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Risk Factors for and Pre-medications to Prevent Cetuximab-Induced Infusion Reactions in Patients with Squamous Cell Carcinoma of the Head and Neck

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Abstract

Objectives—Cetuximab, a chimeric monoclonal antibody, is the only targeted therapy approved for squamous cell carcinoma of the head and neck (SCCHN). Infusion reactions (IRs) occur in 6–18% of patients pre-medicated with diphenhydramine. Evidence for clinical risk factors for IRs is limited and the benefit of additional pre-medication to prevent IRs is unclear.

Materials and Methods—A retrospective, single institution study of 243 SCCHN patients treated with cetuximab to evaluate potential risk factors for IRs and to assess the efficacy of additional pre-medications (nebulized albuterol and intravenous[IV] corticosteroids and/or H₂-blockers) to decrease the risk of IR.

Results—IR (grades 1–4) and high grade (grades 3–4 only) IR occurred in 47(19.3%) and 16(6.6%) patients, respectively. Multivariate analysis identified Caucasian race (OR7.11, p=0.003), medication allergy (OR3.74p=0.002), and blood eosinophils >3%(OR2.75, p=0.01) independently increased the risk of IR; Caucasian race (OR5.57, p=0.007) and medication allergy (OR4.10, p=0.0007) increased the risk of high grade IR. IR (grades 1–4) and high grade IR occurred in 31.8% and 22.7% pre-medicated with diphenhydramine alone. Univariate analysis identified albuterol, famotidine, and corticosteroids decreased the risk of high grade IR. Furthermore, there was a significant difference between the possible combinations of the pre-

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medications and the risk of high grade IR by Fisher Exact test ($p=0.003$) whereby the combination of albuterol, famotidine and corticosteroids was effective in preventing high grade IR. Thirty (64%) of the 47 patients who developed an IR were re-challenged and did not experience a recurrence of an IR.

Conclusion—These data may be used to identify patients at higher risk for cetuximab-induced IR who may be advised to not receive cetuximab or who may benefit from additional pre-medications to decrease the risk of a high grade IR.

Keywords

Cetuximab; infusion reaction; risk factors; pre-medication

Introduction

Cetuximab, a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFR) [1], is approved by the Food and Drug Administration for the treatment of squamous cell carcinoma of the head and neck (SCCHN). The most serious adverse event due to cetuximab is an infusion reaction (IR). An H_1 antagonist such as diphenhydramine is the only pre-medication recommended to prevent cetuximab-induced IRs, yet IRs still occur in 6–18% of patients [2–5] and are high grade (grades 3 & 4) in 1–5% [3–9]. The risk of a high grade IR is much greater (22%) in specific geographic areas including the southeastern region of the United States (Tennessee & North Carolina) [10]. IRs usually occur during the initial administration of cetuximab and present with one or more of the following: urticaria, respiratory distress, hypoxia, hypotension, angioedema, or chest discomfort. IRs frequently lead to permanent discontinuation of cetuximab, additive medical costs, and may result in hospitalization [11] and fatality ($<0.1\%$) [5].

Although yet to be clearly proven, cetuximab-induced IRs are likely mediated by pre-existing IgE-specific antibodies directed to galactose- α -1,3-galactose present on the Fab portion of the antibody [12]. Unfortunately, there are no clinically available laboratory tests to identify patients at high risk for IRs. Evidence for predisposing clinical risk factors to IRs is limited and the potential benefit of pre-medication other than diphenhydramine to prevent IRs is unclear. Indeed, one report of 51 patients did not observe a significant effect of adding a H_2 antagonist or corticosteroids to diphenhydramine [13]. Knowledge of this information may be useful to assess the relative risk-benefit ratio of cetuximab administration and/or the role of additional pre-medications in selected patients to prevent IRs.

In our early experience with cetuximab given to patients with SCCHN, we observed a high risk of IRs following pre-medication with diphenhydramine alone. This observation prompted us to make a series of adjustments in the premedication regimen to reduce the risk of IRs. We conducted a retrospective study of 243 patients with SCCHN treated with cetuximab at our institution over a 12-year period to evaluate potential risk factors for IRs and to assess the efficacy of additional pre-medications, including inhaled nebulized albuterol and intravenous (IV) corticosteroids and H_2 -blockers, to decrease the risk of IR.

