Infusion Reactions:
Diagnosis, Assessment, and Management

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Many cancer therapies administered by IV infusion, including monoclonal antibodies, have the potential for infusion reactions. All infusion reactions involve the immune system; however, some (anaphylactic) are allergic in nature and usually are mediated by immunoglobulin E (IgE), whereas others (anaphylactoid) are not true allergic reactions and are not mediated by IgE. Although reactions can be allergic or nonallergic, the clinical manifestations are the same and require prompt, accurate assessment and astute management to avoid severe adverse events, including fatality. Monoclonal antibodies have a unique side-effect profile that includes the potential for nonallergic infusion reactions caused by cytokine release. Understanding the pathophysiology underlying any infusion reaction will enhance decision making regarding rechallenge and thereby improve treatment outcomes. Rituximab is an example of a drug with the potential for varying types of infusion reactions. This article discusses oncology nurses' role in patient risk assessment, institution of prophylactic measures, administration monitoring, severity grading, management, and follow-up. This understanding will clarify new data regarding the safety of a rapid infusion schedule of rituximab.

Cancer therapies administered by IV infusion may cause infusion reactions. Infusion reactions always involve the immune system; however, some (often called anaphylactic) are allergic in nature and typically are mediated by immunoglobulin E (IgE), whereas others (anaphylactoid) are not true allergic reactions and are not mediated by IgE (Kemp, Lockey, & Simons, 2008). Regardless of whether the reaction is allergic or nonallergic, clinical manifestations are the same and require prompt, accurate assessment and astute management to prevent severe adverse events, which can include death. Understanding the pathophysiology underlying each infusion reaction will enhance decision making regarding rechallenge, thus potentially improving treatment outcomes.

Monoclonal antibodies are a valuable treatment component for many different types of cancers as well as nonmalignant disorders. Monoclonal antibodies also have a unique side-effect profile and generally are better tolerated than chemotherapy in the author's experience. A distinctive side effect of monoclonal antibodies is the potential for nonallergic infusion reactions caused by cytokine release. Less frequently, monoclonal antibodies can cause allergic infusion reactions. Although severe infusion reactions are rare, nurses must be familiar with these adverse events and know how to identify patients at particular risk and take preventive measures.

This article presents an overview of the pathophysiology of infusion reactions precipitated by monoclonal antibodies, particularly rituximab. Rituximab serves as an example of a drug

At a Glance

✦ Monoclonal antibodies have a unique potential for a non-allergic infusion reaction caused by cytokine release.

✦ Recognition and expert management of a cytokine-release reaction may enable patients to be rechallenged with the monoclonal antibody, potentially improving clinical outcome.

✦ The safety of rapid infusions of rituximab is under investigation, and initial findings of several trials reported that after successful first-cycle dosing according to manufacturer's protocol, subsequent doses may be delivered by rapid infusion.

with the potential for varying types of infusion reactions. Much clinical experience can be draw from rituximab because it was one of the first monoclonal antibodies. In addition, oncology nurses' role in patient risk assessment, institution of prophylactic

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measures, administration monitoring, severity grading, management, and follow-up will be defined. New data regarding the safety of a rapid infusion schedule of rituximab also will be examined.

Overview of the Immune System

Reviewing the body's immune response to a foreign substance is helpful to comprehend the origin of an infusion reaction. Essentially, the administration of any foreign drug is likely to elicit some response from the immune system; most often, the response is a minor, subclinical, and transient reaction. Serious symptoms or issues arise when the immune system overreacts (i.e., hypersensitivity), particularly if the immune response is very sudden and severe.

The immune response can be innate, adaptive, or both. An innate response is a nonspecific, rapid response and is the body's first line of defense. Innate immunity is present even prior to any exposure to the foreign substance and is not affected by exposure (Solomon & Komanduri, 2001). In contrast, the adaptive response is an acquired response that is more specific and involves memory. With adaptive immunity, each successive exposure to the foreign substance increases the defensive response of the immune system. Table 1 shows the different cells and chemical messengers involved in both systems, noting overlap.

Adaptive immune responses are directed by lymphocytes and are either humoral or cell-mediated. Two types of lymphocyte exist: B lymphocytes and T lymphocytes. B lymphocytes respond to extracellular foreign substances, whereas T lymphocytes respond to intracellular foreign substances (Solomon & Komanduri, 2001). Every B lymphocyte expresses a unique antibody designed to recognize a specific protein marker (i.e., antigen) located on the surface of foreign cells. The antibody binds with the antigen and so elicits an immune response, marking the cell for destruction. Each B lymphocyte produces daughter cells that will produce the same antibody as the parent; therefore, the term *monoclonal antibody* designates that the antibody was secreted from a particular clone of B lymphocyte.

Antibody-mediated cell destruction occurs in several different ways: recruiting the body's own immune function by triggering phagocytosis, disrupting the cell membrane causing cell lysis, or provoking binding of the foreign cell to specialized cells called natural killer cells. Antibodies also may alter receptors on the foreign cell surface, thus blocking important cell functions such as growth or cell death (apoptosis).

Five different kinds of antibody exist (see Table 2). IgE is the antibody most often involved in allergic reactions. An allergic response is an unnecessary adaptive response to a benign substance; typically, allergic responses increase in severity with each subsequent rechallenge. All antibodies have a characteristic shape and structure and look like a capital Y. The region responsible for binding to the specific target antigen is located on the upper part of the Y (two identical light chains) and is called the Fab (fragment, antigen binding) region. In contrast, the lower tail of the antibody (two identical heavy chains) contains the Fc (fragment crystallizable) region, which is responsible for eliciting a response to the bound antigen (e.g., by activating mast cells).

Cell-mediated immune responses are coordinated by specific T lymphocytes that release cytokines. Cytokines are proteins that serve as part of the innate and adaptive immune systems. Acting as messengers, cytokines coordinate immune and inflammatory responses (Rieger, 2001). In normal immune function, cytokines influence growth, mobility, and differentiation of immune cells and also enlist and activate inflammatory leukocytes (Solomon & Komanduri, 2001). Examples of cytokines that mediate inflammatory responses are interleukins, tumor necrosis factors, and interferons. Hematopoietic growth factors are another type of cytokine. Some cancer cells also may produce and secrete cytokines.

When naturally occurring cytokines are released during an inflammatory response (as with an infection), the body may experience fever, chills, headache, nausea, fatigue, and hypotension (Rieger, 2001). Synthetic cytokines (e.g., interleukin–2, interferons) used in the treatment of infection, autoimmune diseases, or cancer also may produce these symptoms (Vial & Descotes, 1995).

Monoclonal Antibodies

Kohler and Milstein (1975) developed a technique for producing monoclonal antibodies by fusing antibody-producing B lymphocytes (isolated from mice immunized with a specific antigen) with malignant myeloma cells. The resulting immortal mother cells are capable of replicating to give rise to identical or clonal daughter cells, with the capacity to produce the specific antibody of interest.

With Kohler and Milstein's (1975) technique, genetically engineered monoclonal antibodies can be made for any antigen. The antibodies are identical and specific and, therefore, are capable of targeted treatment. Monoclonal antibodies were first used in cancer in the 1980s; since then, considerable advances have been made and the agents, with or without combination treatments, are considered the standard of care for the treatment of many malignant and nonmalignant diseases.

