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Symptom Management and Supportive Care

Management and Preparedness for Infusion and Hypersensitivity Reactions

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Key Words. Hypersensitivity • Infusion reactions • Monoclonal antibodies • Taxanes • Platinum • Rechallenge

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the physiology of the different clinical hypersensitivity and infusion reactions to monoclonal antibodies and chemotherapy.
2. Select appropriate prevention and treatment strategies for hypersensitivity reactions.
3. Describe the differences between acquired and acute hypersensitivity reactions.

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ABSTRACT

Background. **Like nearly all systemic cancer therapies, monoclonal antibodies are associated with hypersensitivity reactions. This article reviews the characteristics and management of hypersensitivity reactions to monoclonal antibodies and commonly used chemotherapy agents.**

Methods. **MEDLINE was searched for recent studies and reviews pertaining to hypersensitivity reactions with monoclonal antibodies (cetuximab, rituximab, trastuzumab, panitumumab, bevacizumab), platinum compounds (carboplatin, oxaliplatin), and taxanes (paclitaxel, docetaxel). Emphasis was placed on articles that provided practical information on hypersensitivity reaction management. Data found in the literature were supplemented with information from the package insert for each agent.**

Results. **Severe hypersensitivity reactions are rare, with an incidence of ≤5%, provided patients receive proper premedication, close monitoring, and prompt intervention when symptoms occur. Hypersensitivity reactions to platinum compounds are generally consistent with type 1 hypersensitivity, occurring after multiple cycles of therapy. Reactions to taxanes and monoclonal antibodies produce similar symptoms, but are generally immediate, occurring during the first few minutes of the first or second infusion. However, 10%–30% of reactions to monoclonal antibodies are delayed, and may occur in later infusions, indicating the importance of close observation of the patient following administration. Mild-to-moderate reactions can be managed by temporary infusion interruption, reduction of the infusion rate, and symptom management. Rechallenge should be considered after complete resolution of all symptoms. Severe reactions may require treatment discontinuation.**

Conclusion. **Hypersensitivity or infusion reactions to platinum compounds are acquired; reactions to taxanes and monoclonal antibodies are immediate and typically occur during the first few minutes of the first infusion. The different time of onset should be considered when developing strategies for preventing and managing hypersensitivity reactions. The decision to rechallenge or discontinue treatment after a reaction occurs depends on the severity of the reaction and other clinical factors.** ***The Oncologist*** 2007;12:601–609

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Disclosure of potential conflicts of interest is found at the end of this article.

Introduction

Nearly all systemic agents used in cancer treatment today are associated with possible hypersensitivity reactions [1]. These reactions range in severity from mild flushing and itching to anaphylaxis and, in some rare cases, death. Nevertheless, hypersensitivity reactions are often reported only sporadically in clinical trials or as case reports. The vague or inconsistent terminology used to describe these reactions may reflect our poor understanding of their pathophysiology, which can vary for different agents. Although severe hypersensitivity reactions are rare, the incidence of mild-to-moderate reactions may be underestimated in the oncology community [2], resulting in a lack of preparedness or unfamiliarity with the grading and management of hypersensitivity reactions. Inappropriate assessment of the nature and severity of the reaction could negatively affect treatment decisions, if patients at high risk for experiencing a second reaction are rechallenged with the drug, or if active treatment is discontinued in patients who may be safely rechallenged. It is therefore imperative that clinicians are aware of the possibility of hypersensitivity reactions when administering therapy and have protocols in place to prevent and manage these reactions, so that their impact on further treatment is minimized.

This article reviews the clinical features and current management strategies of hypersensitivity reactions and of milder infusion reactions for selected, commonly used platinum compounds (carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), and monoclonal antibodies (cetuximab, trastuzumab, rituximab, bevacizumab, and panitumumab). A MEDLINE search was conducted for studies and reviews pertaining to hypersensitivity reactions to these agents. Supplemental information was obtained from the product information provided for each agent. Emphasis was placed on practical information regarding prevention and management of hypersensitivity, and how the occurrence of these reactions affects further treatment.