Methods

Study Design and Patient Selection

In an institutional review board-approved protocol, a retrospective chart review was conducted on patients with SCCHN who were treated with cetuximab as monotherapy or in combination with chemotherapy or radiation from January 1999 to July 2011. The primary objective was to determine the risk of cetuximab-induced IR (grades 1–4 and only high grade [grades 3 & 4]) in patients with SCCHN at our institution. Secondary objectives were to investigate the clinical risk factors that may predispose individuals to cetuximab-induced IR (grades 1–4 or high grade) and to evaluate the potential efficacy of famotidine, inhaled nebulized albuterol, and/or IV corticosteroids (hydrocortisone or dexamethasone) given in addition to diphenhydramine as pre-medication to decrease the risk of cetuximab-induced IR (grades 1–4 and high grade).

Inclusion criteria were: diagnosis of SCCHN, age ≥ 18 years, and first administration of cetuximab. Exclusion criteria were previous exposure to cetuximab or incomplete records. IR was defined as an adverse event due to cetuximab that included flushing, rash, urticaria, fever, bronchospasm, respiratory distress, angioedema, hypotension, chest discomfort, anaphylaxis, and/or death occurring during or within 3 hours after completion of cetuximab administration [14, 15].

Patients were identified by screening the institutional registry database of patients with SCCHN. The following variables were extracted from the patients' charts: demographic information (gender, age, and race), history of allergy to medication, underlying respiratory or allergic disease (asthma, chronic obstructive pulmonary disease [COPD], or allergic rhinitis), smoking status, pre-medications given before cetuximab, IR grade, symptoms and treatment, admission to hospital for IR management, concurrent chemotherapy (if any), and white blood cell count with differential at the time of infusion. A medication allergy history was defined as positive if the patient developed flushing, rash, bronchospasm, angioedema, or anaphylaxis and negative if the listed reaction was a non-allergic side effect (e.g., nausea). The Common Terminology Criteria for Adverse Events (CTCAE) v3 or v4 were used to grade the IR events based on the year of occurrence [14]. In general, grades 1, 2, 3, 4, and 5 IRs were defined as mild, moderate, severe, life-threatening, or death, respectively.

In our early experience with cetuximab administration using pre-medication with diphenhydramine alone (50 or 25 mg/IV), we observed a higher than expected rate of IR, prompting our group to evaluate the effect of additional pre-medications given with diphenhydramine to reduce the risk of IR. Corticosteroids and H₂-blockers were chosen because these agents were used to prevent and treat IRs due to other chemotherapeutics [16, 17]. Albuterol, an inhaled *beta*₂-agonist, was selected because we found this agent to be effective in treating the respiratory distress and hypoxia components of cetuximab-induced IR. Groups of patients were given one or more of these pre-medications, in addition to diphenhydramine, before cetuximab administration. Seven groups were defined by these varying combinations of pre-medications. Routes and doses of these pre-medications were: IV famotidine 20 mg, inhaled nebulized albuterol 2.5 mg, and IV hydrocortisone 100 mg given over 30–60 minutes with or without IV dexamethasone (in doses from 4–20 mg). In

general, corticosteroids were initially added to diphenhydramine followed by the addition of albuterol or albuterol and famotidine. To help prevent hypotension, all patients received at least one liter of IV normal saline as pre-hydration before cetuximab. If medically appropriate, patients were instructed to avoid anti-hypertensive agents and/or *beta*-blockers the night before and the morning of cetuximab administration to prevent exacerbation of the hypotensive and bronchospasm components of an IR.

Statistical Methods

Univariate logistic regression analysis was performed to identify the factors associated with an increased risk of IR (grades 1–4 and high grade) and to evaluate the efficacy of the additional pre-medications by using a chi-square test or Fisher's Exact test. Multivariate analysis was conducted after identifying the factors with *p* values less than 0.1. Alpha was set at 0.05 for the final model inclusion. Non-parametric Kruskal–Wallis and Mann–Whitney tests were used to compare the medians of the times of IR after infusions. SAS version 9.3(SAS Institute, Cary, NC) was used for all analyses.