To date, the U.S. Food and Drug Administration (FDA) has approved 21 monoclonal antibodies; nine (rituximab, trastuzumab, bevacizumab, cetuximab, panitumumab, alemtuzumab, gemtuzumab, tositumomab, and ibritumomab tiuxetan) are cancer therapies, each targeting a specific tumor antigen (Oldham & Dillman, 2008). Rituximab (Rituxan®, Genentech, Inc.) was the first monoclonal antibody approved specifically for cancer

Table 1. Innate and Adaptive Immune Systems

IMMUNITY	CELLS	MOLECULES
Innate	Natural killer cells Mast cells Basophils Dendritic cells Eosinophils Neutrophils Macrophages Monocytes	Cytokines Complement Acute phase proteins
Adaptive	B lymphocytes T lymphocytes	Cytokines Antibodies (immunoglobulins)

Table 2. Antibody Classes

CLASS	FUNCTION
IgA	Main antibody on mucosal surfaces (e.g., gut, respiratory tract, urogenital tract) Prevents pathogens from entering circulation Secreted in breast milk, providing immunity to nursing infants
IgD	Present in small amounts in circulation Involved in regulation of Ig synthesis Functions as an antigen receptor on unexposed B lymphocytes
IgE	Most important Ig in allergic reactions and immunity against parasites Promotes histamine release from mast cells and basophils
IgG	Responsible for most specific antibody reactions in adults May be passed from mother to fetus, which instills neonatal immunity
IgM	First antibody to be formed when B cells are activated, produced early in infection Neutralizes circulating pathogens and activates complement proteins

Ig—immunoglobulin

therapy in 1997; to date, the agent is the most widely used monoclonal antibody in oncology (Oldham & Dillman, 2008).

Rituximab

Rituximab is a genetically engineered chimeric antibody that consists of the variable light- and heavy-chain regions from the murine anti-CD20 antibody IDEC-2B8 and the human IgG1 (heavy-chain) and κ (light-chain) constant regions (Genentech, Inc., 2010; Maloney et al., 1994). Rituximab specifically targets B lymphocytes by recognizing the antigen (i.e., protein marker) CD20, which is found on their surface. The exact mode of action of rituximab is unclear, but the combination of several distinct mechanisms results in the elimination of cancerous B lymphocytes from the body, allowing a new population of healthy B lymphocytes to develop from lymphoid stem cells (Johnson & Glennie, 2003). Although rituximab affects all circulating B lymphocytes, the numbers of mature, normal lymphocytes are reduced only temporarily and return to previous levels after treatment completion. This process of regeneration can take from one to more than six months (Edwards et al., 2004; Maloney et al., 1994).

The Fc portion of rituximab is known to be involved in two processes: complement-dependent cytotoxicity (Reff et al., 1994) and antibody-dependent cytotoxicity (Maloney, Smith, & Appelbaum, 1996). The complement system is a biochemical cascade system that is part of the innate immune system and is ultimately responsible for targeted cell death. Rituximab is believed to bind directly with the complement factor C1q, thus initiating a process that eventually results in the lysis of circulating B lymphocytes (Reff et al., 1994). Antibody-dependent cytotoxicity is another immunologic process eventually resulting in cell death that typically involves activation of specific effector cells by antibodies. Effector cells (e.g., natural killer cells, macrophages) have Fc receptors, which recognize the Fc portion of rituximab (Maloney

et al., 1996). Once bound, the effector cells release cytotoxic substances, which result in death of the attached B lymphocyte (Maloney et al., 1996). Rituximab also is known to have more direct effects, such as upsetting the proliferation and differentiation of malignant B lymphocytes, interfering with the regulation of the cell cycle, and inducing a process known as apoptosis or programmed cell death (Li, Ayer, Lytton, & Deans, 2003; Mathas, Rickers, Bommert, Dorken, & Mapara, 2000; Riley & Sliwkowski, 2000; Shan, Ledbetter, & Press, 2000).

Rituximab has had a major impact on the management of patients with almost every type of B-lymphocyte malignancy (Bello & Sotomayor, 2007). Typically, rituximab is used in combination with chemotherapy for induction treatment and also may be used as a single agent for induction as well as postinduction treatment. For example, in indolent follicular lymphoma, the use of rituximab in combination with chemotherapy as a frontline treatment gives better overall survival, better complete responses, and better disease control than chemotherapy alone (Schulz et al., 2007). In aggressive lymphoma, the benefits associated with the addition of rituximab to the cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy regimen (R-CHOP) are significant and enduring (Coiffier et al., 2007). In chronic lymphocytic leukemia, rituximab has given similarly encouraging results (Hallek et al., 2008; Tam et al., 2008).

Infusion Reactions in Oncology

Most systemic cancer treatments are associated with infusion reactions of some kind. Signs or symptoms can occur during the infusion of a therapeutic agent or on the first day of administration. Clinical manifestations vary in severity and can include many different symptoms involving different body systems (see Table 3).

Generally, infusion reactions are either allergic reactions to foreign proteins (i.e., IgE-mediated allergic responses) and classed as type 1 hypersensitivity responses (Dillman & Hendrix, 2003; Lenz, 2007) or are non-IgE–mediated reactions. Non-allergic infusion reactions are complex; some that result from cytokine release are the most predictable side effects associated with all monoclonal antibodies that react with circulating blood cells (Dillman & Hendrix, 2003).

Chimeric antibodies are a combination of human and animal, often mouse, in which more than 50% of the antibody is human. In humanized antibodies, the human portion is much higher (more than 90%); fully human antibodies are 100% human. Although the development of humanized monoclonal antibodies has reduced the occurrence of human antimouse antibodies in patients, human antihuman antibodies can develop and infusion reactions can still occur. To date, a correlation between infusion reactions and the development of human antimouse antibodies or human antihuman antibodies has not been demonstrated (Lenz, 2007).

The risk for an infusion reaction associated with the use of monoclonal antibodies should be kept in perspective with the risk for infusion reactions associated with other oncologic agents. In general, the incidence of infusion reactions associated with monoclonal antibodies is similar to that associated with taxanes and platinum agents (Chung, 2008). Table 4 lists

Table 3. Signs and Symptoms of Hypersensitivity Reactions

BODY SYSTEM	CLINICAL MANIFESTATION
Cardiovascular	Chest pain, palpitations, hypotension, hypertension, tachycardia, bradycardia, arrhythmia, edema, ischemia or infarction, cardiac arrest
Central nervous system	Headache (throbbing in nature), dizziness, confusion, loss of consciousness
Dermatologic	Rash, pruritis, urticaria, flushing, local or diffuse erythema, conjunctival erythema and tearing, angioedema
Endocrine	Rigors, diaphoresis, fever, generalized feeling of warmth
Gastrointestinal	Nausea, vomiting, metallic taste, diarrhea, abdominal cramping and bloating
Genitourinary	Incontinence, uterine cramping or pelvic pain, renal impairment
Musculoskeletal	Arthralgias, myalgias, fatigue, tumor pain, hypotonia
Psychiatric	Anxiety, sense of impending doom
Respiratory	Cough, dyspnea, nasal congestion, rhinitis, sneezing, hoarseness, tachypnea, wheezing, chest tightness, hypoxemia, bronchospasm, reduced pulmonary expiratory flow, oropharyngeal or laryngeal edema, stridor, pulmonary infiltrates, cyanosis, acute respiratory distress syndrome

common oncologic agents and the risk for infusion or hypersensitivity reactions as given in the prescribing information. When comparing the numbers, immediate obstacles become apparent. Terminology differs between package inserts (e.g., allergic reaction, hypersensitivity, infusion reaction). What grading criteria were used to ascertain the severity of reaction often is unclear. Inserts are vague as to when the reaction occurred (i.e., during or following administration). With some agents, the incidence of reactions varies between tumor or disease types. Incidence also may vary according to agents administered concomitantly. Clearly, defining terminology is essential. Similar impediments often seen in clinical practice and medical literature include variation in terminology, inadequate documentation about the time of onset of the reaction, inconsistency in grading (or the use of "mild, moderate, or severe reaction"), lack of documentation about when the reaction occurred (i.e., first or subsequent infusion), recording of premedications (if any), and inadequate citation of management actions and effectiveness.