Characteristics of Hypersensitivity Reactions

Immunologic Mechanisms

The exact mechanism by which hypersensitivity reactions occur is often unclear and may vary among agents [3]. Most reactions to standard chemotherapeutic agents are consistent with type 1 hypersensitivity, which is characterized by the rapid contraction of smooth muscle and dilation of capillaries, resulting in urticaria, rash, angioedema, bronchospasm, and hypotension [1, 4, 5]. True type 1 reactions are caused by the IgE-mediated release of histamines, leukotrienes, and prostaglandins from mast cells in tissue and basophils in peripheral blood [5, 6]. Hypersensitivity reactions to platinum compounds, such as carboplatin and oxaliplatin, are generally consistent with type 1 IgE-mediated hypersensitivity [7, 8].

Some chemotherapy agents, their metabolites, and vehicles interact directly with mast cells and basophils, producing an anaphylactoid response that is indistinguishable from an IgE-mediated response [1]. The taxanes paclitaxel and docetaxel produce reactions that are clinically similar to type 1 hypersensitivity, but evidence suggests that these reactions are not mediated by IgE [9, 10]. Instead, these reactions may be caused by direct effects on immune cells or other mechanisms. Cremophor EL (polyoxyethylated castor oil), the excipient found in paclitaxel (but not docetaxel), has also been shown to induce histamine release and hypotension and may therefore be responsible in part for hypersensitivity reactions [1, 11]. An albumin-bound form of paclitaxel that does not contain Cremophor EL has been associated with little to no incidence of severe hypersensitivity reactions, even in the absence of premedication [12].

Treatment with monoclonal antibodies has been associated with infusion reactions, some of which are severe. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) distinguish between hypersensitivity reactions and acute infusion reactions induced by cytokine release (Table 1) [13, 14]. The exact mechanism responsible for infusion reactions to monoclonal antibodies is not known, but like the taxanes, these reactions are unlikely to be true, type 1 IgE-mediated hypersensitivity reactions [15]. Theoretically, infusion reactions to chimeric and humanized monoclonal antibodies may be a result of their ability to elicit human antichimeric antibodies (HACAs) and human antihuman antibodies (HAHAs), respectively [16]. This theory is supported by the observation that the incidence of infusion reactions to panitumumab, a fully human monoclonal antibody that targets the epidermal growth factor receptor, is in the range of 1%–5% [17, 18]. However, a correlation between infusion reactions and HACAs or HAHAs has not been demonstrated [19–21].

Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap (Ta-

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Table 1. Grading of HSRs according to the NCI Common Terminology Criteria for Adverse Events v3.0 [13]

	Grade				
	1	2	3	4	5
Hypersensitivity (allergic reaction)	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
Acute infusion reaction (cytokine release syndrome)	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medication indicated for ≥24 hours	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)	Life-threatening; pressor or ventilatory support indicated	Death

Abbreviations: HSRs, hypersensitivity reactions; NCI, National Cancer Institute; NSAIDs, nonsteroidal anti-inflammatory drugs.

ble 2). Mild-to-moderate reactions (grades 1 and 2) are characterized by flushing, rash, fever, rigors, chills, dyspnea, and mild hypotension. Severe reactions (grades 3 and 4) are associated with bronchospasms and hypotension requiring treatment, cardiac dysfunction, anaphylaxis, and other symptoms.

