

Managing Premedications and the Risk for Reactions to Infusional Monoclonal Antibody Therapy

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ABSTRACT

Monoclonal antibodies—including rituximab, alemtuzumab, trastuzumab, bevacizumab, cetuximab, and panitumumab—have improved the treatment of various malignancies. Although generally better tolerated with less toxicity than conventional anticancer agents, monoclonal antibodies may cause infusion-related reactions like other infusional agents. The incidence of infusion reactions varies by agent, but severe events occur only occasionally, mostly with the first or second infusion. Although the exact etiology of infusion reactions remains unclear, they may arise via either IgE- or non-IgE-dependent mechanisms. There is a compelling clinical need to improve the risk assessment for severe infusion reactions. The recent identification of pre-existing IgE crossreacting with cetuximab, its associ-

ation with severe reactions, and regional variation in the prevalence may provide a marker for high-risk assessment. Premedication with antihistamines, acetaminophen, and/or corticosteroids is a common practice to prevent infusion reactions with all monoclonal antibodies. However, a recent observational study suggests that premedication may no longer be necessary after the second infusion of cetuximab if patients did not develop any symptoms with the first two infusions. Considering the heterogeneity of infusion reactions, clinicians need to recognize the underlying nature of these events in order to identify patients at risk as well as provide optimal prophylactic measures and management of symptoms. *The Oncologist* 2008;13:725–732

INTRODUCTION

Most cancer therapeutics—including cytotoxic agents and biologics—carry a risk for infusion reactions, which vary in symptom severity from mild flushing to potentially life-threatening events [1]. Infusion reactions are typically mild to moderate in intensity, develop during the infusion or several hours thereafter, and are most commonly associated

with a complex of chills, fever, nausea, asthenia, headache, skin rash, pruritus, etc. [2]. However, infusion reactions may also present with a variety of signs and symptoms of severe hypersensitivity reaction (Table 1) [2–4]. In a small but significant percentage of patients, severe infusion reactions may be characterized by the acute onset of bronchospasm, hypotension, urticaria,

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Table 1. Common signs and symptoms of infusion reaction	
Common signs and symptoms	Common toxicity criteria
Cytokine release syndrome/acute infusion reactions Allergic/hypersensitivity reaction, arthralgia/myalgia, bronchospasm, cough, dizziness, drug fever, dyspnea, fatigue (asthenia, lethargy, malaise), headache, hypotension/hypertension, nausea/vomiting, pruritus/itching, rash/desquamation, rigors/chills, sweating, tachycardia, onset or exacerbation of tumor pain, urticaria	Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated Grade 2: Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 hours Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life threatening; pressor or ventilator support indicated Grade 5: Death
Allergic reaction/hypersensitivity (including drug fever) Bronchospasm, wheezing, dyspnea, hypertension, hypotension, drug fever, edema/angioedema, flushing, rash, urticaria	Grade 1: Transient flushing or rash; drug fever <38°C (<100.4°F) Grade 2: Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F) Grade 3: Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension Grade 4: Anaphylaxis Grade 5: Death
Adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [3].	

and/or cardiac arrest [2, 4]. Because such events can prove to be fatal without appropriate intervention, it is imperative for clinicians to recognize their symptoms, understand their pathology, and use optimal risk assessment and prophylactic regimens.

The approval of rituximab (Rituxan®; Genentech, Inc., South San Francisco, CA and Biogen Idec Inc., Cambridge, MA) for follicular lymphoma in November 1997 ushered in the age of monoclonal antibody therapy in clinical oncology practice. Since then, the use of monoclonal antibodies has increased dramatically, and should continue to do so as new agents currently in development enter the market [5]. Several different monoclonal antibodies are currently available besides rituximab, including alemtuzumab (Campath®; Genzyme, Cambridge, MA) for B-cell chronic lymphocytic leukemia, trastuzumab (Herceptin®; Genentech, Inc.) for breast cancer, and cetuximab (Erbix®; ImClone Systems Inc., New York and Bristol-Myers Squibb Company, Princeton, NJ), panitumumab (Vectibix®; Amgen Pharmaceuticals, Thousand Oaks, CA), and bevacizumab (Avastin®; Genentech, Inc.) for advanced colorectal cancer [6–8]. Cetuximab is also approved for use in squamous cell carcinoma of the head and neck (SCCHN). These agents target specific cell surface mole-