The inconsistencies present challenges to practicing clinicians. Inconsistent grading of infusion reactions may lead to a false assumption of higher or lower incidence of severe (grade 3 and 4) reactions than what actually occurs. Overestimating the grade of reaction may limit further treatment options for patients by denying any opportunity for rechallenge. In addition, underestimating the grade of reaction might result in inadequate vigilance and preparedness for a potential emergent situation (Lenz, 2007) or place patients at unnecessary risk if the decision to rechallenge is made.

The time that the infusion was initiated and the time the infusion reaction began should be documented. Lack of accurate documentation also can adversely affect patient outcomes. The information enables clinicians to understand the pathophysiology behind the reaction and determine whether the reaction was a true hypersensitivity or a cytokine-release reaction. Such knowledge facilitates informed decision making about the safety of subsequent infusions.

Although the timing of different types of infusion reactions may vary, initial signs and symptoms of cytokine release reactions and anaphylactic reactions often are identical. Initial management procedures also are similar. However, understanding the pharmacologic properties of the oncologic agent and the mechanisms of a reaction are imperative to adequate preparedness and skillful management.

Allergic Infusion Reactions

Any type of infusion reaction that is not mediated by IgE is called an anaphylactoid or a non-IgE–mediated reaction; most reactions to chemotherapeutic agents are IgE-mediated and are true allergic, type 1 hypersensitivities (Lenz, 2007; Zanotti & Markman, 2001). Allergic reactions are immediate and usually occur within minutes of exposure, although delayed reactions (10–12 hours after exposure) can arise. However, quicker onset of symptoms increases the severity of the reaction. During initial exposure, IgE antibodies are produced and bind to receptors on mast cells and basophils. With subsequent exposure, the target-fixed antibodies react to the antigen and trigger the production and release of mediators such as histamines, leukotrienes, and prostaglandins from mast cells in tissues and basophils in peripheral blood. The release of the mediators produces brisk smooth muscle contraction, vasodilation, fluid extravasation, and increased mucosal secretions, resulting in signs and symptoms noted in Table 3. Increased vascular permeability, a hallmark sign of anaphylaxis, may allow a transfer of up to 50% of intravascular fluid into the extravascular space within as few as 10 minutes (Lieberman et al., 2005). Death may occur from hypoxemia or shock (Brown, Mullins, & Gold, 2006).

Hypersensitivity reactions to drugs such as carboplatin, oxaliplatin, and L-asparaginase are considered type I hypersensitivity reactions. Hypersensitivity reactions typically occur only after multiple infusions (Lenz, 2007; Weiss, 1992). The risk for hypersensitivity reactions to carboplatin increases by the sixth infusion and appears to peak around the eighth infusion and declines thereafter (Sliesoraitis & Chikhale, 2005). Reactions to oxaliplatin occur more frequently after five cycles of therapy (Saif, 2006). Premedication may not prevent hypersensitivity to platinum agents, unlike with taxanes (Saif, 2006).

Reactions to taxanes are clinically similar to type I hypersensitivities but are believed to be anaphylactoid (Lenz, 2007) and caused by the direct effect of immune cells. Cremophor EL® (BASF Corp.) is a pharmaceutical vehicle for paclitaxel and consists of polyoxyethylated castor oil and ethanol. Cremophor EL is assumed to cause most hypersensitivity reactions to paclitaxel, initiating the direct release of histamines from circulating cells (Peereboom et al., 1993). Almost all taxane reactions occur early during the first or second infusion and progress rapidly.

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Table 4. Incidence of Reported Infusion and Hypersensitivity Reactions in Common Oncologic Agents

AGENT	OVERALL	GRADE 3–4
Carboplatin	2%[a]	–
Cetuximab	15%–20%, dependent on tumor type	3%[b]
Docetaxel	15%–33% in normal and elevated lactate dehydrogenase treated with premedications	2%
Oxaliplatin	5%–12%	2%–3%
Paclitaxel	41%	2%
Rituximab	77% first infusion, 30% fourth infusion, and 14% eighth infusion in malignant disease 27% first infusion in rheumatoid arthritis	10%
Trastuzumab	40% first infusion 3% allergic reaction	Less than 1%

[a] Listed as allergic reaction and not graded

[b] Higher incidence (up to 22%) was reported in certain areas of the United States, such as Tennessee and North Carolina (O'Neil et al., 2007).

Note. Based on information from Bristol-Myers Squibb, 2007a, 2007b, 2009; Genentech, Inc., 2009, 2010; sanofi-aventis, 2008, 2009.

Infusion Reactions Caused by Cytokine Release

Most infusion reactions related to monoclonal antibodies are caused by cytokine release (Breslin, 2007; Kang & Saif, 2007). When a monoclonal antibody binds with an antigen on the targeted cell, specialized cytokines called chemokines recruit immune-effector cells (e.g., monocytes, macrophages, cytotoxic T cells, natural killer cells) and complement molecules. The immune-effector cells bind to the constant portion of the antibody (Fc region), thus targeting that cell for destruction either by cytolysis or phagocytosis (Breslin, 2007). When the cell is destroyed, the target cells and the immune effector cells both release cytokines (e.g., interleukin, interferon, tumor necrosis factor) into circulation. Antigen-antibody immune complexes in the lungs, liver, or spleen caused by the monoclonal antibody also may contribute to symptoms from this reaction (Breslin, 2007).

The cytokine-release syndrome has an appearance similar to a type 1 hypersensitivity reaction and may be clinically indistinguishable. The symptoms generally are mild to moderate in severity and usually occur within the first couple of hours, most often with the first infusion. Unlike type 1 hypersensitivities, symptoms appear to subside with each subsequent dose, likely because the tumor burden is highest with the first infusion. Therefore, more targeted cells exists and a higher cytokine release occurs related to their destruction (Byrd et al., 1999). Individuals who have not received prior chemotherapy appear to have more severe reactions, most likely because of the higher tumor burden and subsequent cytokine release (Byrd et al., 1999). In contrast to type 1 hypersensitivities, cytokine-release reactions may be managed by short-term cessation of the monoclonal antibody infusion, the administration of histamine blockers, and restarting the infusion at a slower rate (Breslin, 2007; Chung, 2008; Kang & Saif, 2007; Kimby, 2005).

Most monoclonal antibodies have the potential to cause the cytokine-release syndrome. Rituximab and trastuzumab have a higher incidence of the reactions (77% and 40% during the first infusion, respectively) (Genentech, Inc., 2009, 2010; Kimby, 2005). Panitumumab and bevacizumab have a lower incidence of infusion reactions (4% and less than 3% for all grades, respectively) (Amgen Inc., 2008; Genentech, Inc., 2008). However, the incidence of monoclonal antibody–associated infusion reactions may not be directly related to humanized content. For example, ofatumumab, a fully humanized monoclonal antibody, has been investigated in chronic lymphocytic leukemia and was associated with infusion-related adverse events on the first infusion day in 46% of 59 patients with disease that was refractory to fludarabine and in 38% of 79 patients with bulky fludarabine-refractory disease (Osterborg et al., 2008).