Results

Patient Characteristics and IR Risk

We identified 252 patients potentially eligible for this protocol, of which 243 met and 9(3.5%) did not meet inclusion criteria. The characteristics of these 243 patients are summarized in Table 1. Forty-seven patients (19.3%) developed an IR (grades 1–4) due to cetuximab. Sixteen patients (6.6%) developed a high grade IR. The proportions of these 47 patients who developed grades 1, 2, 3, or 4 IR were 29.8%, 36.2%, 21.3%, and 12.8%, respectively. The IR occurred after the first infusion of cetuximab in 97.8% of these patients. Grade 5 IR did not occur.

Risk Factors

Univariate analysis identified race, allergy to medications, respiratory disease (asthma and COPD), and peripheral blood eosinophil percentage >3% as risk factors for an IR (grades 1–4) [Table 2]. However, only race and allergy to medications were associated with increased risk of high grade IR (Table 3). The following variables did not affect the risk of IR (grades 1–4) or high grade IR: age, gender, allergic rhinitis, smoking status, home medications (H₁- or H₂-blockers, corticosteroid inhalers, or montelukast), cetuximab as monotherapy, type of chemotherapy given in combination with cetuximab, or white blood cell count (data not shown). Multivariate analysis identified that the following variables independently increased the risk of an IR (grades 1–4): Caucasian race, allergy to medication, and peripheral blood eosinophil >3%. Multivariate analysis identified Caucasian race and allergy to medication as independent risk factors for high grade IR.

Pre-medications

Twenty-two patients were pre-medicated with diphenhydramine alone. Seven of these patients (31.8%) developed an IR (grades 1–4)(in comparison to 18.1% in the rest of the cohort, *p*=0.15) and five (22.7%) developed a high grade IR (in comparison to 5.0% in the rest of the cohort, *p*=0.009). In the whole cohort of 243 patients, there was no difference

between the two doses (50 mg or 25 mg) of diphenhydramine in preventing IR (risks for grades 1–4 IR 12.5% vs. 20.4%, $p=0.29$ and for high grade IR: 3.1% vs. 7.1%, $p=0.40$). In addition, the proportion of patients in each of the seven pre-medication groups with Caucasian race, allergy to medication, and peripheral eosinophils $> 3\%$ were not significantly different (data not shown).

In the univariate analysis, albuterol, famotidine, or administration of corticosteroids within one hour before the infusion of cetuximab decreased the risk of high grade IR (Table 4). Furthermore, there was a significant difference between the possible combinations of the pre-medications and the risk of high grade IR by Fisher Exact test ($p=0.003$) whereby the combination of albuterol, famotidine and corticosteroids was effective in preventing high grade IR (Table 5). Only one of 100 patients (1%) pre-medicated with the combination of albuterol, famotidine, and corticosteroids along with diphenhydramine developed a high grade IR. Another effective combination to prevent high grade IR was albuterol and corticosteroids (6.3% risk). These data must be interpreted cautiously as three out of the seven possible pre-medication combinations had less than 20 patients each.

When considered as a dichotomous variable (given/not given), none of the following pre-medications were significantly effective in preventing IR (grades 1–4): albuterol ($p=0.08$), famotidine ($p=0.28$), hydrocortisone ($p=0.46$), dexamethasone ($p=0.87$), or administering corticosteroids within one hour before the cetuximab infusion ($p=0.18$). However, a trend for a difference between the seven possible combinations of the pre-medications and the risk of IR (grades 1–4) by Fisher Exact test ($p=0.068$) was seen whereby the combination of albuterol, famotidine and corticosteroids was effective in preventing IR (grades 1–4) [Table 5], though the numbers in three groups were less than 20 patients. Only 15 of 100 patients (15%) who were pre-medicated with the combination of albuterol, famotidine, and corticosteroids along with diphenhydramine developed an IR (grades 1–4).