Table 2. Possible signs and symptoms of acute infusion reactions [13]

Allergic reaction/hypersensitivity (including drug fever)
Pruritus/itching
Rash/desquamation
Urticaria (hives, welts, wheals)
Rigors/chills
Headache
Arthralgia/myalgia
Tumor pain
Fatigue (asthenia, lethargy, malaise)
Dizziness
Sweating
Nausea/vomiting
Cough
Dyspnea
Bronchospasm
Hypotension/hypertension
Tachycardia

Incidence

The incidence of severe hypersensitivity reactions is low and remarkably similar among platinum compounds, taxanes, and monoclonal antibodies (Tables 3 and 4) [1, 4, 20–33]. The reported incidence of any grade hypersensitivity reactions to carboplatin or oxaliplatin is in the range of approximately 12%–19% [2, 7, 8, 23]. For paclitaxel and docetaxel, the reported incidences are about 8%–45% and 5%–20%, respectively [25, 26]. For monoclonal antibodies, mild-to-moderate reactions are also relatively common, particularly during the first infusion (40% with trastuzumab, up to 77% with rituximab, 16%–19% with cetuximab, and 5% with the fully human panitumumab) [18, 20, 21, 27].

Timing

The timing of hypersensitivity reactions varies among agents. Hypersensitivity reactions to platinum compounds typically occur only after multiple cycles of therapy [2, 4, 7, 8, 23]. Markman et al. [23] reported that the incidence of hypersensitivity reactions to carboplatin was 27% in patients with gynecologic cancers receiving seven or more courses of carboplatin, compared with only 1% in patients who received fewer than seven courses. This is consistent with type 1 hypersensitivity reactions, which are associated with repeated exposure to the agent [5].

In contrast, nearly 95% of all reactions to taxanes occur during the first or second infusion, suggesting a non–IgE-mediated mechanism [1, 5, 11]. These reactions occur rapidly, with up to 80% of patients developing

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Table 3. Incidence, management, and prevention of hypersensitivity reactions (HSRs) in select platinum compounds and taxanes

Drug	Severe HSR incidence (%)	Description	Prevention/prophylaxis	Management
Carboplatin [22, 23]	2	Rash, urticaria, erythema, and pruritus; rarely, bronchospasms and hypotension. Can occur at any cycle, most occur after 6–8 cycles.	Contraindicated in patients with prior HSR to cisplatin or other platinum compounds. Risk is increased in patients with other drug allergies, including other platinum agents.	Epinephrine, corticosteroids, and antihistamines to alleviate symptoms.
Oxaliplatin [4, 24]	2–3	Rash, urticaria, erythema, and pruritus; rarely, bronchospasms and hypotension. Can occur at any cycle, most occur after 6–8 cycles.	Contraindicated in patients with known allergy to oxaliplatin or other platinum compounds.	Epinephrine, corticosteroids, and antihistamines to alleviate symptoms. May require discontinuation of therapy.
Paclitaxel [25]	2–4	Dyspnea, flushing, chest pain, tachycardia, hypotension, angioedema, and generalized urticaria. Generally occurs within the first hour of infusion.	Contraindicated in patients with prior HSR to paclitaxel or other drugs formulated in Cremophor® EL. Premedicate with corticosteroids, diphenhydramine, and H_2 antagonists.	Severe reactions (hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, generalized urticaria) require immediate discontinuation and aggressive symptomatic therapy; do not rechallenge. Minor symptoms of flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require treatment interruption.
Docetaxel [26]	1–3	Rash/erythema, hypotension, and/or bronchospasms. Can occur within the first few minutes of infusion.	Contraindicated in patients with prior HSR to docetaxel or polysorbate 80. Premedicate with corticosteroids. Close observation recommended, particularly during the first and second infusion.	Severe reactions require immediate discontinuation of infusion and appropriate supportive therapy; do not rechallenge. Minor reactions (flushing, localized skin reactions) do not require treatment infusion interruptions.

Abbreviation: HSR, hypersensitivity reaction.

symptoms within the first 10 minutes of the infusion [1, 34]. Similarly, infusion reactions to monoclonal antibodies occur primarily during the first infusion [20, 21, 27, 30]. Approximately 90% of severe infusion reactions with cetuximab were observed during the first infusion [20]. For rituximab, the incidence of any-grade infusion reactions during the first, fourth, and eighth infusion was 77%, 30%, and 14%, respectively [27]. This rate of 10%–30% of delayed events in subsequent doses indicates the importance of close monitoring following administration of any infusion.