Although the incidence of reactions varies among monoclonal antibodies, most reactions occur during the first infusion. Premedications (e.g., acetaminophen plus an antihistamine) often are recommended prior to a monoclonal antibody as prophylaxis for cytokine-release syndrome, with the exception of bevacizumab and panitumumab. Alemtuzumab, a humanized anti-CD52 monoclonal antibody used in chronic lymphocytic leukemia, is given in fractionated doses to lessen symptoms of cytokine-release syndrome (Berlex Laboratories, 2001).

Most infusion reactions related to monoclonal antibodies are mild (grade 1 or 2), and the incidence of severe (grade 3 or 4) reactions generally is low. The National Cancer Institute has classified infusion reactions caused by cytokine release into severity grades to standardize the reporting of the side effects (see Table 5).

Rituximab and Cytokine-Release Syndrome

As the first FDA-approved monoclonal antibody, rituximab has been scrutinized closely regarding infusion reactions. The most commonly reported adverse reactions to rituximab are infusion-related reactions, which are associated primarily with the first infusion and rarely necessitate discontinuation of treatment. Cytokine release is believed to be partially responsible for most rituximab-associated infusion reactions, and levels of inflammatory cytokines have been shown to increase significantly during the administration of rituximab (Byrd et al., 2001).

Safety assessments from six studies of rituximab used as a single agent in previously treated patients with indolent non-Hodgkin lymphoma (Davis et al., 1999, 2000; Maloney et al., 1994; Maloney, Grillo-Lopez, Bodkin, et al., 1997; Maloney, Grillo-Lopez, White, et al., 1997; McLaughlin et al., 1998; Piro et al., 1999) gave an incidence of infusion-related reaction in 77% (7% grades 3–4) of patients during the first infusion, 30% (2% grades 3–4) during the fourth infusion, and 14% (no grade 3–4 events) during the eighth infusion. The reactions generally occurred within 30 minutes to two hours after initiation of the infusion and resolved with slowing or interruption of the infusion and supportive care. In patients with previously untreated diffuse large B-cell lymphoma, grade 3 or 4 infusion-related

Table 5. National Cancer Institute Grading Criteria for Cytokine-Release Infusion Reactions

GRADE	DEFINITION
1	Mild reaction; no infusion interruption or intervention necessary
2	Therapy or infusion interruption but responsive to symptomatic treatment
3	Prolonged reaction, not rapidly responsive to symptomatic treatment, with possible recurrence of symptoms following initial improvement Hospitalization indicated for other clinical sequelae
4	Life-threatening; pressor or ventilatory support necessary

Note. Based on information from National Cancer Institute, 2006.

reactions (defined as starting during or within one day of an infusion with rituximab) occurred in about 9% of patients at the time of the first cycle of R-CHOP, but the incidence of grade 3 or 4 infusion-related reactions decreased to fewer than 1% by the eighth cycle of R-CHOP (Coiffier et al., 2002).

A slow initial rate of infusion is recommended to reduce the risk for infusion reactions. For example, rituximab is initiated at 50 mg per hour and increased in increments of 50 mg per hour every 30 minutes to a maximum of 400 mg per hour. However, doing so can be time and labor intensive (Sehn et al., 2007). Rituximab often is used as a postinduction regimen or in patients with prior exposure, so the safety of higher dosing (up to 2,250 mg/m²) and rapid (90-minute) infusions is under investigation in various studies. In a trial of patients with previously treated chronic lymphocytic leukemia, dose escalations (following an initial dose of 375 mg/m²) of up to 2,250 mg/m² rituximab were not found to increase the incidence of infusion reactions (O'Brien et al., 2001). In a study by Sehn et al. (2007), 150 patients with non-Hodgkin lymphoma were treated with a total of 473 accelerated infusions of rituximab in combination with corticosteroid-containing chemotherapy given as a 90-minute infusion schedule delivering 20% of the dose in the first 30 minutes and the remaining dose over 60 minutes. The treatment was well tolerated, and no grade 3 or 4 infusion reactions were noted (Sehn et al., 2007).

Salar et al. (2006) found that rapid infusion over 90 minutes was safely administered with or without steroid premedication in patients who had received a previous rituximab infusion without any grade 3 or 4 toxicity. Another study evaluating the maximum safe infusion rate of rituximab without steroid premedication in patients who had received at least one dose of rituximab within the previous three months found that rituximab can be administered safely at 700 mg per hour (Siano et al., 2008). Of note, the first cycle dosing was delivered according to the manufacturer's protocol and subsequent doses were delivered by rapid infusion in both studies. The ongoing phase III RATE study is evaluating the safety, pharmacokinetics, and pharmacodynamics of alternative rituximab dosing rates in previously untreated patients with lymphoma (visit www.Clinical Trials.gov, identifier: NCT00719472). To date, rapid infusion protocols are confined to clinical trials; additional study will determine the safety of rapid infusion as standard practice.

Prophylactic Management of Hypersensitivities

As all oncologic agents have a potential to cause an infusion reaction, oncology nurses must exercise vigilance in caring for patients receiving the drugs. Rapid recognition of patients at increased risk will improve outcomes (see Figure 1). The route and rate of administration, drug form, whether the drug is given in combination or as a single agent, and concomitant medications all influence a person's risk for a reaction. Test-dosing is not always a reliable indictor of infusion-reaction risk, although it has some documented benefits with certain agents such as L-asparaginase (Gobel, 2005). Taking a thorough history, particularly including any previous allergic reactions, is among the most useful risk-assessment tools for oncology nurses. The history should be documented carefully (Gobel, 2005) and can alert all caregivers of potential risk for future hypersensitivity reactions. Certain unknown host factors (e.g., geographic location) may elevate the risk for an infusion reaction as noted in certain regional populations given cetuximab (O'Neil et al., 2007); therefore, oncology nurses should keep up-to-date with regional trends and experiences of others in the same field.

Oncology nurses require a broad understanding of the treatments they are administering. Familiarity with the infusion risks of each agent is imperative and includes comprehension of what type of infusion reaction is most likely associated with that particular drug. Premedications (e.g., antipyretics, antihistamines, steroids) are recommended before the administration of some chemotherapeutic agents and monoclonal antibodies. For example, acetaminophen and antihistamines are recommended prior to rituximab infusion (Genentech, Inc., 2010; Kimby, 2005). If some premedications are to be taken orally, oncology nurses should ensure that the patient has actually taken them prior to each infusion. No standard regimen exists for all oncologic agents (Gobel, 2005), and oncology nurses may check the manufacturer's recommendations as well as their facility's protocol. If the patient

- Asthma diagnosis
- Atopic patients (i.e., patients who tend to react to specific allergens, such as hay fever, skin irritations, and asthma)
- Circulating lymphocyte counts of 25,000 mm³ or higher (lymphoma or leukemia)
- Concomitant β-adrenergic blocker therapy
- Concurrent autoimmune disease
- Female gender
- Higher than standard drug doses
- Iodine or seafood allergies
- Newly diagnosed, untreated patients
- Older age
- Patients with hematologic malignancies such as mantle cell lymphoma and chronic or small lymphocytic leukemia
- Personal history of drug allergy or previous immediate reaction to a medication
- Preexisting cardiac or pulmonary dysfunction
- Previous exposure to the drug

Figure 1. Risk Factors for Hypersensitivity Reactions
Note. Based on information from Breslin, 2007; Gobel, 2005; Kang & Saif, 2007; Kimby, 2005; Saif, 2006.

has a high tumor volume and is believed to be at risk for tumor lysis syndrome, then allopurinol for at least 7–10 days and increased hydration also may be prescribed (Kimby, 2005).

