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Management of Infusion Reactions in Clinical Trials and Beyond

The US and EU Perspectives

ABSTRACT

Monoclonal antibodies have expanded our cancer-fighting armamentarium in both the United States and Europe. While in general, monoclonal antibodies are well tolerated and do not have significant overlapping side effects with traditional cytotoxic agents, severe infusion reactions (IRs)—sometimes severe enough to be life threatening—have been reported. The pathophysiology of severe infusion reactions associated with monoclonal antibodies is poorly understood, but mechanisms are beginning to be elucidated. Geographic differences in the incidence of IRs have become apparent. Understanding the risk, recognizing the signs and symptoms, and being ready to promptly manage severe IRs are key for the clinician to avoid unnecessarily discontinuing these effective anticancer agents and prevent potentially tragic consequences for their patients. To date, clinical trials have incorporated monoclonal antibodies into combinations with standard cytotoxic regimens; it is expected that in time clinical trials will be testing promising new combinations utilizing multiple targeted agents, resulting in improved toxicity profiles and efficacy for cancer patients.

Infusion reactions (IRs) can be broadly categorized by their immunologic mechanism. Anaphylaxis is a systemic, immediate hypersensitivity reaction mediated by factors released from interactions between immunoglobulin E (IgE) and mast cells that produce an antigen-antibody reaction.[1] Anaphylactoid reactions can be differentiated from anaphylaxis by the fact that they are not IgE-mediated but rather cytokine-mediated.

Despite the mechanistic disparities, there are no significant differences in clinical manifestations from both reactions and the immediate management of both reactions is the same. They can involve cutaneous, respiratory, gastrointestinal, or cardiovascular systems. Both terms are often used interchangeably in the literature when describing severe infusion reactions. One

difference, however, is that patients who experience cytokine-mediated anaphylactoid reactions, which are commonly less severe, can be rechallenged using stronger premedications and slower infusion rates.

Most infusion reactions occur rapidly, but not all; in general, the more rapid the onset is, the more severe the reaction.[2] The fatal outcome can occur rapidly. Therefore, realizing the risks and recognizing the early signs and symptoms is crucial in the management of severe infusion reactions.

The United States Experience

Infusion Reactions With Cytotoxic Agents

Infusion-related reactions have been noted with the administration of a number of commonly used cytotoxic

agents, such as the platins and taxanes: carboplatin, oxaliplatin (Eloxatin), paclitaxel, and docetaxel (Taxotere). The incidence of reactions with these agents is variable, some occurring with the first dose (paclitaxel) and others after multiple administrations (oxaliplatin) (Paraplatin package insert, 2007; Eloxatin package insert, 2008; Taxol package insert, 2007).[3]

Infusion Reactions With Earlier MoAbs

Rituximab (Rituxan), a chimeric anti-CD20 monoclonal antibody, is associated with IRs in up to 85% of patients in some reports. Serious reactions, including bronchospasm,

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Table 1

Monoclonal Antibodies and Characteristics of Infusion Reactions in the United States

Monoclonal Antibody	Indication	Target	Type	Incidence of Grade 3/4 IR	Time Course
Trastuzumab	HER2+ breast cancer	HER2	IgG1 Humanized	< 1%	Most during first administration, all within 24 h
Rituximab	B-cell NHL, CLL, rheumatoid arthritis	CD20	IgG1 Chimeric	7%	80% with first administration, then declines; occurs within 30 to 120 min of infusion initiation
Cetuximab	Squamous cell head and neck cancer, colorectal adenocarcinoma	EGFR	IgG1 Chimeric	2%–5%	> 90% occur within 15 min of starting first infusion; geographic differences related to preformed IgE
Panitumumab	Colorectal adenocarcinoma	EGFR	IgG2 Fully human	< 1%	Most during first administration
Bevacizumab	Colorectal adenocarcinoma, NSCLC	VEGF	IgG1 Humanized	0.2%	Vast majority with first dose

CLL = chronic lymphocytic leukemia; EGFR = epidermal growth factor receptor; IR = infusion reaction; NHL = non-Hodgkin's lymphoma; NSCLC = non-small-cell lung cancer; VEGF = vascular endothelial growth factor.

angioedema, myocardial infarct, arrhythmias, and acute lung injury were also reported in 2% to 10% of patients. Postmarketing experience reports fatal IRs in 0.04% to 0.07% of patients.

