation of 96 mL. The minimum volume of infusion was 6 mL, and the maximum was 370 mL for patients with reactions. After reaction with cetuximab, 12 patients (57%) were discharged and sent home, whereas 9 patients (43%) were sent to the ER. Five patients (24%) were required to stay overnight in the hospital, and three of these patients (14% of all reactions) had to be admitted to an intensive care unit (ICU).

Odds ratio estimates for the multivariate model predicting hypersensitivity reaction are shown in Table 3. Hypersensitivity reactions were defined as the event of interest, with patients with no hypersensitivity reaction serving as the reference group. When controlling for all other factors, patients with head and neck cancer were significantly more likely to have a reaction than patients with colon cancers.

## DISCUSSION

Our results show a high rate of hypersensitivity reactions upon administration of cetuximab to patients with head/neck, colon, and other cancers at Duke University's Medial Center. In fact, 29% of patients experienced hypersensitivity reactions on first infusion, even considering the fact that all received premedication before administering cetuximab. The rate of hypersensitivity reactions was 62% among head/neck cancer patients, 29% among colon cancer patients, and only 10% among the relatively small group of patients with other cancer types. This suggests that the reactions may be related to the condition, other treatments specific to the condition, or patient specific characteristics related to the condition (such as tobacco use). Patients experiencing reactions were more likely to be on a single therapeutic agent (i.e., cetuximab), and the majority

Table 1. Sample characteristics

| Characteristic                         | Subjects with hypersensitivity reactions (n = 21) | Subjects without hypersensitivity reactions (n = 51) | p value |
|----------------------------------------|---------------------------------------------------|------------------------------------------------------|---------|
| Age in years, mean (SD)                | 59.3 (11.6)                                       | 59.4 (11.8)                                          | 0.974   |
| Race, n (%)                            |                                                   |                                                      | 0.496   |
| Caucasian                              | 17 (81)                                           | 37 (72.5)                                            |         |
| African American                       | 4 (19)                                            | 11 (21.6)                                            |         |
| Other                                  | 0                                                 | 3 (5.9)                                              |         |
| Gender, n (%)                          |                                                   |                                                      | 0.039   |
| Male                                   | 17 (81)                                           | 28 (54.9)                                            |         |
| Female                                 | 4 (19)                                            | 23 (45.1)                                            |         |
| Malignancy type, n (%)                 |                                                   |                                                      | 0.014   |
| Colon                                  | 6 (28.6)                                          | 30 (58.8)                                            |         |
| Head/neck                              | 13 (61.9)                                         | 13 (25.5)                                            |         |
| Other                                  | 2 (9.5)                                           | 8 (15.7)                                             |         |
| Stage of malignancy, n (%)             |                                                   |                                                      | 0.087   |
| I                                      | 0                                                 | 0                                                    |         |
| II                                     | 0                                                 | 1 (2)                                                |         |
| III                                    | 7 (33.3)                                          | 6 (11.8)                                             |         |
| IV                                     | 14 (66.7)                                         | 44 (86.3)                                            |         |
| Any allergy history, n (%)             | 8 (38.1)                                          | 9 (17.6)                                             | 0.065   |
| Type of prior reaction, n              |                                                   |                                                      | 0.400   |
| Hives                                  | 6                                                 | 6                                                    |         |
| Anaphylactic                           | 1                                                 | 0                                                    |         |
| Other                                  | 1                                                 | 3                                                    |         |
| Allergic to pain medication, n (%)     | 3 (14.3)                                          | 5 (9.8)                                              | 0.585   |
| Allergic to antibiotic, n (%)          | 5 (23.8)                                          | 6 (11.8)                                             | 0.200   |
| Patients received premedication, n (%) | 21 (100)                                          | 51 (100)                                             |         |
| H1 blocker, n (%)                      | 20 (95.2)                                         | 49 (96.1)                                            | 0.872   |
| H2 blocker, n (%)                      | 6 (28.6)                                          | 9 (17.6)                                             | 0.303   |
| Steroid, n (%)                         | 12 (57.1)                                         | 33 (64.7)                                            | 0.550   |
| Chemotherapy, n (%)                    |                                                   |                                                      | 0.356   |
| Monotherapy                            | 12 (57.1)                                         | 23 (45.1)                                            |         |
| Combination therapy                    | 9 (42.9)                                          | 28 (54.9)                                            |         |

p-Value for age was obtained for a two-way ANOVA, all other p-values were obtained from Cochran-Mantel-Haenszel tests; SD = standard deviation.

of the reactions experienced were grade IV. Demographic variables were not significant predictors of hypersensitivity reactions.

Results of this study can be compared with similar previous studies. For example, in a study done by Chung *et al.*<sup>8</sup> 33% experienced hypersensitivity reactions with cetuximab. This compares with the 29% of patients experiencing hypersensitivity reactions in our study. Serious reactions were more common in our study (grade III reactions 29% and grade IV reactions 33%) when compared with numbers reported by O'Neil (grades III and IV - 21%),<sup>9</sup> Cunningham (grades III and IV - 1.2%),<sup>2</sup> and the drug label (3%).

