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Cetuximab hypersensitivity infusion reactions: Incidence and risk factors*

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Abstract

Introduction: Cetuximab is a chimeric mouse-human (30:70) IgG1 monoclonal antibody that competitively inhibits the binding of epidermal growth factor. Cetuximab is generally well tolerated; however, hypersensitivity infusion reactions have been reported. The incidence at the University of Oklahoma was currently unknown, though anecdotally high. The purpose of this study was to determine the incidence of severe HIRs and secondarily to determine risk factors for cetuximab-induced hypersensitivity infusion reactions.

Methods and results: A retrospective chart review was conducted and included all patients that received cetuximab from 2005 to 2010 at the outpatient clinics of the Oklahoma University Health Sciences Center. A total of 153 patients were included in the analysis. The overall incidence proportion of severe hypersensitivity infusion reactions was 12.4%. Male patients had an increased incidence of severe hypersensitivity infusion reactions compared to female patients (20.6% vs. 5%, $p = 0.0036$). Current smokers had an increased incidence of severe hypersensitivity infusion reactions of 23.6% when compared to never smokers or former smokers, $p = 0.0012$. Cervical cancer had a significantly decreased risk of severe hypersensitivity infusion reactions when compared to other tumor types (5.3% vs. 16.7%, $p = 0.0387$). Multivariate analysis identified risk factors associated with severe HIRs to be: male gender, $RR = 3.9$, $p = 0.01$ and current smokers, $RR = 3.98$, $p = 0.0048$.

Conclusion: Patients at the University of Oklahoma had an increased incidence of severe hypersensitivity infusion reactions when compared to the national average. Male patients and current smokers were found to be at increased risk for severe hypersensitivity infusion reactions in our study. Further investigation is warranted.

Keywords

Anaphylaxis, immunology, monoclonal antibodies, drug hypersensitivity/prevention and control, incidence, risk factors

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Introduction

Cetuximab is a chimeric IgG₁ monoclonal antibody, which competitively inhibits the binding of epidermal growth factor by specifically binding to the epidermal growth factor receptor (EGFR).¹ EGFR is a transmembrane glycoprotein that regulates cellular growth and survival and is overexpressed or mutated in many tumors.² Cetuximab binds to the extracellular domain of EGFR and prevents natural ligands of EGFR such as epidermal growth factor (EGF) and transforming growth factor- α (TGF- α) from binding.³ This action blocks receptor-dependent signal transduction pathways such as anti-apoptosis, angiogenesis, and metastasis.³ Cetuximab causes internalization and downregulation of EGFR, antibody-dependent cellular cytotoxicity, and increased efficacy of radiation and chemotherapy.³ Presently cetuximab is FDA approved for EGFR-expressing metastatic colorectal cancer, as a single agent after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens; also in combination with irinotecan in metastatic colorectal cancer in patients who are refractory to irinotecan-based chemotherapy.¹ Cetuximab is also FDA approved in head and neck cancer for locally or regionally advanced squamous cell carcinoma in combination with radiation, in recurrent locoregional or metastatic head and neck cancer in combination with platinum-based chemotherapy with 5-fluorouracil, or as a single agent in recurrent or metastatic squamous cell carcinoma after progression after platinum-based chemotherapy.¹ It is administered initially with a loading dose of 400 mg/m² IV given over 2 h followed by 250 mg/m² IV given over 1 h weekly.¹

The most common adverse reactions to cetuximab are an acne-like rash, diarrhea, and hypomagnesemia.^{1,4} Rare but serious reactions to cetuximab are hypersensitivity reactions that can result in anaphylaxis. Nationally, the incidence of cetuximab hypersensitivity infusion reactions (HIRs) is 3%.¹ However, there is a reported increased incidence in the middle and southeastern United States.⁵⁻⁸ O'Neil and colleagues report a 22% rate of grade 3 or 4 hypersensitivity reactions in patients treated in North Carolina and Tennessee, which is similar to other retrospective studies performed in this geographical area.⁵⁻⁸