Severe reactions were more common in females, patients with pulmonary infiltrates, the elderly, and patients with chronic lymphocytic leukemia or mantle cell lymphoma.[4] These symptoms are more common and tend to be more severe during the first infusion, with time of onset being 30 to 120 minutes. The risk of a rituximab IR is significantly reduced after the first cycle (Rituxan package insert, 2008).[5] Although true anaphylactic or hypersensitivity reactions are reported, most of the reactions from rituximab are considered to be, at least partially, due to increased cytokine release.[4]

Trastuzumab, a recombinant DNA-

derived humanized MoAb used extensively in HER2/neu-positive breast cancer, is also associated with IRs with up to 40% occurring during the first infusion in patients experiencing these reactions.[6-9] Infusion reactions were observed less frequently with subsequent infusion of the antibody. Most reactions occur within 2 hours after the start of the infusion. Fatal IRs have been reported rarely. A retrospective study revealed that patients with dyspnea at rest or patients with predisposing malignancy-related pulmonary compromise are at a greater risk of developing fatal IRs.

Bevacizumab (Avastin), a recombinant humanized monoclonal IgG1 antibody that inhibits vascular endothelial growth factor (VEGF), is associated with IRs in less than 3% of patients (Avastin package insert, 2008).[10] Severe reactions were noted in 0.2% of patients. The efficacy of premedication is unclear; therefore it is not routinely administered.

Infusion reactions to earlier MoAbs are summarized in Table 1.

Infusion Reactions With Newer Agents

Severe cetuximab (Erbix) IRs are observed in approximately 3% of patients with fatal outcomes in 0.1% of patients. The majority, up to 90%, of severe reactions occur within minutes

of initiating the first dose of cetuximab despite routine use of premedication. Needle and colleagues reported that all grade 4 IRs occur within minutes of the first infusion, but less severe reactions could appear with the second or subsequent reactions, indicating a possible difference in mechanisms underlying mild and severe IRs. In clinical trials, grade 3 to 4 IRs occurred in 2% of patients with cetuximab monotherapy. Approximately 25% of patients experience IRs of all grades with cetuximab (Erbix package insert, 2008).[11,12]

Panitumumab (Vectibix) is a fully human IgG2 monoclonal antibody that in a randomized phase III trial was shown to improve outcomes when added to best supportive care in patients with chemotherapy-refractory metastatic colorectal cancer. In phase I to III trials, panitumumab was safe and well tolerated, with most of its adverse effects related to some form of skin toxic effect. In the randomized trial, infusion-related reactions of all grade occurred in less than 1% of patients. No patients experienced grade 3 to 4 reactions.

Across clinical trials including 1,336 patients, 3% of patients experienced IRs of all grades and severe reactions were extremely rare, occurring in approximately 1%. A fatal

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Table 2

Grading of Hypersensitivity Reactions According to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0*

	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 ± 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 (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≥ 24 h	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion), recurrence of symptoms following initial improvement, hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening, pressor or ventilatory support indicated	Death

NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs.

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case of angioedema occurring 2 days after panitumumab administration has recently been reported (personal communication, Dr. Volker Wagner, Amgen, Inc). The proposed low immunogenicity of panitumumab was also supported by immunoassays designed to detect antipanitumumab antibodies. In approximately 1% of patients, serum tested positive for neutralizing antibodies (Vectibix package insert, 2008).[13-15]

Clinical Manifestations and Grading

Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap. However, certain criteria have to be fulfilled to categorize a reaction as an HSR or IR (see Table 2 in the article by Drs. Gleich and Leiferman that begins on page 7 of this supplement).