The incidence of increased reactions in patients with head/neck cancers is of particular interest. Although our study cannot say exactly why hypersensitivity reactions are more common among head/neck

cancers, there are several plausible explanations as to why we may have observed this finding. First, many head and neck cancer patients are current or past smokers. Tobacco smoke causes an increase in epithelial growth factor receptor ligands ultimately over expressing EGFR, which can lead to head/neck cancers.<sup>15,16</sup> It is possible that overexpression of EGFR might also be involved in the hypersensitivity reactions. Other possibilities of hypersensitivity reactions include the presence of preexisting IgE antibodies as proposed by the study done in patients from Tennessee, Arkansas, and North Carolina.<sup>8</sup> One plausible explanation for individual developing antibodies to IgE in the United States is exposure to tick bites.<sup>17</sup> Since much of North Carolina and the surrounding region are densely wooded with favorable conditions for ticks, this might also be a factor. Further research is needed to determine whether factors such as tobacco

**Table 2. Summary of hypersensitivity reactions and cetuximab infusion information**

| Characteristic                                       | Patients with hypersensitivity reactions (n = 21) |
|------------------------------------------------------|---------------------------------------------------|
| Grade of reaction, n (%)                             |                                                   |
| I                                                    | 3 (14.3)                                          |
| II                                                   | 5 (23.8)                                          |
| III                                                  | 6 (28.6)                                          |
| IV                                                   | 7 (33.3)                                          |
| Patients restarted on cetuximab that day, n (%)      | 5 (23.8)                                          |
| Patients restarted on cetuximab at later date, n (%) | 4 (19.0)                                          |
| Infusion volume (mL), mean (SD)                      | 65.7 (95.9)                                       |
| Patients went to ER after reaction, n (%)            | 9 (42.9)                                          |
| Patients overnight stay in hospital, n (%)           | 5 (23.8)                                          |
| Number of days of stay in hospital, mean (SD)        | 2.6 (3.6)                                         |
| Patients admitted to ICU after reaction, n (%)       | 3 (14.3)                                          |
| Number of days in ICU, mean (SD)                     | 1 (0)                                             |

ER = emergency room; SD = standard deviation; ICU = intensive care unit.

use or tick bites are truly related to cetuximab hypersensitivity reactions.

This study has several limitations. First, our inclusion of consecutively treated patients at a single medical center limits generalizability and might introduce other biases related to characteristics of the patients or treatment protocols of this clinic. Second, our small sample size of only 72 patients limits our ability to test hypotheses, so we view these analyses as more exploratory rather than confirmatory. This might be particularly important for interpreting variables such as sex or allergy history. For example, although we know that patients with a history of allergic disorders are more likely to experience severe hypersensitivity reactions,<sup>18</sup> we did not identify allergic history to be a statistically significant predictor. This is in spite of numeric trends indicating that hypersensitivity reactions were more common among patients with previous allergic reactions. Finally, our analysis considered only variables which could be reasonably extracted from clinical databases. There may be additional unmeasured confounding contributing to hypersensitivity reactions and subsequent ER or ICU visits.

Our results support earlier studies that revealed high incidence of hypersensitivity reactions in North and South Carolina, Tennessee, northern Georgia, Virginia, Missouri, and Arkansas.<sup>7-9</sup> Further investigation to understand why hypersensitivity reactions may be more frequent in the south (or at least

**Table 3. Multivariate associations between subject characteristics, malignancy type, allergy history, premedications, and chemotherapy**

| Covariate                                     | Odds ratio | 95% Confidence limits |
|-----------------------------------------------|------------|-----------------------|
| Age                                           | 0.965      | 0.912 1.021           |
| Race (non-Caucasian vs Caucasian)             | 0.729      | 0.161 3.304           |
| Sex (female vs male)                          | 0.255      | 0.060 1.080           |
| Malignancy (colon vs head/neck)               | 0.177      | 0.036 0.858           |
| Malignancy (other vs head/neck)               | 0.194      | 0.020 1.929           |
| Stage IV vs I, II, III                        | 0.793      | 0.146 4.319           |
| Allergic to pain medications                  | 2.022      | 0.318 12.865          |
| Allergic to antibiotics                       | 2.347      | 0.495 11.132          |
| Premedication: H1 blocker                     | 0.964      | 0.059 15.750          |
| Premedication: H2 blocker                     | 0.668      | 0.121 3.691           |
| Premedication: steroid                        | 1.007      | 0.227 4.470           |
| Chemotherapy: multiple agents vs single agent | 1.083      | 0.236 4.975           |

documented more frequently) compared to the rest of the country is needed. In the meanwhile, physicians and other health care practitioners should be sensitive to the fact that patients with head/neck cancer may be more likely than other patients to have hypersensitivity reactions, and extra precautions should be taken among these patients.

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