Time to Onset of IR after Cetuximab Infusion

IR occurred within minutes of administration of cetuximab (median: 15 minutes, range: 2–140). The time from start of cetuximab to onset of IR correlated inversely with the grade of the IR, whereby the onset of the IR occurred much earlier with grade 4 IR and later with lower grades of IR (median to onset of grades 4, 3, 2, and 1 IR were 5, 13.5, 22, and 25 minutes, respectively, $p=0.04$) [Figure 1].

Cetuximab Re-Challenge

Based on a successful experience with one patient, we re-challenged patients with cetuximab if they had grade 1–3 IRs that rapidly reversed (within 1 hour) with appropriate therapy and if they were medically stable. Patients who experienced a grade 4 IR were not re-challenged. Thirty-seven patients were re-challenged with cetuximab within a few days of the initial exposure. In 30 patients (81%), re-challenge with cetuximab did not result in recurrence of an IR. In the other seven patients (19%), four developed grade 4 IR upon re-challenge with cetuximab, and the other three developed grade 1–3 IRs. Three of the four patients who developed grade 4 IR upon re-challenge with cetuximab had a prior grade 3 IR with their

initial exposure to cetuximab. Of the 10 patients who were not re-challenged with cetuximab, 8 had a prior high grade IR.

Treatment of IR and Admission to the Hospital

Upon onset of an IR (grades 1–4), cetuximab administration was stopped and IV fluids and supplemental oxygen were administered as needed. Appropriate medical treatment of IRs was delivered with H₁-blockers, corticosteroids, H₂-blockers, inhaled nebulized albuterol, or epinephrine in 80.9%, 59.6%, 23.4%, 21.3%, 12.8% of the events, respectively. Of the 47 patients who developed an IR, nine (19%) were admitted to the hospital and one of the nine was admitted to the intensive care unit. Five of the patients admitted to the hospital had a grade 4 IR, and four patients had a grade 3 IR. One of the patients admitted to the hospital developed acute myocardial infarction during a high grade IR. This patient was later found to have critical coronary artery obstruction, which was undiagnosed and asymptomatic before the cetuximab administration. None of the patients died as a result of a cetuximab-induced IR. Most admitted patients were hospitalized for only a short time (median: 1 day, range:1–4).

Discussion

This is the largest study to evaluate risk factors for and pre-medications to prevent IRs due to cetuximab in patients with SCCHN. We conducted a retrospective analysis of 243 patients with SCCHN treated with cetuximab at our institution. The overall risks of an IR (grades 1–4) and of a high grade IR due to cetuximab were 19.3% and 6.6%, respectively. We evaluated potential risk factors for an IR due to cetuximab. In multivariate analysis, the following variables independently increased the risk of an IR (grades 1–4): Caucasian race (OR=7.11, p=0.003), allergy to medication (OR=3.74, p=0.002), and peripheral blood eosinophils >3% (OR=2.75, p=0.01). Multivariate analysis identified Caucasian race (OR=5.57, p=0.007) and allergy to medication (OR=4.10, p=0.0007) as independent risk factors for the occurrence of high grade IR. A novel observation from our study is that Caucasians have a seven-fold higher risk of an IR (grades 1–4) with cetuximab compared to African-Americans. Another perspective of these data is that African-Americans have a very low risk for development of a cetuximab-induced IR (grade 1–4)(5.9%) or a high grade IR (0%). The association of race with risk for a cetuximab-induced IR has not been previously reported.

An atopy phenotype, denoted by a history of allergy to medications and/or increased peripheral blood eosinophils, may be a broad risk factor for cetuximab-induced IRs. In our study, patients with an atopy phenotype had a 34–40% risk of an IR (grades 1–4) and a 17% risk of a high grade IR following cetuximab. In agreement with our study, others have reported a higher risk of IR due to cetuximab in patients with allergy history [10, 18–19].