Currently, most oncologists use the National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events v3.0 (Table 2).[16] The NCI-CTC distinguish between hypersensitivity reactions and acute infusion reactions induced by cytokine release. 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 bronchospasm and hypotension requiring treatment, cardiac dysfunction, anaphylaxis, and other symptoms.

There are inconsistencies in the grading criteria, and the time points for what are truly anaphylactic reactions are not fully defined, such as whether symptoms develop within 24 hours or beyond. In addition, the condition defining a grade 3 reaction in the current CTC system includes an association with the use of any parenteral medication. This needs to be reevaluated because most patients will be receiving IV medications at the earliest sign of allergy. Current grading does not allow differentiating between any type of reaction vs anaphylaxis. To correct this disparity, it is prudent to separate grading criteria for IgE and non-IgE anaphylaxis.

Host Factors

There is a need for better risk stratification. Identification of risk factors for severe IR will help clinicians to reduce the incidence and prevent more IRs. Atopic patients are generally at

higher risk of developing anaphylactic reactions.[17] Female gender, older age, history of pulmonary infiltrates, dyspnea at rest, malignancy-related pulmonary infiltrates, and chronic lymphocytic leukemia and mantle-cell lymphoma have been identified as risk factors for severe IR in previous experiences with rituximab and trastuzumab.[5,9]

One peculiar aspect of cetuximab-associated infusion reactions in the United States is the markedly regional differences in incidence. O'Neil and colleagues confirmed an anecdotal observation that patients in specific regions of the southeastern United States treated with cetuximab-containing regimens in clinical trials at three institutions had a 22% frequency of grade 3 to 4 hypersensitivity.[17] There was no association between race or gender and the risk of experiencing an IR. All reactions occurred during the first dose and despite the use of prophylactic use of H₁ antagonists. Glucocorticoid

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Table 3

Rates of Infusion-Related Reactions During Monoclonal Antibody Infusions Reported From European Cancer Trials

Monoclonal Antibody	Tumor	Chemotherapy Combination/ Single Agent	Study Phase	Sample Size	Toxicity Grade			Reference
					1/2	3/4	5	
Chimeric								
Cetuximab	Gastric	Oxaliplatin/5-FU	II	52	0	0	1 (2%)	Lordick 2007[22]
	Esophageal	Cisplatin/5-FU	II	32	0	0	0	Lordick 2008[23]
	Colorectal	Oxaliplatin/5-FU	II	77	NR	5 (6%)	0	Ciuleanu 2008[24]
	Colorectal	Irinotecan/5-FU	II	74	NR	1 (1%)	0	Ciuleanu 2008[24]
	Gastric	Irinotecan/5-FU	II	38	0	0	0	Pinto 2007[25]
	Colorectal	Oxaliplatin/5-FU	II	43	6 (14%)	1 (2%)	0	Tabernero 2007[26]
	Colorectal	Oxaliplatin/5-FU	I/II	49	NR	3 (6%)	0	Arnold 2008[27]
	Rectal	CapOx-RT	I/II	48	5 (10%)	1 (2%)	0	Rödel 2008[28]
Lung	Cisplatin/vinorel- bine	II	43	NR	1 (2%)	0	Rosell 2008[29]	
Humanized								
Matuzumab	Pancreas	Gemcitabine	I	17	0	0	0	Graeven 2006[30]
	Lung	Paclitaxel	I	18	1 (5%)	0	0	Kollmannsberger 2006[31]
Trastuzumab	Various	Single agent	I	22	0	0	0	Vanhoefter 2004[32]
	Breast	Docetaxel	III	54	13.5%	5.8%	0	Joensuu 2006[7]
	Breast	Vinorelbine	III	61	10%	0	0	Joensuu 2006[7]
	Breast	Single agent	III	3,388	NR	NR	0	Piccart 2005[6]
Bevacizumab	Breast	Docetaxel	II	92	NR	1 (1%)	0	Marty 2005[9]
	Colorectal	CapOx	III	197	15 (8%)	6 (3%)	0	Tol 2008[33]
	Colorectal	CapOx	II	56	NR	0	0	Gruenberger 2008[34]
Fully Human								
Panitumumab	Colorectal	Single agent	III	229	1 (0.4%)	0	0	Van Cutsem 2007[13]
	Colorectal	Single agent	NA	176	1 (0.5%)	0	0	Van Cutsem 2008[35]
	Colorectal	Oxaliplatin/5-FU	III	903	4 (0.4%)	0	0	Siena 2008[36]
	Colorectal	Irinotecan/5-FU	III	1,097	3 (0.3%)	0	0	Peeters 2008[37]