If the patient is identified as being at high risk for a cytokine-release reaction, a stepwise manner of infusion or fractionated dosing may be considered. For example, Byrd et al. (1999) recommend a 100 mg dose of rituximab in 1,000 ml of normal saline on day 1 and the remainder of the prescribed dose on day 2, both with standard premedications, in higher risk patients. Other fractionated dosing regimens are described in the medical literature for various agents, and hospitalization might be considered for patients at highest risk.

Patients and family members must be well educated about the potential for an infusion reaction and should understand the need to report reactions immediately. When administering monoclonal antibodies, oncology nurses can reassure patients that most infusion reactions are caused by cytokine release, are mild to moderate in severity, and are managed easily. Patients also should be taught about the possibility for a delayed reaction following discharge from the infusion facility and should understand what needs to be reported to their healthcare providers promptly.

Monoclonal antibodies as well as chemotherapeutic agents should be administered piggy-back into the distal port of a main IV line, following specific manufacturer's recommendations. Monoclonal antibodies are never given as an IV bolus, and an infusion pump should be used. Baseline assessments including vital signs and cognition should be documented carefully prior to the start of treatment. During infusions, oncology nurses must assess the patient frequently, monitoring vital signs and watching for any signs or symptoms of an infusion reaction. The first hour is the most likely time for infusion reactions to occur, but vigilance is necessary throughout every infusion as a reaction could occur at any time. Any delay in recognition of the signs of anaphylaxis can compromise the patient's outcome (Lieberman et al., 2005).

Any facility that is administering oncologic agents must have the necessary emergency equipment, medications, and a thoroughly trained staff readily available. A basic emergency plan should be written, and each oncology nurse must be familiar and comfortable with the protocol. Standing orders for emergent treatment of infusion hypersensitivities are prudent and enable immediate intervention without waiting for the clinician order. Figure 2 lists basic emergent supplies necessary for infusion facilities. Emergent medications for a facility are based on what prescribing clinicians deem expedient for successful resuscitation and the extent of reliance upon local emergency services, which may vary between facilities and institutions because no standard protocols or regulatory requirements exist (Gobel, 2005). Emergent supplies should be kept in an easily accessible and well-known location. At minimum, all staff should be proficient in basic life support. Each staff member must understand their role in any potential emergent situation. Practice drills are recommended to better equip oncology nurses in crisis management (Lieberman et al., 2005).

Managing an Infusion Reaction

Anaphylaxis, a true type 1 hypersensitivity, occurs as a continuum (Kemp et al., 2008; Lieberman et al., 2005). What appears to be a relatively mild reaction could rapidly progress to a life-

- Ambu® (Ambu A/S) bag
- Alcohol wipes
- Catheter and butterfly needles
- Large-gauge IV catheters
- Latex-free gloves
- Normal saline and lactated Ringer's solution
- Oral airway
- Oxygen mask
- Oxygen nasal prongs
- Oxygen tank
- Oxygen tubing
- Stethoscope and sphygmomanometer
- Suction apparatus
- Supply of emergent medications
  - Albuterol
  - Aminophylline
  - Anticonvulsants
  - Atropine
  - Calcium gluconate
  - Dopamine
  - Corticosteroids
  - Epinephrine
  - Histamine 1 and 2 antagonists
  - Lidocaine
  - Ranitidine
  - Sodium bicarbonate
- Syringes and needles

Figure 2. Basic Emergency Supplies for Managing an Infusion Reaction

threatening cardiovascular and respiratory event. The severity of a reaction cannot be predicted at its onset. Although anaphylactic reactions to monoclonal antibodies are rare, they have been reported occasionally. Differentiating between an anaphylactic reaction and a cytokine-release reaction may be impossible at the onset of symptoms. Anaphylactic reactions usually occur within the first few minutes of the infusion, so documentation of the time symptoms began is important. The more rapid the occurrence of the hypersensitivity, the more likely it is to be a true anaphylaxis and increase in severity (Lieberman et al., 2005). Cytokine-release symptoms usually occur within 30–120 minutes of the beginning of the infusion. However, the timing of symptom onset alone cannot determine the cause, severity, or treatment of the reaction.

When an oncology nurse first suspects that an infusion reaction is occurring, the infusion should be stopped but vascular access should be maintained with normal saline. Airway, breathing, and circulation should be assessed immediately. During this assessment, another staff member should ready emergent equipment and medication, including epinephrine, if possible. Patency of airway should be ensured and oxygen therapy initiated at the first sign of compromise. Oxygen is essential in patients with prolonged reactions or with preexisting respiratory or cardiac disease (Lieberman et al., 2005). Vital signs should be obtained and the patient should be placed into a recumbent position with elevation of the lower extremities if hypotensive. Vital sign assessment should be repeated every two to five minutes until the patient is stable. Tachycardia and hypotension occur in anaphylaxis, although tachycardia may be absent in patients with conduction defects or in those who take sympatholytic medications (Lieberman et al., 2005). During the first few minutes, one healthcare team member should be assigned to call for emergency medical assistance and another assigned to document treatment and times of treatment (Lieberman et al., 2005). Differential diagnoses should be considered. Figure 3 is a nonexhaustive list of other clinical conditions that mimic an infusion reaction or anaphylaxis.

Nurses should observe for cutaneous manifestations because most anaphylactic incidents have some sort of cutaneous symptom (Lieberman et al., 2005), although up to 20% of cases may have none (Brown et al., 2006). Urticaria and angioedema are most

commonly seen in anaphylaxis but may be absent or delayed. Erythema (diffuse or localized) may be seen. Level of consciousness also should be assessed because a decreased level of consciousness may indicate hypoxia. Auscultation of the lungs should be performed, listening for stridor or wheezing. Dysphonia, cough, and shortness of breath also should be noted. Nurses should document any gastrointestinal symptoms such as nausea, vomiting, abdominal pain, or diarrhea and question the patient about light headedness, uterine cramping, headache, or other symptoms.

Whether an infusion reaction is a true anaphylactic reaction or a cytokine-release reaction may be difficult to determine quickly. If the nurse has any doubt, the reaction should be assumed to be anaphylactic and treated as such. Anaphylaxis is strongly suspected if acute onset of symptoms associated with respiratory symptoms or hypotension occurs. Many infusion reactions will resolve once the offending agent has been discontinued and supportive care is given, which usually is the case when a monoclonal antibody is given and cytokine-release syndrome occurs. If symptoms begin to resolve when the infusion is stopped, continue to monitor the patient and readminister the histamine blocker. Corticosteroid administration also may be considered. Once symptoms are totally resolved, usually within 30 minutes, the infusion may be restarted at 50% of the infusion rate and titrated to tolerance (Breslin, 2007).