Management of Hypersensitivity and Infusion Reactions

Current attempts to identify patients who are likely to develop hypersensitivity have met with limited success [23, 33]. General factors that increase the likelihood of experiencing a type 1 hypersensitivity reaction have been identi-

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Table 4. Incidence, management, and prevention of IRs in select monoclonal antibodies

Drug	Severe IR incidence (%)	Description	Prevention/prophylaxis	Management
Chimeric				
Rituximab [27, 28]	<10	Urticaria, hypotension, angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Most severe reactions occur 30–120 minutes after starting first infusion.	Epinephrine, antihistamines, glucocorticoids, i.v. fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available. Close monitoring during all infusions for patients with pre-existing cardiac and pulmonary conditions, prior clinically significant cardiopulmonary adverse events, or high numbers of circulating malignant cells (≥25,000/mm^3). Contraindicated in patients with known hypersensitivity to murine proteins.	Interruption of infusion, supportive care (i.v. fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, acetaminophen) and monitoring until symptoms resolve. Rechallenge with 50% reduction in infusion rate can be considered. Most patients with non–life-threatening reactions are able to complete the full course of therapy.
Cetuximab [20]	3	Rapid onset of airway obstruction (bronchospasms, stridor, hoarseness), urticaria, hypotension, and/or cardiac arrest. Ninety percent of severe reactions occur during first infusion.	Premedicate with diphenhydramine. Epinephrine, corticosteroids, i.v. antihistamines, bronchodilators, and oxygen should be available. Patients should be observed for 1 hour after infusion. Use with caution in patients with known HSR to cetuximab or murine proteins.	Severe reactions require immediate interruption of infusion and discontinuation of therapy, symptomatic treatment, and monitoring until symptoms resolve. Mild-to-moderate reactions require infusion interruption until symptoms resolve; subsequent infusions can be given with a reduced infusion rate (50%) and premedication (e.g., diphenhydramine).
Humanized				
Trastuzumab [21, 29]	<1	Anaphylaxis, urticaria, bronchospasms, angioedema, and/or hypotension. Symptoms mostly occur during infusion (many within the first 2 hours) or within 24 hours.	Not reported.	Treatment interruption, supportive therapy (epinephrine, corticosteroids, diphenhydramine, oxygen, i.v. fluids), and monitoring until symptoms resolve. Discontinuation should be strongly considered for patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome. Rechallenge with premedication (antihistamines and/or corticosteroids) is successful in some patients.

(continued)

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Table 4. (continued)

Drug	Severe IR incidence (%)	Description	Prevention/prophylaxis	Management
Bevacizumab [30]	<1	Hypertension, hypertensive crises associated with neurological signs and symptoms, wheezing, oxygen desaturation, grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis.	Not reported.	Treatment interruption and supportive therapy. Adequate information on rechallenge is not available.
Alemtuzumab [31]	Not reported	Hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash.	Premedicate with diphenhydramine and acetaminophen. Contraindicated in patients with known hypersensitivity to alemtuzumab.	Antihistamines, acetaminophen, antiemetics, meperidine, and corticosteroids were used to prevent or ameliorate infusion-related events.
Panitumumab [32]	0.1	Anaphylactic reaction, bronchospasm, fever, chills, hypotension.	Not standardized in clinical trials.	Mild-to-moderate events require reductions in infusion rate by 50%. Severe events require immediate and permanent discontinuation of treatment.

