

Severe first infusion reaction related to cetuximab in cancer patients in Arkansas

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Abstract

Introduction: Cetuximab, a chimeric monoclonal antibody, is a commonly used anticancer drug that prevents binding of epidermal growth factor to epidermal growth factor receptor. It has been widely used in a variety of cancers since its initial approval by the FDA in 2004. Despite its efficacy, it has met with some genuine concerns especially regarding the anaphylactoid reactions occurring after first infusions. Cetuximab-related first infusion reaction has been found to be much more prevalent in the Southeastern United States with several studies from the southern United States supporting it. The purpose of our study was to determine the rate of first infusion reaction in the state of Arkansas and the factors that could predispose to first infusion reaction.

Methods and results: We performed a retrospective chart review of consecutive patients who received cetuximab between January 2004 and December 2016 at the University of Arkansas for Medical Sciences. We included a total of 220 patients in our analysis out of which 32 (14.5%) developed cetuximab-related first infusion reaction. There was a statistically significant increased risk in males versus females (18.2% vs. 8.4%, $P = 0.045$) and trend toward significance for the difference between Caucasians and Blacks (16.5% vs. 7.1%, $P = 0.054$).

Conclusion: There is increased incidence of cetuximab-related first infusion reaction in Arkansas which is much higher than the national average but comparable to the incidence in other neighboring states in the Southeastern United States. This increased incidence tends to cluster in Caucasian males. Safer alternatives should be preferred for treatment of cancers particularly in the Southeastern United States whenever possible.

Keywords

Cancers, cetuximab, epidermal growth factor receptor, first infusion reaction

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Introduction

Major advances in the treatment of cancer were achieved over the past three decades thanks to better understanding of the biology of the disease and to translational research targeting mechanistically relevant pathways. Epidermal growth factor (EGF)/epidermal growth factor receptor (EGFR) pathway is upregulated in many epithelial cancers including colon, lung, head and neck, and others and has been targeted with monoclonal antibodies. Overexpression of EGFR is the main mechanism responsible for its upregulation in up to 20%–40% of these cancers.^{1,2} In fact, overexpression of EGFR can be seen in up to 80% of patients with head and neck cancers.^{2,3}

With advances in translational research came the era of monoclonal antibodies that specifically target these receptors. Cetuximab was the first such agent that was approved by the Food and Drug Administration (FDA) for the treatment of the patients with

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irinotecan-resistant colon cancer and squamous cell carcinoma of the head and neck. It is actually a human-mouse chimeric immunoglobulin G1 monoclonal antibody that prevents binding of EGF to EGFR leading to inhibition of signaling through this pathway.^{4,5}

Despite their efficacy, the use of monoclonal antibodies is sometimes associated with infusion reactions (IR), which are described as a type of hypersensitivity or anaphylactoid reaction.⁵ The symptoms include fever, chills, rigors, urticarial rash, dyspnea, bronchospasm, hypotension, and it can rarely be fatal. Erbitux package insert described that grades 3–4 reactions happened in 2%–5% of 1373 patients, with fatal outcome in 1%.⁵ During postmarketing surveillance, several studies came out that showed higher rates of severe (grade 3–4) IR compared to the original data, especially in the Southeastern United States. First such study was done at the University of North Carolina (UNC). In this retrospective study on 88 patients from North Carolina and Tennessee, the rate of severe IR was estimated as 22%, which was significantly higher than any other study published at that time.⁶

Subsequent retrospective study on 153 patients by Hopps et al.⁷ showed an incidence of 12.4% for severe IRs among the population from Oklahoma. Touma et al.⁸ conducted a retrospective study on 243 patients with squamous cell carcinoma of the head and neck treated with cetuximab at a university hospital in Missouri and estimated the rate of severe IR at 6.6%, which was higher than the national average but significantly lower than the rate previously reported by studies conducted in the surrounding region. The rate of severe IR from another retrospective study on 125 patients from different parts of North Carolina was found to be 14.4%.⁹ Contrary to these studies, there was a recent retrospective study done on 71 patients treated with cetuximab in one Southeastern Appalachian medical center and the rate of grade 3 or higher IR was 1.4% which is lower than the usual rate noted in the studies done in the same geographic region and in fact comparable to the studies done elsewhere.¹⁰ These results lend support to the hypothesis that lone star ticks (*Amblyomma americanum*) may be responsible for the development of cross-reacting IgE antibodies to cetuximab further leading to hypersensitivity reactions and that Appalachian may provide a protective effect against lone star tick and hence cetuximab-related IRs.^{11,12}