Management of an infusion reaction is individualized based on patient symptoms and status, available emergency resources, and the skill and medical decisions of the clinician. Figure 4 is a suggested algorithm for the management of a hypersensitivity reaction. Clinicians should evaluate the need for epinephrine administration at each step during management of the hypersensitivity because epinephrine is considered the drug of choice in an anaphylactic reaction (Kemp et al., 2008). If the clinician has any doubt, administering epinephrine is better than not (Lieberman et al., 2005) because no absolute contraindication exists in the setting of a potential anaphylaxis (Kemp et al., 2008). Epinephrine often is delayed, underused, or underdosed in emergent infusion reactions, contributing to poor patient outcome (Kemp et al., 2008). Many experts believe that any symptoms of anaphylaxis (e.g., generalized pruritus, erythema, urticaria, angioedema) should be treated immediately with intramuscular doses of epinephrine to prevent a more serious event from occurring (Kemp et al., 2008). Dosing of epinephrine is determined by the severity of the reaction, but expert evidence recommends 0.2–0.5 mg at a ratio of 1 to 1,000 (1 mg in 1 ml) aqueous solution.

Dopamine may be given for hypotension unresponsive to epinephrine, but continuous hemodynamic monitoring is critical. Dopamine 400 mg in 500 ml of 5% dextrose is administered at a rate of 2–20 mg/kg per minute and titrated to maintain a systolic blood pressure of greater than 90 mm Hg (Lieberman et al., 2005). A glucagon infusion (1–5 mg) may be considered if the patient is taking a β-adrenergic blocking agent that complicates treatment (Lieberman et al., 2005). The glucagon infusion is given IV over five minutes.

Fluid replacement with normal saline is administered at a rate of 5–10 ml/kg over the first five minutes (Lieberman et al., 2005). For a person weighing 150 lbs, the dose would be 350–650 ml within five minutes. A maximum of 50 ml/kg over the first 30 minutes can be given (Brown et al., 2006). Patients with comorbidities such as congestive heart failure or chronic renal dysfunction should be observed carefully for signs of fluid overload.

Histamine antagonists (H_1 and H_2) may be given in supportive management, particularly for pruritus, angioedema, and urticaria (Brown et al., 2006; Lieberman et al., 2005). However, the agents are considered inferior to epinephrine because of the slower onset of action and should not be given alone in the treatment of true anaphylaxis (Lieberman et al., 2005). Diphenhydramine 25–250 mg may be given slowly via IV. Oral doses may be appropriate in mild reactions. Diphenhydramine (50 mg) and ranitidine (50 mg diluted in 5% dextrose to 20 ml) given together for anaphylaxis are superior to diphenhydramine given alone (Lieberman et al., 2005), particularly with tachycardia and cutaneous symptoms. Although no controlled studies recommend one H_2 antagonist over another, ranitidine has fewer potential drug interactions and cimetidine may cause hypotension if infused too rapidly.
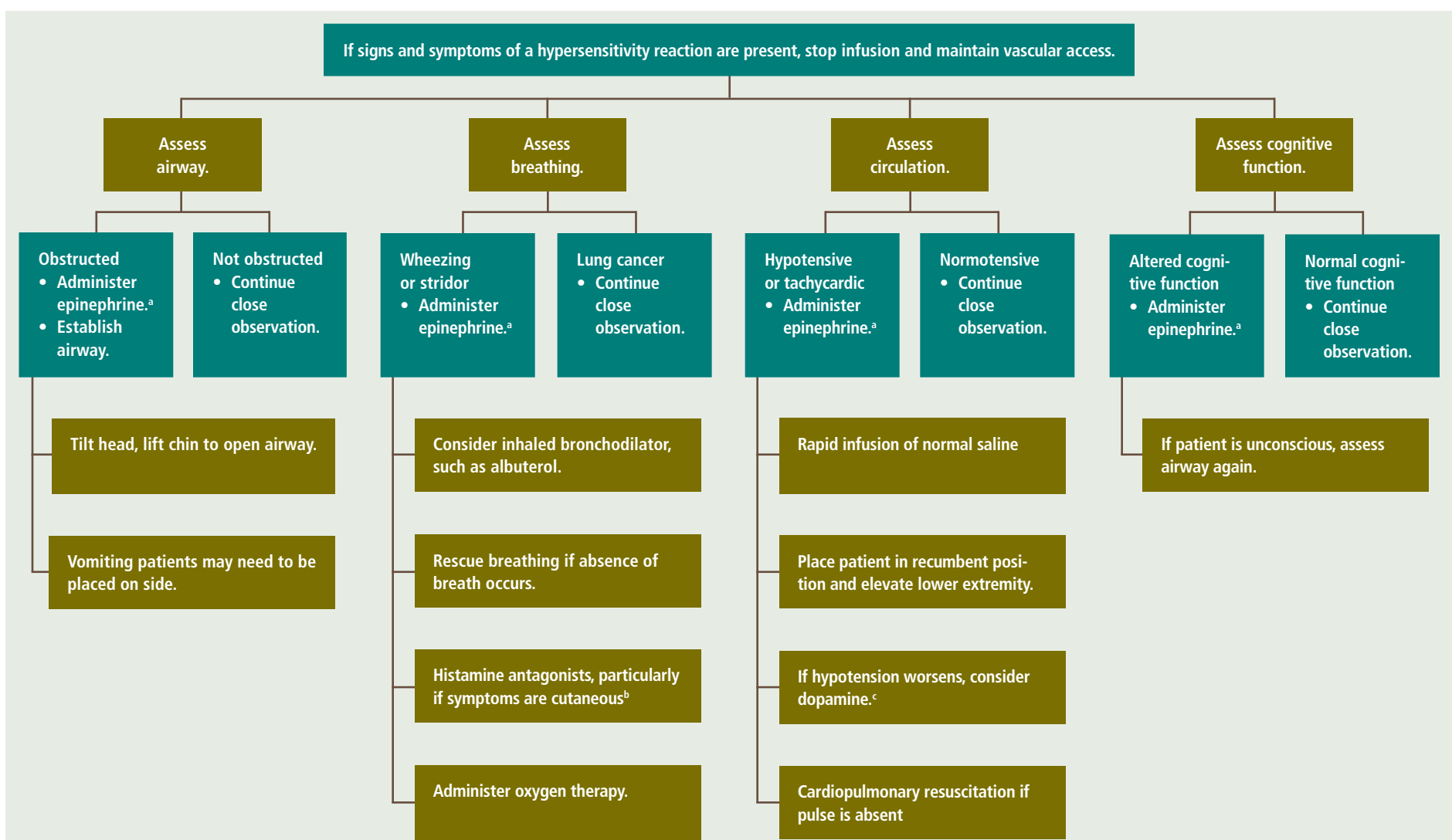
Bronchodilators are given for bronchospasm. Persistent stridor may be treated with continuous nebulised epinephrine in addition to parenteral epinephrine (Brown et al., 2006). Patients with preexisting cardiac or pulmonary dysfunction may not be able to tolerate some symptoms of infusion reactions (Breslin, 2007). These patients may require intensive treatment and subsequent hospitalization. Oxygen therapy is of particular importance in prolonged reactions, preexisting hypoxemic states, patients with myocardial dysfunction, or patients who require multiple doses of epinephrine (Lieberman et al., 2005). Continuous pulse oximetry or blood gas determinations (if available) will guide oxygen therapy.