Abbreviations: HSR, hypersensitivity reaction; IRs, infusion reactions.

fied [5]. These factors include repeated exposure to the agent and a history of drug hypersensitivity, particularly if related to a drug of the same chemical class (e.g., carboplatin and oxaliplatin). Intravenous administration is associated with a higher risk for type 1 hypersensitivity, although reactions can occur after administration by any route. The clinical implications of these risk factors and their applicability to agents that cause non–IgE-mediated reactions are not fully understood [23, 33].

Prevention

Pharmacological prophylaxis with antihistamines, corticosteroids, or both is generally recommended to reduce the frequency and severity of hypersensitivity reactions (Tables 3 and 4) [1, 11, 35]. For example, standard premedication for paclitaxel includes dexamethasone, diphenhydramine, and an H_2 antagonist (cimetidine, famotidine, or ranitidine), although other simplified approaches have been used successfully [11, 36]. Premedication with diphenhydramine is recommended before each infusion of cetuximab [20]. Timoney et al. [37] recently reported that premedication can be safely discontinued after the first infusion of cetuximab if no hypersensitivity reaction is observed. At University of Southern California (USC), diphenhydramine is often replaced by loratadine, a nonsedating antihistamine, in patients who do not experience an infusion reaction during the first infusion of cetuximab.

Patients should be monitored closely during and immediately after all infusions. Particularly close monitoring is warranted when the risk of hypersensitivity reactions is higher, such as during the first infusion of taxanes or monoclonal antibodies or after multiple cycles of platinum therapy. Vital signs should be checked before, during, and after the infusion [5]. The possibility of a delayed reaction, which may occur hours or days after an infusion, should also be considered. In addition to careful monitoring, patients should be strongly encouraged to notify a clinician immediately if they notice any discomfort during the infusion.

Hypersensitivity reactions are unpredictable and can occur at any time, despite preventive measures. Therefore, clinicians should be prepared for a reaction to occur during each administration [1]. Standing orders should be in place to allow immediate intervention if a reaction occurs, without waiting for a physician [5]. A "crash cart" with the resources needed for resuscitation should be readily available. This includes not only pharmacological agents such as epinephrine and aerosolized bronchodilators, but

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also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator. Sufficient medical resources should be available to sustain a patient who experiences a severe infusion reaction until they can be admitted [38].

Management

Prompt recognition and immediate medical attention are essential to reducing the risk of severe symptoms [3]. Oncology nurses administering medication should have a protocol on hand that outlines the emergency management of hypersensitivity reactions [5]. At USC, for example, we have developed standing orders that include specific interventions for symptoms of hypersensitivity (Fig. 1). These protocols allow for immediate intervention by the nursing staff if a reaction occurs, without waiting for a physician. When an infusion reaction occurs, the infusion should be interrupted and supportive care should be administered until the symptoms resolve. In most cases, mild-to-moderate reactions will resolve after a brief infusion interruption and the administration of supportive care.

Most patients who experience a mild-to-moderate reaction (grade 1 or 2) during the first exposure, such as those often seen with taxanes and monoclonal antibodies, will tolerate readministration of the agent using a slower infusion rate and premedication after all symptoms have resolved [1, 6, 11, 14, 20, 27, 39]. Rechallenge is generally discouraged in patients who have a severe initial reaction (grade 3 or 4), underscoring the need for accurate grading of hypersensitivity reactions and infusion reactions (Table 1). Premedication for rechallenge typically includes antihistamines and corticosteroids [6]. For monoclonal antibodies, reducing the infusion rate by half (e.g., from 100 mg/hour to 50 mg/hour for rituximab or from a maximum rate of 5 ml/minute to 2.5 ml/minute for cetuximab) is recommended [20, 27]. Desensitization protocols have been used with some success in patients who experience severe hypersensitivity reactions to taxanes [9, 11, 39].

Mild-to-moderate reactions to platinum compounds generally do not require treatment discontinuation [7]. Many patients can continue therapy or be rechallenged after symptoms have resolved using pretreatment with antihistamines and corticosteroids [4, 5, 7, 23]. However, rechallenge with platinum compounds is generally less successful than with taxanes: approximately 50% of patients rechallenged with platinum compounds experience recurrent hypersensitivity reactions despite premedication [1].