cules on tumor cells, or in the case of bevacizumab, a growth factor important to tumor growth and metastasis. Monoclonal antibodies are generally better tolerated with less severe toxicity than conventional cytotoxic drugs. Nevertheless, severe infusion reactions have been reported with all monoclonal antibodies in trials and in clinical practice. The potential impact of these events has warranted the inclusion of “warnings and cautions” in the prescribing information for all therapeutic monoclonal antibodies. This article discusses the incidence, etiology, prophylaxis, and management of infusion reactions associated with monoclonal antibodies.

INCIDENCE AND TIMING OF INFUSION REACTIONS
Rituximab and trastuzumab produce the highest incidence of infusion reactions among the monoclonal antibodies (Fig. 1) [6–13]. In clinical trials, rituximab caused mild-to-moderate infusion reactions in most lymphoma patients, usually within 30–120 minutes of starting the first infusion [9]. The incidence declined from 77% during the first infusion to 30% with the fourth infusion and 14% with the eighth infusion. Severe infusion reactions, usually reversible with appropriate interventions and supportive care, were reported in approximately 10% of patients, but in rare

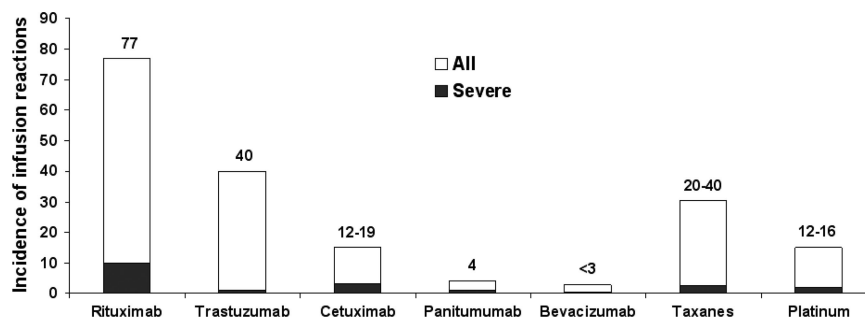


Figure 1. Incidence of infusion reactions with monoclonal antibodies [6–13].

cases proved fatal [14]. Approximately 80% of fatal infusion reactions were associated with the first rituximab infusion (Table 2) [6–10, 15].

Trastuzumab produced mostly mild-to-moderate infusion reactions during the first infusion in approximately 40% of patients, and then only infrequently during subsequent infusions [10]. Severe infusion and hypersensitivity reactions including anaphylaxis, however, were also reported during the initial investigational development of the agent, although the overall incidence of these severe events is rare (<1%). In most cases, symptoms occurred during or within 24 hours of the first infusion, and rarely were fatal.

With cetuximab, mild-to-moderate infusion reactions were usually associated with the first infusion and ranged in incidence from 12% (SCCHN patients receiving cetuximab in combination with radiation therapy) to 19% (advanced colorectal cancer patients receiving single-agent therapy) [16–18]. Overall, pooled results indicate that severe infusion reactions have occurred in 46 of 1,485 patients (3%) treated in clinical trials, but were rarely fatal (<1 in 1,000) once the infusion was discontinued and supportive measures provided [6]. Approximately 90% of the severe infusion reactions were associated with the first cetuximab infusion.

In the case of panitumumab, infusion reactions occurred in approximately 4% of patients, and were severe in approximately 1% of cases. Excluding those treated with panitumumab in combination with carboplatin (Paraplatin®; Bristol-Myers Squibb Company) and paclitaxel (Taxol®; Bristol-Myers Squibb Company), 43 of 1,336 patients (3%) had infusion reactions, of which six (0.4%) cases were severe [7]. None was fatal. Finally, infusion reactions occurred in <3% of patients during the first infusion of bevacizumab, and were severe in 0.2% of cases [8].