HIRs can have substantial morbidity for patients, resulting in dose delay, permanent discontinuation of cetuximab, the need for emergency services, or hospitalization.⁹ The incidence of infusion reactions requiring medical intervention was also found to be higher than rates reported in clinical trials, and the economic cost is substantial.¹¹ Foley and colleagues reported a mean adjusted cost of US\$13,863 for cetuximab administrations that caused an HIR requiring an ER visit or

hospitalization and US\$6280 for an HIR that was managed in the outpatient setting; this is in comparison to \$4555 for cetuximab administration without an HIR. Death has also resulted from cetuximab-induced hypersensitivity reactions.^{9,10}

Though the exact reason is unknown, an IgE antibody specific for galactose- α -1,3-galactose has been identified as a potential cause of hypersensitivity reaction in the middle and southeastern United States.⁵ Galactose- α -1,3-galactose is an oligosaccharide found in both of the Fab portions of the heavy chains of cetuximab.⁵ In a retrospective study conducted by Chung et al.,⁵ the presence of the IgE antibody correlated well with patients that had reacted during a cetuximab infusion.

Other possible risk factors identified in retrospective studies include tumor type and prior history of atopic allergy.^{7,8} In these studies non-small cell lung cancer and head and neck cancer have trended towards increased hypersensitivity reactions when compared to other tumor types.^{7,8}

Although the true incidence is unknown, the health-care staff at the Oklahoma University Health Sciences Center in Oklahoma City, Oklahoma has observed a higher incidence of HIRs than the national average. This study was undertaken to report the reaction rate at our center and compare it to national trends, as well as identify potential risk factors for developing HIRs.

Methods

Study design and patient selection

A retrospective chart review was conducted on all patients that received cetuximab from 1 July 2005 to 1 August 2010 at the oncology or gynecology/oncology outpatient clinics of the Oklahoma University Health Sciences Center. The primary objective of the study was to estimate the incidence of grade 3 or 4 HIRs after the administration of cetuximab. The secondary objective was to determine risk factors for developing HIRs. Inclusion criteria included administration of at least one dose of cetuximab. Exclusion criteria included pediatric patients, pregnant patients, or patients with incomplete records. Patients were identified through billing reports, study protocols, and pharmacy records. Documentation of hypersensitivity reaction, demographic information, tumor type, treatment regimen, premedications received (if any), comorbidities, and smoking status were obtained from the patient charts. Hypersensitivity reactions were graded retrospectively based on the Common Terminology Criteria for Adverse Events v4.0.¹² The clinic nurses follow a policy in which they must report every reaction that

occurs and document these reactions in the patient's medical record.

Grade 3 and 4 reactions were defined as severe HIRs.¹² Premedications were defined as the documentation in the patients' chart as receiving one of the following before the administration of cetuximab: antihistamine, steroid, H-2 receptor antagonist, or bronchodilator. HIRs were documented in the patients' charts as well as treatment, and ER or hospital admission.

Statistical methods

Independent associations with severe HIRs and each predictor variable were assessed using the Chi-square or Fisher's exact test. A manual, reverse step-wise Poisson regression analysis was performed on all factors with a bivariate analysis alpha value ≤ 0.2 and any logical two-way interaction. Alpha was set at 0.05 for final model inclusion. Confounding was assessed by observing parameter estimates before and after a factor was removed from the model. A factor was considered confounding if a 15% change was observed in any significant parameter estimate when removed from the model (none were observed in this study). Generalized estimating equations (GEE) estimation was used to adjust for potential overdispersion of the Poisson regression model.

An a priori, two-sided alpha level of 0.05 was considered significant for all analyses. SAS v9.2 was used for all analyses.