Corticosteroids may be administered; corticosteroids do not work in the acute management of anaphylaxis but may decrease the duration of a reaction or prevent a biphasic (recurrent) reaction (Brown et al., 2006; Lieberman et al., 2005). Corticosteroids may be helpful in the management of patients who have comorbid diseases treated with corticosteroids, such as asthma (Lieberman et al., 2005). The agents may be given via IV or orally; oral administration is sufficient in less severe anaphylactic events.

Follow-Up After Stability

Observation

Once the patient is stable, vital signs should be assessed at 15-minute intervals. The patient should be observed for recurrence of symptoms, particularly in cases in which the half-life of the oncologic agent is longer than the high-life of the rescue

- Asthma
- Dystonic reactions
- Flushing syndromes caused by peptide-secreting tumors, alcohol, or medullary carcinoma of the thyroid
- Foreign body aspiration
- Hypoglycemia
- Laryngospasm
- Myocardial infarction
- Panic or anxiety attack
- Pulmonary embolus
- Seizure disorder
- Stroke
- Vasovagal reaction

Figure 3. Differential Diagnosis of a Hypersensitivity Reaction

Note. Based on information from Brown et al., 2006; Lieberman et al., 2005.

If signs and symptoms of a hypersensitivity reaction are present, stop infusion and maintain vascular access.

Assess airway.

Assess breathing.

Assess circulation.

Assess cognitive function.

Obstructed
- Administer epinephrine.[a]
- Establish airway.

Not obstructed
- Continue close observation.

Wheezing or stridor
- Administer epinephrine.[a]

Lung cancer
- Continue close observation.

Hypotensive or tachycardic
- Administer epinephrine.[a]

Normotensive
- Continue close observation.

Altered cognitive function
- Administer epinephrine.[a]

Normal cognitive function
- Continue close observation.

Tilt head, lift chin to open airway.

Consider inhaled bronchodilator, such as albuterol.

Rapid infusion of normal saline

If patient is unconscious, assess airway again.

Vomiting patients may need to be placed on side.

Rescue breathing if absence of breath occurs.

Place patient in recumbent position and elevate lower extremity.

Histamine antagonists, particularly if symptoms are cutaneous[b]

If hypotension worsens, consider dopamine.[c]

Administer oxygen therapy.

Cardiopulmonary resuscitation if pulse is absent

[a] Epinephrine dosing is based on severity of the reaction. Epinephrine autoinjector intramuscularly (0.3 mg for adults) in lateral thigh may be given through clothing. Epinephrine 0.2–0.5 mg 1 to 1,000 solution intramuscularly or subcutaneously may be repeated for five minutes as needed. Epinephrine also may be inhaled or given sublingually, via endotracheal tube, or via IV.

[b] Diphenhydramine is considered secondline to epinephrine and should never be administered alone in the treatment of anaphylaxis. Dosage is 25–50 mg IV. Combinations of H_1 and H_2 histamine antagonists are superior to single agent.

[c] Dopamine may be administered if hypotension is not controlled by epinephrine. Dosage is 400 mg in 500 ml of 5% dextrose at a rate of 2–20 mcg/kg per minute and titrated to patient's blood pressure.

Figure 4. Suggested Algorithm for the Management of a Hypersensitivity Reaction

medications. Emergency personnel who may be transporting the patient to the emergency room must be made aware of this potential. Each patient should be observed for at least four hours after symptom resolution; patients who have experienced a severe infusion reaction may require close observation for the following 24 hours because of the risk for a biphasic episode (Brown et al., 2006; Lieberman et al., 2005). People with reactive airway disease also may need longer observation periods (Brown et al., 2006).

Biphasic (recurrent) reactions occur in 1%–20% of anaphylactic cases (Kemp et al., 2008). Symptoms may recur within the first eight hours to up to 72 hours after resolution of the initial phase (Kemp et al., 2008). Biphasic occurrence has no reliable predictors. Patients should be monitored closely for at least the first 24 hours following a severe reaction. If the patient is discharged, factors such as comorbid conditions and distance from patient's home to an emergency facility must be taken into consideration. The patient should be discharged with an epinephrine autoinjector following instructions on usage.

Grading and Documentation

Prompt and accurate documentation of the infusion event is critical. Accurate grading of the event will enable the prescribing clinician to decide whether rechallenge is feasible and safe. Documentation should include
- Preinfusion assessment (i.e., the drugs administered, doses, number of previous infusions of the agent, and infusion rates)
- Initial symptoms and course of progression
- The timing of symptom onset
- Intervention, timing, and patient response
- Time of symptom resolution
- Discharge instructions or transfer to emergency services.
Proper and thorough documentation will assist the clinician in deciding on additional treatment.

Rechallenge

The decision to restart an infusion will depend on the nature of the reaction and discretion of the clinician. No straightforward protocol exists for the decision to retreat (Weiss, 1992). The decision is dependent on the drug, the pathophysiology behind the reaction, the severity of the reaction, patient treatment goals, and the comfort level of the patient as well as the clinician. Rechallenge should not be attempted in patients who have had a true and severe anaphylaxis.

Most patients experiencing moderate infusion reactions may be considered for rechallenge, but methods to minimize hypersensitivity such as premedication with antihistamines and corticosteroids must be undertaken (Weiss, 1992). Increasing the infusion duration also may be beneficial (Saif, 2006). Desensitization protocols also have been used with certain drugs with varying success. In desensitization, the clinician prescribes an initial small, diluted dose of the agent with a prolonged infusion time and gradually escalates the dose. However, no standard desensitization protocols exist (Gobel, 2005).

Rechallenging patients with a monoclonal antibody may be reasonable, as most reactions to this class of drug are likely to be caused by cytokine-release and not true anaphylaxis. Each patient case should be considered individually, taking into account the severity of the initial reaction, comorbidities, goals of therapy, and evaluation of the risk of rechallenge versus potential benefits of successful treatment. Rechallenge will involve premedicating with antihistamines and corticosteroids and readministration of the drug at a reduced infusion rate (Kang & Saif, 2007).

Conclusion

All oncologic agents are associated with a risk for infusion reactions, which can be unpredictable. Oncology nurses should maintain high vigilance for such reactions. Astute assessment of patients prior to drug administration may identify those at higher risk. Understanding the drug and the pathophysiology of the different types of infusion reactions is critical to early recognition of clinical signs and symptoms as well as prompt and expert management of reactions. Rituximab, like most other monoclonal antibodies, is associated with infusion reactions that are caused primarily by cytokine release rather than true allergic reactions. Therefore, rechallenge will be possible in most cases with accurate analysis and documentation of the event. Rechallenge may include the readministration of antihistamines and corticosteroids, followed by administration of the agent at a reduced rate.

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References

Amgen Inc. (2008). *Vectibix® (panitumumab)* [Package insert]. Thousand Oaks, CA: Author.

Bello, C., & Sotomayor, E.M. (2007). Monoclonal antibodies for B-cell lymphomas: Rituximab and beyond. *Hematology, 2007,* 233–242. doi: 10.1182/asheducation-2007.1.233

Berlex Laboratories. (2001). *Campath® (alemtuzumab)* [Package insert]. Richmond, CA: Author.

Breslin, S. (2007). Cytokine-release syndrome: Overview and nursing implications. *Clinical Journal of Oncology Nursing, 11*(1, Suppl.), 37–42. doi: 10.1188/07.CJON.S1.37-42

Bristol-Myers Squibb. (2007a). *Paraplatin® (carboplatin aqueous solution) injection* [Package insert]. Princeton, NJ: Author.