CapOx = capecitabine/oxaliplatin; 5-FU = fluorouracil; NA = not available; NR = not reported; RT = radiation therapy.

administration prior to MoAb infusion did not prevent the allergic reaction. Furthermore, investigation into specific patient records demonstrated that a personal phenotype of atopy to

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a variety of other environmental and pharmaceutical agents was present in the majority of those who experienced cetuximab reactions. This phenomenon has also been observed in nearby South Carolina, northern Georgia, Arkansas, and Missouri, suggesting an exposure to an environmental antigen that cross-reacts with cetuximab in this geographic region.

Preexisting immunoglobulin IgE was initially postulated to cross-react with the amino acid mouse region of the cetuximab molecule; however, subsequent analysis has revealed IgE specific for galactose- α -1,3-galactose on both Fab segments of the heavy chain.[18] As a consequence of this complication, the utilization of cetuximab in these geographic regions has

been adversely affected, particularly when an alternative therapeutic agent is available.

An assay to prescreen patients being considered for treatment with this cetuximab has been developed (ImmunoCAP) and is currently being evaluated for approval by the US Food and Drug Administration. This assay is not expected to be necessary for all regions of the United States, nor will it capture all patients at risk for IRs. Cytokine-mediated IRs (ie, non-IgE-mediated) will still occur. In association with a thorough clinical history investigating prior atopy as well as an assessment of potential drug alternatives, the assay may, however, be clinically useful to significantly reduce the likelihood of this adverse event in IR endemic areas.

Another result of certain geographic regions in the United States carrying much higher risk of IRs is the clinical use of heavier premedication regimens, including H_1 and H_2 blockers and corticosteroids, by physicians practicing in high-risk areas. Although this practice may reduce the severity of cytokine-mediated reactions, it is not expected to affect IgE-mediated reactions.

A recent retrospective study presented at the 2008 annual meeting of the American Society of Clinical Oncology investigated the risk factors associated with IRs with cetuximab.[19] Data regarding demographics and premedication history were collected from 51 colorectal cancer patients (27 males and 24 females) and 50 head and neck cancer patients (38 males and 12 females) who were treated with cetuximab. Seventy (69.3%) patients were Caucasian and 31 (30.7%) were African-American.

All patients were premedicated with diphenhydramine prior to cetuximab administration. Data regarding famotidine, dexamethasone, and hydrocortisone sodium succinate (A-Hydrocort, Solu-Cortef) premedication were available for 84 patients. Of these, 14 (16.7%) received famotidine, 32 (38.1%) received dexamethasone, and 25 (29.8%) received hydrocortisone sodium succinate. Twenty-four patients (48%) with head and neck cancer also received albuterol.