Results

One hundred and seventy patients were identified. Seventeen patients were excluded due to incomplete records (i.e. no of documentation of cetuximab administration). A total of 153 patients were included in the analysis, Table 1 details the demographic information. The majority of patients either had a head and neck tumor (50.3%) or a cervical tumor (37.2%). Other tumor types included colorectal, non-small cell lung, and ovarian cancer. All patients received diphenhydramine as a premedication, the majority of patients received a steroid (87.5%), and fewer patients received an H-2 receptor antagonist (33.3%) or a bronchodilator (15%). Forty-seven patients received a test dose given prior to chemotherapy. The test dose varied and was either 20 mg IV or 100 mg IV prior to receiving cetuximab.

The overall-incidence proportion of grade 3 or 4 HIRs was 12.4%. Male patients had increased incidence at 20.6% grade 3 or 4 HIRs, compared to female patients who had an incidence proportion of 5%, $p = 0.0036$. All patients that experienced a severe

Table 1. Baseline characteristics.

Characteristic	Result, N (%)
Total	153
Median age (range)	57 (22–93)
Male gender	73 (47.7)
Race	
Caucasian	132 (86.2)
African American	10 (6.5)
Hispanic	5 (3.2)
Asian	3 (2)
Native American	3 (2)
Tumor type	
Head and neck	77 (50.3)
Cervical	57 (37.2)
Colorectal	16 (10.4)
Non-small cell lung	2 (1.3)
Ovarian	1 (0.01)
Regimen	
Combination w/chemo	96 (62.7)
Single agent	57 (37.2)
Radiation	56 (36.6)
Premedication	
Diphenhydramine	153 (100)
Steroid	134 (87.5)
H-2 receptor antagonist	51 (33.3)
Bronchodilator	23 (15)
Test dose	47 (30.7)
Comorbidity	
COPD	17 (11.1)
Asthma	7 (4.5)
Smoking history	
Current smoker	55 (35.9)
Never smoker	48 (31.3)
Former smoker	43 (28.1)
Unknown	7 (4.5)
Clinical trial	
No	95 (62)
Yes	58 (37.9)

COPD: chronic obstructive pulmonary disease.

HIR reacted on their first cycle. Amongst tumor type, head and neck cancer had the highest incidence of grade 3 or 4 HIRs of 18.1%. Patients that were current smokers had an incidence of 23.6%, which was significantly higher than former or never smokers, $p = 0.0012$ (Table 2). Patients that received cetuximab as a single agent had a higher incidence proportion of severe HIRs than those that received it in combination with chemotherapy (24.6% vs. 5.2%, respectively), $p = 0.0004$. Patients that received radiation therapy experienced

Table 2. Independent associations with severe HIRs.

Variable	N	Severe-reaction N (%)	RR	95% CI	Chi-square	p-Value
Gender						
Female	80	4 (5.00)	0.24	0.08 to 0.70	8.48	0.0036
Male	73	15 (20.55)				
Cervical cancer ^a						
Yes	57	3 (5.26)	1.21	0.13 to 11.04	^b	1.00
No	23	1 (4.35)				
Radiation						
Yes	56	9 (16.07)	1.56	0.67 to 3.61	1.08	0.30
No	97	10 (10.31)				
Steroids						
Yes	134	17 (12.69)	1.21	0.30 to 4.81	^b	1.00
No	19	2 (10.53)				
COPD						
Yes	17	3 (17.65)	1.50	0.49 to 4.62	^b	0.45
No	136	16 (11.76)				
Drug allergies						
Yes	53	6 (11.32)	0.87	0.35 to 2.16	0.09	0.76
No	100	13 (13.00)				
Smoker						
Former	43	2 (4.65)	0.74	0.13 to 4.25	^b	1.00
Never	48	3 (6.25)				
Current smoker						
Yes	55	13 (23.64)	4.30	1.62 to 11.41	10.44	0.0012
No	91	5 (5.49)				
Never smoker						
Yes	48	3 (6.25)	0.41	0.12 to 1.34	2.44	0.12
No	98	15 (15.31)				
H2 receptor antagonist						
Yes	51	9 (17.65)	1.80	0.78 to 4.15	1.92	0.17
No	102	10 (9.8)				

^aFemales only.^bFisher's exact test.

HIRs: hypersensitivity infusion reactions.