Therefore, the incidence of infusion reactions varies among monoclonal antibodies, occurring predominantly with the first infusion. Except for rituximab, the inci-

dence is generally comparable with that seen with taxanes and platinum compounds. Docetaxel and paclitaxel produced infusion reactions in 20%–40% of patients in clinical trials, with 2%–4% of cases being severe even with premedication [11, 12]. Nearly 95% of infusion reactions occurred during the first or second taxane infusion [1]. Carboplatin and oxaliplatin caused infusion reactions in approximately 12%–16% of patients, with about 2%–4% of cases being severe; unlike taxanes or monoclonal antibodies, reactions to these platinum compounds typically occurred after six or more infusions [13, 19–23].

ETIOLOGY OF INFUSION EVENTS

Cytokine-Dependent Infusion Reactions

The mechanisms by which monoclonal antibodies elicit infusion reactions remain unclear. Monoclonal antibodies may interact with their molecular targets on circulating blood cells, tumor cells, or effector cells recruited to the tumor site (e.g., rituximab with CD20), thereby promoting the release of inflammatory cytokines. When released into the circulation, cytokines can produce a wide range of symptoms characteristic of infusion reactions [24]. During the first infusion of rituximab to patients with relapsed B-cell chronic lymphocytic leukemia or low-grade B-cell lymphoma, serum levels of tumor necrosis factor (TNF)- α and interleukin (IL)-6 peaked at 90 minutes and were accompanied by fever, chills, nausea, vomiting, hypotension, and dyspnea [25]. The severity of the infusion reaction was related to the number of circulating lymphocytes. Patients with lymphocyte counts $>50 \times 10^9/l$ were significantly more likely to have severe symptoms than those having lower baseline lymphocyte counts ($p = .0017$). Anecdotally, infusion reactions resulting from cytokine release can also be caused idiosyncratically: the release of TNF- α and IL-6 with accompanying symptoms of chills, fever, hypo-

Table 2. Incidence of mild/moderate and severe infusion reactions (IRs) in cytotoxic and monoclonal antibody therapy [6–10, 15]

Drug	Mild/moderate IR incidence (%)	Severe IR incidence (%)
Rituximab [9]	Majority of patients	<10
Alemtuzumab [15]	Overall: rigors, 89; fever, 83; nausea, 47; vomiting, 33; hypotension, 15	
Trastuzumab [10]	40	<1
Cetuximab [6]	12	3
Bevacizumab [8]	<3	0.2
Panitumumab [7]	3	~1

tension, nausea, vomiting, and abdominal pain has also been reported following infusion of oxaliplatin in colorectal cancer patients [26].

Cytokine-dependent infusion reactions should not be confused with tumor-lysis syndrome, in which the destruction of large numbers of rapidly proliferating tumor cells gives rise to hyperuricemia, hyperphosphatemia, and other metabolic abnormalities usually within 24 hours of infusion [2]. Isolated cases of tumor-lysis syndrome associated with rituximab therapy have been reported [27, 28]. Other reports indicate that cytokine-related reactions may occur in complex clinical presentations, in which infusion-related symptoms during an initial dose of rituximab (severe rigors, fever, bronchospasm, hypoxemia, and thrombocytopenia) are accompanied by a rapid and pronounced decline in blood tumor cells without prominent laboratory abnormalities; this mixed presentation could be attributed to initial tumor cell agglutination, followed by cytokine release and finally tumor lysis [29].

When massive cytokine release occurs, it may precipitate life-threatening infusion reactions. A cytokine storm was recently reported in all six healthy volunteers who received a novel anti-CD28 monoclonal antibody in a phase I clinical trial, which presented initially as severe headache, lumbar myalgias, gastrointestinal symptoms, rigors, erythema, and peripheral vasodilation by 60–90 minutes after the infusion [30]. Hypotension accompanied by tachycardia occurred by 4 hours, and was followed by fever, lymphopenia, and monocytopenia. All patients developed multiorgan failure by 16–20 hours, with respiratory deterioration, renal impairment, and disseminated intravascular coagulation. No evidence of anaphylaxis was seen. All patients survived after intensive cardiopulmonary support and high-dose corticoste-

roid therapy, although two patients required intensive organ support for 8 and 16 days, respectively. Because a cytokine-dependent mechanism does not depend on prior sensitization, it may contribute to infusion reactions that occur with the first infusion of a monoclonal antibody.