Eleven patients (10.9%) developed hypersensitivity reactions (HSRs). Serious grade 3/4 HSRs were seen in nine patients (8.9%). Race was strongly associated with HSR. All 11 patients who developed HSRs were Caucasian (Fisher's exact $P = .017$). No grade 3/4 HSRs were seen in the group who received albuterol (Fisher's exact $P = .077$). There were no statistically significant effects of premedication with dexamethasone, famotidine, or hydrocortisone sodium succinate on the risk of HSR, although the small numbers were limiting. Age and gender also had no effect on the risk of HSR. The authors concluded that race is a strong predictor for HSR. The authors also suggest that additional premedication with albuterol may prevent grade 3/4 HSRs.

One additional consequence of monoclonal antibody-related IRs in the United States is how these agents have been incorporated into treatment combinations using cytotoxics, rather than using MoAbs as single agents. If a given patient is unexpectedly intolerant of the targeted agent, the remaining drugs can be continued. This also fits the oncologic paradigm of using agents with different mechanisms of action together with the expectation of higher tumor response rates and avoiding overlapping toxicity.

Timing

The observed IR to monoclonal antibodies occurs primarily during the first infusion. Approximately 90% of severe infusion reactions with cetuximab were observed during the first infusion (Erbitux package insert, 2008). The rate of delayed events in subsequent doses ranges from 10% to 30%, indicating the importance of close monitoring following administration of any infusion.

Premedication

There seems to be a consensus among oncologists that premedication with an antihistamine should be administered prior to the cetuximab loading dose and first weekly dose. It remains debatable whether routine use of antihistamines is beneficial prior to each subsequent dosing. A recent report by Timoney and associates suggests that administration of

cetuximab without diphenhydramine premedication does not increase risk of severe IRs.[20]

The European Union Experience

No obvious differences in the incidence of infusion-related reactions have thus far been reported within Europe. Such differences may exist, however, since the incidence of atopy and allergic asthma has been shown to be heterogeneously distributed over Europe. Significantly higher prevalence of atopy and allergic asthma were observed in the early 1990s among populations living in Western compared with populations in Eastern European countries. Changes in lifestyle after the fall of the communist system were associated with an increasing trend of atopic sensitization and hay fever in former East Germany only 6 to 8 years after the Germany reunification.

The increased prevalence of allergic asthma decades earlier in Western Europe than Eastern Europe is probably attributable to changes in lifestyle that had already occurred rather than to air pollution. The factors of a Western lifestyle (diet, hygiene, varied allergen exposure) that have determined the difference in allergic asthma prevalence across Europe are not yet fully identified.[21] Whether the heterogeneous distribution of atopy across Europe translates into regional differences in infusion-related reactions is not yet known, but does certainly merit further investigations.

Rates of Mild and Severe IRs in the European Union

In European cancer studies, different rates of monoclonal antibody infusion-related reactions have been reported, as delineated in Table 3. Infusion-related reactions tended to be more commonly reported in trials where chimeric antibodies were given and appear to be less common when the structure of the administered antibody has more homology with the human protein. Adverse events with a fatal outcome are very rare. Nevertheless, there was a large difference in the reported IR incidence rates from different clinical trials. It is not known,

whether this is due to regional differences, differences in premedication, or differences in the documentation and reporting of infusion-related adverse events and reporting.

Perspectives From the Clinic

With the increasing use of monoclonal antibodies in treating cancer in Europe, infusion-related reactions will be an increasing concern in the management of patients. European investigators should try to assess whether regional differences exist and whether specific factors associated with an increased risk for infusion-related reactions, such as history of atopy or specific preexisting IgE antibodies can be identified.[17,38] The importance of documentation and reporting of infusion-related reactions occurring within clinical trials and during routine administration should be reinforced.

With the use of chimeric and humanized antibodies, most centers in Europe give combined pharmacologic blockade of the histamine-1 and histamine-2 receptors as premedication to reduce the probability or severity of an infusion-related reaction. This is an empiric approach and it is not clear how efficacious or for which patients this strategy is indicated.