The package insert for cetuximab recommends an H₁ antagonist such as diphenhydramine as the only pre-medication [4], yet IRs still occur in 6–18% of patients [2–5] and high grade IRs occur in 1–5% [3–9]. Higher risks of IR were reported in geographic areas nearby to our institution [10, 18–21]. We observed that the risk of a high grade IR was 22.7% when pre-medicated with diphenhydramine alone. An objective of our study was to assess the efficacy

of additional pre-medications, including inhaled nebulized albuterol, IV corticosteroids, and H₂-blockers, along with diphenhydramine to decrease the risk of high grade IRs. Albuterol, famotidine, and corticosteroids, as a group, significantly ($p=0.003$) decreased the risk of a high grade IR. Only one of 100 patients (1%) who were pre-medicated with the combination of albuterol, famotidine, and corticosteroids along with diphenhydramine developed a high grade IR. Since several possible combinations included less than 20 patients each, it is possible that the other premedication combinations could be as effective as inhaled nebulized albuterol, IV corticosteroids, H₂ blockers, and diphenhydramine. These data support that medications used to prevent and treat high grade IRs due to other chemotherapeutic and biologic agents are also effective as a group in decreasing cetuximab-induced high grade IR's.

We observed a risk of IR (grades 1–4) of 31.8% with pre-medication using diphenhydramine alone. The overall risk of IR (grades 1–4) were not significantly decreased with the addition of albuterol ($p=0.08$), famotidine ($p=0.28$), or corticosteroids ($p=0.18$). However, a trend for a difference between the seven possible combinations of the pre-medications and the risk of IR (grades 1–4) [$p=0.068$] was seen whereby the combination of albuterol, famotidine and corticosteroids was effective in preventing IR (grades 1–4). Only 15 of 100 patients (15%) who were pre-medicated with the combination of albuterol, famotidine, and corticosteroids along with diphenhydramine developed an IR (grades 1–4).

It is difficult to determine from our study the relative importance of each pre-medication in preventing IRs due to cetuximab. Other studies have been helpful in this regard. In a post-hoc analysis of the MABEL trial, adding corticosteroids (hydrocortisone or dexamethasone) to an H₁ antagonist decreased the risk of IRs due to cetuximab from 25.6% to 9.6%[3]. Groups with a high risk of an IR also showed a benefit of dexamethasone as a pre-medication [10, 19]. Our study could not confirm the independent effectiveness of corticosteroids in preventing an IR. H₂ blockers have been used as a standard pre-medication in some institutions [18–20]; however, studies have not found H₂ blockers to be effective in preventing IRs (grades 1–4) or high grade IRs. In our univariate analysis, an H₂ blocker was useful to protect from a high grade IR. Respiratory disease (asthma) has been found to be a risk factor for an IR [10], which could explain in part the efficacy of albuterol as an effective prevention modality.

Our study contrasts with the findings of other reports where there were no clear risk factors for cetuximab-induced IRs and no benefit of additional pre-medications [13]. This may be due to differences in patient characteristics, geography, cancer diagnosis, numbers of patients overall and within subgroups, dosing regimens of pre-medications, definition of an IR, and grading of an IR.

We were able to successfully re-challenge 30 of 47(64%) of patients with cetuximab soon after they had experienced an IR. In these patients, re-challenge with cetuximab did not result in a repeat IR. Arguably, it would be reasonable to re-challenge a patient who experienced a grade 1 IR. In our dataset, 14 of 14 patients (100%) with grade 1 IR, 12 of 15 patients (80%) with grade 2 IR, and 4 of 8 patients (50%) with grade 3 IR who were re-challenged with cetuximab did not experience a subsequent IR. We carefully selected

patients for re-challenge to include only those patients who had prior grade 1–3 IRs that had rapidly reversed (within 1 hour) with appropriate therapy and were medically stable. In addition, all patients were pre-medicated with diphenhydramine, famotidine, albuterol and/or corticosteroids before re-challenge with cetuximab. Since 50% of patients who had prior grade 3 IRs developed a high grade IR with re-challenge to cetuximab, we do not recommend re-challenging these patients. Common practice is to permanently stop cetuximab for grade 2–4 IRs, and often even for grade 1 IR [22]. However, our data strongly support that most patients who experience a mild-moderate IR due to cetuximab may be safely re-challenged. The importance of this novel observation is that cetuximab is a key therapeutic agent in SCCHN, representing one of the few drugs shown to improve the OS in patients with curable disease and the only drug shown to improve OS in patients with incurable disease [5, 23]. However, caution should be exercised by carefully considering a balance of risks, benefits, and alternatives when deciding on whether or not to re-challenge a patient with cetuximab.