Hypersensitivity Reactions

Infusion reactions may have a hypersensitivity basis, in which the molecular structure of the anticancer drug or a component of the drug formulation is recognized as an antigen by the immune system. Type 1 or immediate-type hypersensitivity reactions are mediated by IgE. On initial exposure to the “antigen,” specific IgE is produced, which sensitizes mast cells located on cutaneous and mucosal surfaces as well as on circulating basophils [31, 32]. Importantly, this initial exposure does not trigger symptoms, but on subsequent exposures, the anticancer drug binds to the cell-bound IgE to stimulate release of histamine, leukotrienes, and prostaglandins. These proinflammatory mediators induce smooth muscle contraction, capillary dilation, and vascular permeability, leading to the development of urticaria, rash, angioedema, bronchospasm, and hypotension [1]. Mast cells also have the capacity to release cytokines, including TNF- α , via an IgE-dependent mechanism, which may further augment symptoms [33]. Anaphylaxis, the most severe form of IgE-mediated hypersensitivity, is a life-threatening condition that may appear within minutes of starting an infusion. It is characterized by respiratory distress, laryngeal edema, and severe bronchospasm, which may be accompanied by cutaneous and gastrointestinal symptoms, and may lead to a hypotensive crisis [34]. Anaphylactoid reactions present with symptoms similar to those of anaphylaxis, but occur in the absence of IgE.

Because prior sensitization is required for IgE-mediated hypersensitivity, it would not be expected to occur with the first infusion of a monoclonal antibody. However, a pre-existing IgE that crossreacts with cetuximab (C-IgE) has been detected prior to cetuximab infusion in the serum samples from cancer patients and healthy volunteers. In our retrospective analyses, the infusion reaction was significantly higher in patients with detectable C-IgE in their pretreatment sera [35]. Among the 76 cetuximab-treated patients, infusion reactions of any grade were reported in 25 patients (grade 1 or 2, $n = 13$; grade 3 or 4, $n = 12$) whereas 17 of the 25 patients (68%) had detectable C-IgE. The presence of C-IgE could not account for every reaction event; however, patients with C-IgE had more severe reactions receiving cetuximab, with a 92% (11 of 12) incidence of severe (grade 3 or 4) reactions. Patients with pre-existing C-IgE were immediately discontinued from further cetuximab therapy by the treating physicians, whereas five of eight patients with negative C-IgE were rechallenged with cetuximab and could complete the infusion without further reaction after slowing the infusion and premedication.

Furthermore, there is strong evidence that the prevalence of infusion reactions to cetuximab is geographically distributed. Recently, O'Neil et al. [36] published that grade 3 or 4 infusion reactions occur at a rate of 22% in selected centers in Tennessee and North Carolina while the national average is 3%. Also, in our study, C-IgE was detected in 20.8% (15 of 72) of healthy volunteers from Tennessee whereas only 6.1% (3 of 49) and 0.6% (2 of 341) of sera or plasma collected from California and Massachusetts, respectively, were positive for C-IgE [35]. In the review of clinical characteristics, O'Neil et al. [36] observed the association of infusion reaction with the history of atopy, whereas the association was not seen in our study [35]. Because both studies were retrospective studies subject to potential biases, a prospective study with careful clinical data collection and testing of C-IgE should be the next step.

MANAGEMENT OF SEVERE INFUSION REACTIONS

Mild-to-moderate infusion reactions to monoclonal antibodies may generally be managed by slowing the infusion rate, but severe reactions require emergency measures [6, 7, 9, 10]. The infusion should be immediately stopped, and medical therapy and supportive care deployed as appropriate for the presenting symptoms. Because of the possibility of such reactions, medical therapy including epinephrine, corticosteroids, i.v. antihistamines, bronchodilators, oxygen, and vasopressors

should be readily available when monoclonal antibodies are infused. Physicians and nurses working in chemotherapy infusion rooms are certainly prepared to address severe infusion reactions based on their experience with platinum compounds and taxanes.