In view of the increasing economic pressure that is put on treating physicians and institutions, time spent in the preparation and the administration of premedication and the observation of the patients postinfusion should also be considered in future pharmacoeconomic analyses comparing treatment strategies with and without monoclonal antibodies or treatments with different monoclonal antibodies.

Diagnostic Tools

Even with our best efforts, some IRs are unavoidable when using monoclonal antibodies therapeutically. Therefore, clinicians must accurately analyze the nature and severity of the reactions to avoid repeat reactions and to assess the feasibility of rechallenging a reacting patient with the reaction-associated agents.

• **Blood and Urine Tests**—Timely measurement of urine histamine levels or serum tryptase levels can

confirm the diagnosis of anaphylaxis, rather than relying on clinical signs and symptoms. This provides a more accurate assessment for physicians to use as a basis when formulating a subsequent treatment plan.[39]

• **Test Doses**—A lack of reaction to test doses of 20 mg of cetuximab is not a reliable predictor of severe infusion-related reaction. No data are yet available to identify patients more likely to have severe reactions to cetuximab infusion.

Rechallenge

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.

Continuing active treatment, however, 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.

• **Challenge With Panitumumab in Patients Who Developed IRs to Cetuximab**—Scarce data are available on the safety of panitumumab in patients who developed IRs to cetuximab.[40-42] One anecdotal report published in May 2007 described a 53-year-old male with metastatic colorectal cancer who was pretreated with diphenhydramine before receiving an infusion with cetuximab.[40] During the infusion, the patient developed an HSR, infusion was stopped, and the patient was treated with diphenhydramine at 50 mg and dexamethasone at 4 mg. The patient was switched to panitumumab at 6 mg/kg and began treatment 5 weeks

after his reaction to cetuximab. He received one dose every 2 weeks and completed six doses of panitumumab without premedication and without incident, before experiencing further disease progression. A decision was made by the patient and his family to cease active therapy and he was referred to hospice.

A similar case describes a 39-year-old white male with metastatic colorectal cancer who received cetuximab monotherapy as third-line treatment and experienced an IR with massive facial urticaria within 5 minutes, despite premedication with dexamethasone, clemastine fumarate, and ranitidine.[43] A second attempt was made at a reduced infusion rate 90 minutes later with the same response. No subsequent cetuximab was given. The patient was premedicated with cetirizine and given panitumumab. No IR occurred. The patient received a total of six infusions of panitumumab every 2 weeks. Personal experience shows a similar response, demonstrating a decrease in the incidence of severe IRs to panitumumab, but requiring no premedication, when switched to cetuximab. The most severe reaction to panitumumab presented as a grade 2 acneiform rash.

Recently a report was presented on three patients who underwent successful rechallenge with panitumumab following grade 3 hypersensitivity reactions to cetuximab.[44] These patients were challenged with a standard dose of panitumumab (6 mg/kg), after experiencing grade 3 IRs with prior cetuximab, under strict observation and no premedication. The first patient, a 58-year-old male with metastatic colorectal cancer, developed grade 3 IR during his eighth dose of cetuximab. The second patient was a 58-year-old female with metastatic colorectal cancer who developed a grade 3 IR during her 12th dose of cetuximab. The third patient was a 61-year-old male with pancreatic cancer who experienced a grade 3 IR during administration of the loading dose of cetuximab. All patients were Caucasians with an average age of 59 years and no history of prior allergy. No patient received any premedication. The first patient received panitumumab for 2 months; the second patient was treated for 6 months; and the third patient, who was rechallenged

1 week after the IR to cetuximab, had a partial response following 6 months of therapy.