Similar to taxanes, desensitization protocols modifying infusion times have been used with success to reduce the risk of a second reaction to platinum agents [2, 4, 8, 40]. Some of these protocols are based on reinstating treatment at a low concentration and progressively increasing the concentration of the drug by administering a sequence of serial dilutions (i.e., $1{:}10^4$, $1{:}10^3$, $1{:}10^2$, 1:10), over extended infusion periods. This approach has been successful in rechallenging patients who had experienced reactions to carboplatin and oxaliplatin. As those patients undergo safe infusions after a reaction, premedications can be used for subsequent doses [41].

MONITORING Vital Signs per Nursing Practice Standards Other: _____

- ❑ EPINEPHRINE 0.5 mg 1:1,000 solution i.m. prn for hypotension or airway obstruction symptoms. May repeat q 20 minutes x 1.
- ❑ DIPHENHYDRAMINE (Benadryl®) 50 mg IVP prn for signs/symptoms of hypersensitivity/anaphylaxis.
- ❑ HYDROCORTISONE _____ mg IVP prn for signs/symptoms of hypersensitivity/anaphylaxis.
- ❑ ALBUTEROL (Ventolin®) inhaler 2 puffs prn for breathing problems. May repeat q 4 hours.

Figure 1. University of Southern California standing order for the management of hypersensitivity reactions.

Abbreviations: IVP, intravenous push; prn, as needed; q, every.

In any circumstance, the decision to rechallenge with any agent should be based on several clinical factors, including the risk for a serious recurrent reaction and the potential clinical benefit of further treatment. For example, if the drug is given as salvage therapy or as palliative care, the long-term clinical benefits of continued treatment are likely to be small and may not warrant the risk for severe toxicity. In this case, switching to an alternative agent, if available, may be appropriate. However, continuing active treatment should be a priority for patients who have mild-to-moderate reactions, and strategies that safely allow continuation should be considered, particularly if the goal of therapy is to prolong survival. The decision to continue or discontinue treatment must be made on a case-by-case basis after weighing all of the relevant clinical factors. Accurate grading of hypersensitivity and infusion reactions, including distinguishing between moderate and more severe reactions, may be critical to determine the best treatment plan following resolution of symptoms.

Conclusions

Although severe reactions are rare, mild-to-moderate hypersensitivity or infusion reactions occur frequently with many commonly used systemic cancer therapies, including platinum compounds, taxanes, and monoclonal antibodies. The clinical symptoms of these reactions are remarkably similar, regardless of the type of agent or proposed mecha-

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nism. One important difference among these agents is the time of onset of symptoms. Hypersensitivity to platinum compounds typically develops after multiple cycles of therapy, suggesting that it is an acquired, anaphylactic reaction consistent with type 1 hypersensitivity. In contrast, reactions to taxanes and monoclonal antibodies are immediate, often occurring within the first few minutes of the first infusion, which suggests that these reactions occur by alternative mechanisms.

The risk for severe hypersensitivity reactions can possibly be reduced by checking for a history of drug allergies, adequate premedication, careful patient monitoring, and prompt intervention when signs of hypersensitivity occur. Accurate grading of reactions is essential in determining how to proceed with treatment. Mild-to-moderate reactions are managed by temporarily interrupting the infusion and administering supportive care for symptoms. Most patients can be safely rechallenged with the drug following complete resolution of symptoms using a reduced infusion rate, premedication, and/or a desensitization protocol. For severe reactions, the infusion should be stopped, supportive care should be provided, and, in most cases, treatment should be discontinued.

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Disclosure of Potential Conflicts of Interest

H.-J.L. has acted as a consultant for Bristol-Myers Squibb, Merck, ImClone, and Sanofi-Aventis, and has served as a Board member for Merck.

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