Our experience with IgE-mediated events indicates that they have a particularly fast and severe onset, although some non-IgE-mediated reactions can be very severe and mimic anaphylaxis. Unfortunately, clinicians may not be able to clinically discriminate between IgE-mediated and non-IgE-mediated reactions. If IgE-mediated anaphylaxis, such as those reactions observed with cetuximab in the Tennessee and North Carolina area, is suspected, the immediate treatment should include epinephrine with i.v. steroid and antihistamines. Frequently, an epinephrine autoinjector such as the EpiPenTM (DEY, L.P., Napa, CA) is used for epinephrine administration in the acute reaction setting because of its convenience and safety. Guidelines for the diagnosis and management of anaphylaxis have been published by a joint task force representing several professional societies involved in the fields of allergy, asthma, and immunology [34]. In these guidelines, epinephrine is recommended as first-line therapy when life-threatening symptoms (i.e., stridor, respiratory distress, wheezing, hypotension, arrhythmia, shock, seizures, or unconsciousness) are present.

RISK ASSESSMENT AND RECHALLENGE AFTER SEVERE INFUSION REACTIONS

Guidelines regarding rechallenge once symptoms have fully resolved following infusion reactions vary by agent. The standard recommendation is to immediately and permanently discontinue infusion in patients experiencing severe infusion reactions [6, 7]. However, with recent advances in the understanding of these events, perhaps more individualized approaches could be considered.

In the case of rituximab, infusion can generally be resumed with a 50% reduction in the infusion rate once symptoms completely resolve [9]. Patients with pre-existing cardiac and pulmonary conditions, prior clinically significant cardiopulmonary adverse events, and high numbers of circulating malignant cells are at a higher risk for infusion reactions and consequently require close monitoring during all rituximab infusions [9, 37]. With trastuzumab, there is no optimal method for identifying which patients can be safely rechallenged following a severe infusion reaction [10]. Of 39 patients with severe infusion reactions, 33 (85%) were success-

fully rechallenged without recurrence of symptoms [38]. According to the prescribing information, permanent discontinuation of trastuzumab should be strongly considered in patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome [10]. With bevacizumab, the infusion should also be interrupted, although no data are available to guide rechallenge [8].

In the case of cetuximab, once a severe event has occurred, rechallenge is not recommended. Assessment of risk using test doses (e.g., 20 mg) has not been a reliable indicator of infusion reaction risk in cetuximab clinical trials, but a history of allergic conditions or respiratory distress appears to be associated with higher risk [6, 36]. The decision to rechallenge patients with mild reactions is more difficult because of concerns about developing a more severe reaction with rechallenge. It could now be postulated that patients with mild infusion reactions may be successfully rechallenged if they do not have pre-existing IgE against cetuximab based on the underlying etiology of the first event as well as the patient's overall risk. However, if the reaction is identified as an IgE-mediated anaphylactic event, standard premedication with antihistamines and/or corticosteroids, including the commonly used 2-day dexamethasone regimen to prevent taxane- or contrast dye-induced reaction, is not appropriate and not enough to prevent the reaction in most cases.

In conclusion, the decision to rechallenge largely depends on the underlying etiology of the severe infusion reaction, and understanding the mechanism of reaction for each therapeutic agent is important. Rechallenge with rituximab at a lower infusion rate may be recommended, because severe infusion reactions appear as a result of cytokine-mediated mechanisms [25, 29]. In the case of cetuximab, however, many severe reactions appear to be IgE mediated, in which case rechallenge is not recommended, especially in the southeastern region of the U.S., with a high prevalence of C-IgE. In a few patients who had previously experienced severe hypersensitivity reactions, desensitization protocols using gradual dose escalation, as seen in platinum agents and taxanes, have been successfully used [39–41]. A similar dose-escalation protocol, combined with s.c. immunotherapy has been successful in patients experiencing reactions to trastuzumab [42]. However, the safety and efficacy of this type of desensitization protocol with other monoclonal antibodies are yet to be determined.