Desensitization

Often, a patient has limited therapeutic alternatives if standard treatments cause a hypersensitivity reaction. Therefore, the ability to safely retreat a patient with an agent that previously led to an adverse event could be clinically useful.[45] There are multiple anecdotal reports of successful uses of desensitization protocols after severe IRs from cetuximab in the literature. Graded challenge, which gradually increases the dose until the targeted dose is reached, may be appropriate to avoid repeat reaction that may be fatal.[46]

Although anecdotal reports suggest successful challenge with panitumumab following IR with cetuximab,[44] the safety of cetuximab after IR with panitumumab is not known. We recently reported two patients who were successfully desensitized after IR with cetuximab and safely retreated with panitumumab and cetuximab.[46] Both patients were premedicated with 50 mg of oral prednisone 24, 12, and 3 hours prior to receiving cetuximab, and with 50 mg IV diphenhydramine and 20 mg IV famotidine prior to cetuximab. They then received a desensitization protocol for cetuximab after a test dose of 20 mg IV over 10 minutes, followed by a slow infusion at 10% of the original rate for 2 hours, followed by 25% of the original rate in the interval between 2 and 2.5 hours, then a 50% reduced rate between 2.5 and 3 hours, and finally 100% of the infusion rate after 3 hours. The patients were observed for 4 hours after completion of infusion.

Our experience suggests that in cases where options are limited, such patients can be successfully retreated with cetuximab in a hospital setting with close monitoring after appropriate desensitization and premedication. Further studies focusing on desensitization and identifying hypersensitivity profiles of different anti-epidermal growth factor receptor antibodies are warranted.

How Should Patients Be Followed?

Biphasic reactions may occur in up to 20% of patients experiencing

anaphylactic reactions. Therefore, an observation period with close monitoring is indicated even after symptoms resolve. The reported time intervals between the initial reaction and the second-phase reaction may extend up to 72 hours. Thus, close monitoring of patients who have experienced a severe infusion-related reaction is advisable.[47]

Effect of Monoclonal Antibody IRs on Clinical Trials

Two potential conflicts arise when monoclonal antibodies are incorporated into clinical trials. The first is the potential dilemma in intent-to-treat efficacy results. This could create problems in evaluating phase III randomized trials after a number of patients demonstrate grade 3 or 4 IRs that preclude them from being rechallenged with a monoclonal antibody. Should patients be prescreened for hypersensitivity before trial enrollment using a test dose? Should these patients be excluded from final efficacy results? Certainly this is not a significant issue if IRs are either low in incidence or not severe and can be rechallenged. This problem has not been systematically evaluated, nor have consensus opinions for future trials been developed.

The second potential conflict concerns those geographic areas endemic to high rates of IRs. Should these regions be excluded, expecting that 20% to 25% of patients enrolled in trials in those areas will not complete therapy? Could future trials delay patient enrollment in these facilities until reliable assays could prescreen their patients for preformed IgE? Could a prior history of atopy in individual patients be acceptable for exclusion? Again, no consensus has been developed; at the present time clinicians must use their own experience and training to determine which patients are appropriate for any given trial incorporating monoclonal antibodies in the regimen.

Conclusions

Monoclonal antibodies are important new therapeutic tools for treating many different types of cancers; these agents are often used along with cytotoxic chemotherapy. It appears that humanized and fully human antibodies engender anaphylaxis less often than do agents

that contain mouse derived sequences.

Clinicians, patients, and nurses should be alert to the early signs of anaphylaxis such as sneezing, tachypnea or tachycardia, dyspnea, or a sense of impending illness. Because of geographic variations in the incidence of severe IRs, patients who live in or have lived in the southeastern United States should be observed with special vigilance. When such severe adverse events occur, rapid use of epinephrine and discontinuation of the antibody infusion are vital. Patients should have blood and urine tests to determine if the reaction is IgE mediated. If the reaction is consistent with an IgE-mediated event, then rechallenge with the same agent should only be contemplated in a circumstance where immediate observation and intervention are available.

Some patients can be desensitized to allergens, including monoclonal antibodies. In the event that a patient reacts to cetuximab, there are anecdotal reports of subsequent safe use of the fully human monoclonal antibody panitumumab. In the near future, blood tests that will help to determine which patients are at high risk for these types of reactions may be available.

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