As has been described in the package insert, 90% of the severe infusion-related reactions occur with the first infusion despite premedication with antihistamines.⁵ In a multicenter, prospective registry study of 2126 patients who received cetuximab for colorectal cancers in Japan, 22 patients (1.1%) developed grade 3–4 IRs

and 20 out of these 22 reactions occurred within the first hour of the first dose which supported the hypothesis that the specific IgE against or cross-reacting with cetuximab are already present in the high-risk patients and leads to immediate hypersensitivity reaction.¹³ A study conducted by Dupont et al.¹⁴ on 301 patients showed that the proportion of severe IRs in patients with high levels of anti-cetuximab IgE was significantly higher than that in those with low levels (13.2% vs. 1.4%, $P=0.0027$; odds ratio = 10.4; 95% confidence interval = 2.4–45.6). Studies by O'Neil et al.⁶ and Touma et al.⁸ showed that the history of prior allergy was significantly associated with the risk of severe IRs. Male gender and Caucasian race are other potential risk factors.^{7,8} French pharmacovigilance database analysis by Grandvuillemin et al.¹⁵ showed a higher rate of severe IR in patients with head and neck cancer. The multinational MABEL study of 1147 patients showed that the addition of steroids to antihistamine as compared to antihistamine alone significantly decreased the rate of cetuximab-related IRs.¹⁶ Although subsequent studies showed conflicting results regarding the efficacy of pre-cetuximab steroids, premedication with both antihistamine and steroid has become more or less a standard protocol to prevent cetuximab-related IRs.

We have experienced a higher rate of severe IR related to cetuximab in our area over the years, which is similar to our neighboring states. A first report was presented by our group at the American Society of Clinical Oncology annual meeting in 2011 for the period from 2004 to 2011,¹⁷ and this is the full report on our Arkansas population until 2016. Severe cetuximab IR has both short-term and long-term implications for the patient, the family, the ancillary staff, and the physicians. Since severe IR predominantly occurs during the first infusion reaction (FIR), we have limited our study to first cetuximab infusion, and we are determining potential risk factors associated with the severe FIR that occurred in our patients who received cetuximab in our practice over the span of 13 years.

Methods

Patient selection

Medical records of consecutive patients who received cetuximab between January 2004 and December 2016 were reviewed using an electronic database system after approval from the Institutional Review Board at the University of Arkansas for Medical Sciences (UAMS). Patients were identified using pharmacy database and the patients who had a pharmacy order for cetuximab but did not receive any dose were excluded from the study.

Data collection

Data includes age, sex, race, ethnic background, geographical region, cancer type, date at diagnosis, stage at diagnosis, prior or concomitant chemotherapy or radiotherapy, history of allergies, use of allergy medications, and use of tobacco and alcohol. Severe FIR was defined as hypotension with drop of systolic <100 mm Hg and/or diastolic <50 mm Hg, severe dyspnea and wheezing suggestive of bronchospasm, hypoxemia with oxygen saturation falling below 92% on room air in previously normal subjects, development of angioedema, diffuse and severe rash and hives with itching, and syncope. Severe FIR in our study is similar to grade 3–4 hypersensitivity reaction associated with the first infusion as described in the package insert and the other studies.

Statistical analysis

The primary endpoint was defined as the proportion of patients developing severe FIR. The incidence of severe FIR in our local population was compared to the general oncology population in the United States using available data from the cetuximab package insert and the other published studies especially the ones reported in the Southeastern United States. Chi-square and *z*-tests were used to determine statistical significance for potential risk factors and for differences in incidence. *t*-Test was used to assess the significance of the difference in the history of allergy, tobacco or alcohol use and the use of premedication between the patients who developed FIR and those who did not. One-sided and two-sided *P*-values were calculated. All *P* values are reported numerically and interpreted for significance using the sliding-scale approach of Mendenhall et al.¹⁸ as follows: $P < 0.01$ is “highly significant,” $0.01 < P < 0.05$ is “statistically significant,” $0.05 < P < 0.10$ is “trending toward significant,” and $P > 0.10$ is “not significant.”

Results

A total of 220 patients were identified and included in our study. One hundred fourteen patients with head and neck cancer, 68 patients with colorectal cancer and the remaining patients with the following cancers: gastroesophageal/intestinal CA (11), NSCLC (7), squamous cell carcinoma (SCC) of the anus (5), SCC of the cervix (4), SCC of the skin 2 and carcinoma of liver, unknown primary, and mesothelioma (1 each) and others (6). The incidence of FIR for the whole study was 14.5% (32/220); of whom four patients or 1.8% (4/220) had severe anaphylactic shock requiring activation of the code and admission to the ICU, but no death has occurred (Table 1).

Table 1. Demographics and cancer types of patients who received cetuximab.

	2004–2011	2011–2016	2004–2016
Age, median ($\pm$ SD)	55 ($\pm$ 11.1)	59.5 ($\pm$ 10.7)	56 ($\pm$ 11.4)
Sex, M:F	101/65	36/18	137/83
Race, W/B/O	133/33/0	42/9/3	175/42/3
Cancer type			
H&N	66	48	114
Colorectal	66	2	68
Skin	2	2	4
Small bowel	1	1	2
Esophageal	8		8
Gastric	2		2
Anal	5		5
Cervix	4		4
Lung	7		7
Others	5	1	6
FIR	25 (15%)	7 (12.9%)	32 (14.5)
Total	166	54	220

M: male; F: female; W: White; B: Black; O: others; H&N: head and neck; SD: standard deviation.