OPTIMAL PROPHYLAXIS

The optimal prophylaxis, like risk assessment, depends on the nature of the event. Premedication with cortico-

steroids at commonly used antiemetic doses (dexamethasone, 8–20 mg or equivalent) may prevent or dampen non-IgE mediated infusion or inflammatory reactions. In the Monoclonal Antibody Erbitux in a European Pre-License trial, which evaluated cetuximab plus irinotecan in patients with epidermal growth factor receptor-positive metastatic colorectal cancer who had last failed irinotecan-based therapy, premedication with an antihistamine plus corticosteroid was associated with fewer infusion reactions overall (9.6% versus 25.6%) as well as fewer severe infusion reactions (1.0% versus 4.7%) than premedication with an antihistamine alone [43]. The antitumor efficacy was unaffected by the nature of the premedication.

A recent retrospective analysis suggests that it is feasible and safe to omit antihistamine premedication after the first two cetuximab infusions [44]. This strategy is based on the recognition that the vast majority of infusion reactions occur with the first cetuximab infusion, and that antihistamines are not expected to be effective in preventing non-IgE-mediated events. At Memorial Sloan-Kettering Cancer Center (MSKCC), patients treated with cetuximab outside a clinical trial during the first 28 months of its commercial availability (February 2004 to June 2006) were identified by a retrospective search of computerized pharmacy records. A total of 453 patients received 50 mg of diphenhydramine prior to the initial 400-mg loading dose of cetuximab, and then 25 mg of diphenhydramine before the second cetuximab dose in accordance with MSKCC institutional guidelines. Seven patients (1.5%) experienced grade 3 infusion reactions that presented as urticaria, bronchospasm, and/or hypotension, all of which occurred with the first infusion after diphenhydramine premedication. Seventeen patients (4%) had mild-to-moderate infusion reactions, and again all had received diphenhydramine premedication. Patients who did not experience infusion reactions during the first two infusions subsequently received cetuximab without antihistamine premedication. None of the 429 patients experienced infusion reactions of any grade during a total of 4,138 cetuximab infusions without premedication. It is now current institutional practice at MSKCC to omit diphenhydramine premedication after the first two infusions in patients who did not have infusion reactions initially [44]. Our study supports these findings in that antihistamine administration alone is not enough to prevent the IgE-mediated hypersensitivity reaction to cetuximab that occurs at the first infusion because of the presence of pre-existing C-IgE [35]. It may therefore be safe to omit antihistamine premedication in a low C-IgE-prevalence area.

Management of patients in high C-IgE-prevalence areas is challenging, particularly when the antihistamine and antiemetic doses of steroid premedication do not appear to fully prevent C-IgE-mediated anaphylaxis, based on retrospective analyses. Optimal premedication and desensitization regimens, as done with platinum and taxanes, remain to be studied [39, 40]. Finally, the development of predictive tests—such as the detection of C-IgE—would be important for determining which patients are at the highest risk for severe IgE-mediated hypersensitivity reactions, and which patients with severe infusion reactions can be safely managed with rechallenge [35].

CONCLUSION

Monoclonal antibodies, like other infusional agents, are associated with a risk for infusion reactions, although for most, the incidence of severe events is rare. Improving risk assessment for infusion reactions has become a compelling medical need. Patients with pre-existing C-IgE are at high risk for severe IgE-mediated hypersensitivity

reactions to cetuximab [35], whereas those with high circulating malignant cell counts are at risk for severe infusion reactions to rituximab [37]. Premedications are considered standard procedure for minimizing the risk for infusion reactions. However, because most infusion reactions with monoclonal antibodies occur after the first or second infusion, the value of premedication on subsequent infusions may decrease. An observational study suggests that discontinuation of antihistamine premedication starting with the third cetuximab infusion may not compromise tolerability [44]. Whether similar strategies can be used safely for other monoclonal antibodies needs to be studied further. Considering the heterogeneity of infusion reactions, clinicians need to better understand the underlying nature of these events in order to identify patients at risk and provide optimal prophylactic measures and symptom management.

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