An inverse relationship was observed between the time to onset of an IR and the grade of the IR. The reason for this is unclear, although it is possible that patients destined to develop a high grade IR have higher levels of pre-existing antibodies to cetuximab which may promote earlier onset of the IR. Previous reports found a relation between the severity of asthma and the level of IgE [24, 25]. The clinical relevance of this observation is that early onset IRs (those that occur within 15 minutes of initiation of cetuximab) are likely to be very serious and require prompt discontinuation of cetuximab, and close patient assessment, monitoring and aggressive management.

Our study has limitations. This is a retrospective analysis of patients with SCCHN at a single, but large, institution. The study's findings should be validated by a carefully designed prospective, randomized trial that stratifies each group for the known risk factors for IRs. Several of the pre-medication groups included small numbers of patients. Anaphylactic hypersensitivity reactions and anaphylactoid infusion reactions present with similar clinical manifestations such that it is unclear if the pre-medication combination of albuterol, corticosteroids, H₂ blocker and diphenhydramine were preventing cetuximab-induced anaphylactic hypersensitivity reactions. We defined an IR to occur within 3 hours of administration of cetuximab and to include fever only; therefore, it is possible that some of these IRs were not true cetuximab-mediated reactions. We gave all patients IV normal saline as pre-hydration before cetuximab and patients were instructed to avoid anti-hypertensive agents and/or *beta*-blockers the night before and the morning of cetuximab administration to prevent exacerbation of a hypotensive component of an IR. These strategies may have had an influence on outcomes, for which we could not independently control. Also, these data may or may not apply to geographic regions with lower risks of IRs.

In conclusion, we observed that Caucasian race, allergy to medications, and peripheral blood eosinophils >3% were independent high risk factors for cetuximab-induced IRs and that pre-medication with albuterol, famotidine, and corticosteroids as a group in addition to diphenhydramine were effective in decreasing the risk of cetuximab-induced high grade IR. However, the limited number of patients in other possible combinations does not preclude that other pre-medication combinations may be as effective. These data may be used to

identify patients at higher risk for an IR who may be advised to not receive cetuximab or who may benefit from additional pre-medications along with diphenhydramine before cetuximab to decrease the risk of a high grade IR. Our data also supports that most patients who develop a mild-moderate IR due to cetuximab may be successfully re-challenged. These observations have direct relevance to clinical practice, particularly in geographic areas such as ours known to be at high risk for IRs or in all patients who develop a cetuximab-induced IR.

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Highlights

- Cetuximab infusion reactions(IR) were common (31.8%) with diphenhydramine alone
- Caucasian race, medication allergy, and peripheral eosinophils >3% were risk factors
- Albuterol, famotidine, and corticosteroids reduced the risk of high grade IR.
- Most patients who develop an IR due to cetuximab may be successfully re-challenged.
- These findings have direct relevance to clinical practice.

Figure 1.
Time to onset of infusion reaction, grouped by grade, after initiation of cetuximab infusion.

Table 1

Patient characteristics

	All Patients N(%)	Diphenhydramine Alone N(%)	Additional pre-medications N(%)	p value
N	243(100)	22(9.1)	221(90.9)	
Age (years) Median(range)	57(19–86)	57(19–77)	58(33–86)	0.07
Sex				
Male	193(79.4)	19(86.4)	174(78.7)	0.58
Female	50(20.6)	3(13.6)	47(21.3)	
Race				
Caucasian	192(79.0)	16(72.7)	176(79.6)	0.42
African-American	51(21.0)	6(27.3)	45(20.4)	
Respiratory and allergy history				
COPD	28(11.5)	1(4.5)	27(12.2)	0.48
Asthma	8(3.3)	1(4.5)	7(3.2)	0.54
Allergic rhinitis	5(2.1)	1(4.5)	4(1.8)	0.38
Allergy to medication	35(14.4)	6(27.3)	29(13.1)	0.10
Smoking History				0.23
Never	38(15.6)	1(4.5)	37(16.7)	
Previous smokers	67(27.6)	7(31.8)	60(27.1)	
Current smokers	138(56.8)	14(63.6)	124(56.1)	
Cetuximab (as monotherapy)	115(47.3)	6(27.3)	109(49.3)	0.07

COPD=chronic obstructive pulmonary disease.