HIRs at a higher incidence proportion of 16%, than those who did not receive radiation therapy (10.3%), $p=0.2978$. Patients that received steroids experienced HIRs at a similar incidence as those that did not receive a steroid as premedication (12.7% vs. 10.5%, respectively, $p=1$). Patients that received an H2 receptor antagonist also had higher incidence of severe HIRs than those that did not receive this premedication, (17.65% vs. 9.8%, respectively, $p=0.17$). Patients with chronic obstructive pulmonary disease (COPD) had a higher incidence of HIRs compared to those without COPD (17.65% vs. 11.76%, respectively, $p=0.45$).

Out of the 47 patients that received a test dose, 10 patients experienced a severe HIR, in which 8 out

of 10 patients reacted on the test dose and 2 out of 10 patients reacted with the subsequent full dose.

The multivariate analysis identified risk factors with cetuximab HIRs to be male gender $RR=3.87$, 95% CI (1.35–11.07), $p=0.0117$, and current smokers $RR=3.93$, 95% CI (1.45–10.08), $p=0.0066$.

Discussion

The overall incidence of 12.4%, found in this study, is higher than the national average of 3%.¹ The incidence of HIRs in cervical cancer was lower than head and neck cancer and other malignancies; however, when comparing HIRs of patients with cervical to only

other female patients, regardless of disease, this incidence is not significant. The incidence of HIRs with cetuximab in patients with a gynecologic malignancy has not previously been reported. Statistical analysis has identified female gender as a potential important protective risk factor, rather than cervical cancer. For females, the incidence proportion of HIRs is 5% when compared to males it is 20.55%, $p = 0.0036$ (Table 2). Reasons for this decreased rate in females require further investigation.

Premedications did not seem to play a protective role against severe HIRs. This is difficult to assess in our study because all patients received diphenhydramine, and the majority of patients received a steroid. The addition of an H2-receptor antagonist or bronchodilator did not seem to change the incidence of severe HIRs significantly; however, these numbers are small, and other retrospective studies report no difference in the incidence of severe HIRs with different premedication regimens.^{6,8} To date there has been no prospective study comparing different premedication regimens. The package insert only recommends diphenhydramine;¹ however, it is common to add a steroid to the regimen.⁸ A post hoc analysis from the Mabel study has reported benefit of reduced infusion reactions with a combination of diphenhydramine and a corticosteroid.¹³ Other commonly used premedications include a bronchodilator and an H2 receptor antagonist, although the benefit has not been proven to our knowledge.

Current smokers had a significantly higher rate of HIRs versus nonsmokers or former smokers. O'Neil and colleagues⁸ in their retrospective chart review of cetuximab-induced HIRs found a trend in increased incidence of HIRs in patients with non-small cell lung cancer. It was suggested that this could possibly be due to an exposure to tobacco byproducts leading to pre-sensitization to cetuximab. However, in our study we found that former smokers had a non-significant decrease in the incidence of severe HIRs.

The majority of patients that received a test dose that experienced a severe HIR, did react on the test dose (8 out of 10 patients). In a previous retrospective study, a test dose did result in 87% cost savings, by discontinuing the full dose of cetuximab before it was prepared, although our study did not analyze the cost-effectiveness.⁶

Male gender and being a current smoker increases the risk of severe HIRs by nearly 4 fold. Further investigation is needed to further elucidate why male gender and current smokers have an increased risk for severe HIRs. Smoking could elicit a more severe HIR due to decreased lung function.

Currently it is unknown if the increase in HIRs in Oklahoma is due to an IgE antibody specific for

galactose-alpha-1,3-galactose, which has previously been reported by Chung et al.⁵ An enzyme-linked immunosorbent assay (ELISA) has been developed to detect the IgE antibodies directed at cetuximab.¹⁴

This study is consistent with an increased incidence of HIRs in the middle and southern United States. It appears from our study male gender and current smokers are important potential risk factors for severe HIRs. This study is limited by its retrospective design and small sample of patients, therefore prospective studies are needed to confirm these findings.

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