Median age was 56 (SD 11.2) for patients with FIR versus 57 years old (SD 10.9) for patients without ($p > 0.05$). The incidence of this complication in our population remained relatively stable at 14.5% (15% in the first period and 12.9% in the second period, two-sided $P = 0.70$). The difference of FIR rates by sex at 18.2% (25/137) in males versus 8.4% (7/83) in females was significant ($P = 0.045$). FIR rates by race were 16.5% (29/175) among Caucasians versus 7.1% (3/42) among African Americans; but the difference trended toward significance only with a *P*-value at 0.054, contrary to our previous report that covered the first reporting period (Table 2).

Premedication used, personal history of allergy, alcohol use and cancer type did not seem to play a role (Table 2). Only tobacco use seemed to be associated with an increased risk of FIR, which trended toward significance with a *P*-value at 0.08. Steroid and antihistamine became standard of care after 2011 in our practice, and yet the incidence of FIR for the period from 2011 to 2016 was not statistically different from the first reporting period (12.9% vs. 15%, respectively; $P = 0.70$).

Discussion

This retrospective single institution study reports on the incidence of cetuximab FIR in patients with different cancers who received their first cetuximab in our institution over the course of the 12-year period. The study

Table 2. Difference of FIR incidence by sex (statistically significant) and race (trended toward significance).

	FIR	No FIR	
All	32	188	Two-sided <i>P</i>
Age median ($\pm$ SD)	56 ($\pm$ 11.2)	57 ($\pm$ 10.9)	NS
Sex			
M	25 (18.2%)	112	<i>P</i> = 0.0454
F	7 (8.4%)	76	
Race			
W	29 (16.5%)	146	<i>P</i> = 0.0539
B	3 (7.1%)	39	
O		3	
History of allergy			
Yes	12	47	<i>P</i> = 0.24
No	20	141	
History of tobacco use			
Yes	22	117	<i>P</i> = 0.08
No	10	71	
History of alcohol use			
Yes	4	23	<i>P</i> = 0.39
No	28	165	
Premedication			
Yes	32	174	<i>P</i> = 0.43
No	0	14	

Note: Difference in history of allergy, alcohol use, and premedication between those who developed FIR and those who did not was compared and the difference was not statistically significant. The difference in tobacco use between the groups trended toward significance suggesting an increased risk of FIR in tobacco users.

M: male; F: female; W: White; B: Black; O: Others; H&N: head and neck; SD: standard deviation.

can be divided into two reporting periods: from 2004 to 2011 and from 2011 to 2016 depending on our earlier reporting of the results (ASCO 2011)¹⁷ and the current report that include the previous cohort and an additional 54 patients from 2011 to 2016. The incidence of this complication in our population remained relatively stable at 14.5% (15% in the first period and 12.9% in the second period, two-sided *P* = 0.70) over the span of the study. Adding steroid and antihistamine premedication did not seem to have affected the incidence of this complication. The incidence of severe or life-threatening FIR to cetuximab is four- to fivefold higher in Arkansas than in the rest of the country (3%). There is a higher incidence of FIR in Caucasian men but this difference by race—that appeared significant at the first reporting period in 2011—was no longer statistically significant after the completion of the whole study. Considering the small numbers of patients in our study, it is possible that this difference may be true if the study were conducted in a larger population. Tobacco use seemed to be associated with increased risk of FIR, but this association only trended toward significance.

It is worthwhile noticing the shift in our practice pattern between the two reporting periods. The approval of safer monoclonal antibodies for use in colorectal cancer¹⁹ resulted in a practical halt of the use of Cetuximab in this population (CRC patients represented 39% of patients who received cetuximab in our institution in the first reporting period compared to 3.7% in the second reporting period; a tenfold drop).

The cause of this persistent high rate of FIR in our population remains unclear. The reactions occur acutely after the first infusion without presensitization to the antibodies, and they are of anaphylactic nature suggesting the preexistence of these antibodies prior to the exposure to the drug. The most accepted hypothesis to explain this phenomenon is the possibility of exposure to naturally occurring antigens in our state that mimic cetuximab. Chung et al.¹¹ identified IgE antibodies against galactose- α -1,3-galactose that were significantly associated with FIR to cetuximab.

Since a personal history of allergy and the type of cancer had no impact on the incidence of this complication, it does not seem that screening for these factors will play a role in identifying patients at risk. Using the galactose- α -1,3-galactose enzyme-linked immunosorbent assay (Alpha-Gal), Weiss et al. were able to select outpatients with high antibody titers against galactose- α -1,3-galactose and give the drug to those who had low titers only.²⁰ The incidence of FIR in this group was “0” with a negative predictive value of 100%.

Premedication with steroids and antihistamine may be used, but it was of little benefit in our hands. The use of the Alpha-Gal assay may help select the patients who are unlikely to have a reaction. For the other patients, it is wise to consider other alternatives whenever possible. If therapeutic alternatives are not possible, it is recommended to use premedication and have the emergency intervention team ready with injectable epinephrine handy. If the reaction does not happen with the first infusion, it is unlikely that it would happen later with subsequent infusions.

Declaration of Conflicting Interests

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