Table 2

Significant risk factors for IR (grades 1–4).

	N	IR (grades 1-4) N(%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Race								
Caucasian	192	44(22.9)	4.76	1.41-16.02	0.002	7.11	1.94-26.11	0.003
African-American	51	3(5.9)	Ref			Ref		
Allergy to medications								
Yes	35	14(40.0)	3.54	1.63-7.65	0.030	3.74	1.62-8.64	0.002
No	208	33(15.9)	Ref			Ref		
Asthma or COPD								
Yes	36	12(33.3)	2.46	1.12-5.37	0.021	2.27	0.96-5.37	0.06
No	207	35(16.9)	Ref			Ref		
Peripheral eosinophils(%)								
>3%	38	13(34.2)	2.62	1.22-5.62	0.017	2.75	1.20-6.32	0.01
3%	205	34(16.6)	Ref			Ref		

IR=infusion reaction; COPD=Chronic obstructive pulmonary disease; OR=odds ratio; CI=confidence interval.

Table 3

Significant risk factors for high grade IR.

	N	High grade IR N(%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p value	OR	95% CI	p value
Race								
Caucasian	192	16(8.3)	NA ^a	NA ^a	0.027 ^a	5.57	1.60–19.33	0.007
African-American	51	0(0.0)				Ref		
Allergy to medications								
Yes	35	6(17.1)	4.10	1.39–12.12	0.017	4.10	1.82–9.22	0.0007
No	208	10(4.8)	Ref			Ref		

IR=infusion reaction; OR=odds ratio; CI=confidence interval.

^aFisher's Exact test.

Table 4

The effect of pre-medication on risk for high grade IR (Univariate analysis).

	N	High Grade IR N(%)	OR	95% CI	p value
Albuterol					
Yes	180	6(3.3)	0.18	0.06–0.53	0.001
No	63	10(15.9)	Ref		
Famotidine					
Yes	110	2(1.8)	0.16	0.04–0.71	0.004
No	133	14(10.5)	Ref		
1h steroids^a					
Yes	216	11(5.1)	0.24	0.08–0.74	0.023
No	27	5(18.5)	Ref		
Albuterol + famotidine + 1h steroids^a					
Yes	100	1(1.0)	0.09	0.01–0.66	0.001
No	143	15(10.5)	Ref		

IR=infusion reaction; OR=odds ratio; CI=confidence interval.

^aHydrocortisone or dexamethasone given 1 hour from cetuximab infusion.

Table 5

The effect of the seven different combinations of pre-medications on the risk of IR (grades 1–4) and high grade IR. All seven combinations received diphenhydramine.

	N	IR (Grades 1–4): N(%)	High Grade IR: N(%)
P value^b		0.068	0.003
Albuterol + famotidine + 1h steroids ^a	100	15(15)	1(1.0)
Albuterol+1h steroids ^a (no famotidine)	79	14(17.2)	5(6.3)
1h steroids ^a (no famotidine or albuterol)	31	7(22.6)	4(12.9)
Famotidine + 1h steroids ^a (no albuterol)	6	3(50.0)	1(16.7)
No albuterol, famotidine, or 1h steroids ^{a,c}	22	7(31.8)	5(22.7)
Famotidine(no albuterol or 1h steroids ^a)	4	0(0.0)	0(0.0)
Albuterol (no famotidine or 1h steroids ^a)	1	1(100.0)	0(0.0)

IR=infusion reaction.

^aHydrocortisone or dexamethasone given 1 h from cetuximab infusion.

^bFisher's Exact test.

^cThis group was pre-medicated with diphenhydramine alone.