Bristol-Myers Squibb. (2007b). *Taxol® (paclitaxel) injection* [Package insert]. Princeton, NJ: Author.

Bristol-Myers Squibb. (2009). *Erbitux® (cetuximab) solution for intravenous injection* [Package insert]. Princeton, NJ: Author.

Brown, S.G., Mullins, R.J., & Gold, M.S. (2006). Anaphylaxis: Diagnosis and management. *Medical Journal of Australia, 185,* 283–289.

Byrd, J.C., Murphy, T., Howard, R.S., Lucas, M.S., Goodrich, A., Park, K., . . . Flinn, I.W. (2001). Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small

lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *Journal of Clinical Oncology, 19,* 2153–2164.

Byrd, J.C., Waselenko, J.K., Maneatis, T.J., Murphy, T., Ward, F.T., Monahan, B.P., . . . White, C.A. (1999). Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance. *Journal of Clinical Oncology, 17,* 791–795.

Chung, C.H. (2008). Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. *Oncologist, 13,* 725–732. doi: 10.1634/theoncologist.2008-0012

Coiffier, B., Feugier, P., Mounier, N., Franchi-Rezgui, P., Van Den Neste, E., Macro, M., . . . Tilly, H. (2007). Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor-risk patients [Abstract 8009]. Retrieved from http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=30903

Coiffier, B., Lepage, E., Briere, J., Herbrecht, R., Tilly, H., Bouabdallah, R., . . . Gisselbrecht, C. (2002). CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New England Journal of Medicine, 346,* 235–242. doi: 10.1056/NEJMoa011795

Davis, T.A., Grillo-Lopez, A.J., White, C.A., McLaughlin, P., Czuczman, M.S., Link, B.K., . . . Levy, R. (2000). Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: Safety and efficacy of re-treatment. *Journal of Clinical Oncology, 18,* 3135–3143.

Davis, T.A., White, C.A., Grillo-Lopez, A.J., Velasquez, W.S., Link, B., Maloney, D.G., . . . Levy, R. (1999). Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: Results of a phase II trial of rituximab. *Journal of Clinical Oncology, 17,* 1851–1857.

Dillman, R.O., & Hendrix, C.S. (2003). Unique aspects of supportive care using monoclonal antibodies in cancer treatment. *Supportive Cancer Therapy, 1,* 38–48. doi: 10.3816/SCT.2003.n.003

Edwards, J.C., Szczepanski, L., Szechinski, J., Filipowicz-Sosnowska, A., Emery, P., Close, D.R., . . . Shaw, T. (2004). Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *New England Journal of Medicine, 350,* 2572–2581. doi: 10.1056/NEJMoa032534

Genentech, Inc. (2008). *Avastin® (bevacizumab)* [Package insert]. San Francisco, CA: Author.

Genentech, Inc. (2009). *Herceptin® (trastuzumab)* [Package insert]. San Francisco, CA: Author.

Genentech, Inc. (2010). *Rituxan® (rituximab)* [Package insert]. San Francisco, CA: Author.

Gobel, B.H. (2005). Chemotherapy-induced hypersensitivity reactions. *Oncology Nursing Forum, 32,* 1027–1035. doi: 10.1188/04.ONF.1027-1035

Hallek, M., Fingerle-Rowson, G., Fink, A., Busch, R., Mayer, J., Hensel, M. . . . Fischer, K. (2008). Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL) [Abstract]. *Blood, 112,* 125.

Johnson, P., & Glennie, M. (2003). The mechanisms of action of rituximab in the elimination of tumor cells. *Seminars in Oncology, 30*(1, Suppl. 2), 3–8. doi: 10.1053/sonc.2003.50025

Kang, S.P., & Saif, M.W. (2007). Infusion-related and hypersensitivity reactions of monoclonal antibodies used to treat colorectal cancer—Identification, prevention, and management. *Journal of Supportive Oncology, 5,* 451–457.

Kemp, S.F., Lockey, R.F., & Simons, F.E. (2008). Epinephrine: The drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy, 63,* 1061–1070. doi: 10.1111/j.1398-9995.2008.01733.x

Kimby, E. (2005). Tolerability and safety of rituximab (MabThera). *Cancer Treatment Reviews, 31,* 456–473. doi: 10.1016/j.ctrv.2005.05.007

Kohler, G., & Milstein, C. (1975). Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature, 256,* 495–497.

Lenz, H.J. (2007). Management and preparedness for infusion and hypersensitivity reactions. *Oncologist, 12,* 601–609. doi: 10.1634/theoncologist.12-5-601

Li, H., Ayer, L.M., Lytton, J., & Deans, J.P. (2003). Store-operated medication entry mediated by CD20 in membrane rafts. *Journal of Biological Chemistry, 278,* 42427–42434.

Lieberman, P., Kemp, S.F., Oppenheimer, J., Lang, D.M., Bernstein, I.L., Nicklas, R.A., . . . Fink, J. (2005). The diagnosis and management of anaphylaxis: An updated practice parameter. *Journal of Allergy and Clinical Immunology,* 115(3, Suppl. 2), S483–S523. doi: 10.1016/j.jaci.2005.01.010

Maloney, D.G., Grillo-Lopez, A.J., Bodkin, D.J., White, C.A., Liles, T.M., Royston, I., . . . Levy, R. (1997). IDEC-C2B8: Results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. *Journal of Clinical Oncology, 15,* 3266–3274.

Maloney, D.G., Grillo-Lopez, A.J., White, C.A., Bodkin, D., Schilder, R.J., Neidhart, J.A., . . . Levy, R. (1997). IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood, 90,* 2188–2195.

Maloney, D.G., Liles, T.M., Czerwinski, D.K., Waldichuk, C., Rosenberg, J., Grillo-Lopez, A., & Levy, R. (1994). Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. *Blood, 84,* 2457–2466.

Maloney, D.G., Smith, B., & Appelbaum, F.R. (1996). The antitumor effect of monoclonal anti-CD20 antibody (mAb) therapy includes direct anti-proliferative activity and induction of apoptosis in CD20 positive non-Hodgkin's lymphoma (NHL) cell lines. *Blood, 88,* 637.

Mathas, S., Rickers, A., Bommert, K., Dorken, B., & Mapara, M.Y. (2000). Anti-CD20- and B-cell receptor-mediated apoptosis: Evidence for shared intracellular signaling pathways. *Cancer Research, 60,* 7170–7176.

McLaughlin, P., Grillo-Lopez, A.J., Link, B.K., Levy, R., Czuczman, M.S., Williams, M.E., & Dallaire, B.K. (1998). Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. *Journal of Clinical Oncology, 16,* 2825–2833.

National Cancer Institute. (2006). Common Terminology Criteria for Adverse Events [v3.0]. Retrieved from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

O'Brien, S.M., Kantarjian, H., Thomas, D.A., Giles, F.J., Freireich, E.J., Cortes, J., . . . Keating, M.J. (2001). Rituximab dose-escalation trial in chronic lymphocytic leukemia. *Journal of Clinical Oncology, 19,* 2165–2170.

Oldham, R.K., & Dillman, R.O. (2008). Monoclonal antibodies in cancer therapy: 25 years of progress. *Journal of Clinical Oncology, 26,* 1774–1777.

O'Neil, B.H., Allen, R., Spigel, D.R., Stinchcombe, T.E., Moore, D.T., Berlin, J.D., & Goldberg, R.M. (2007). High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *Journal of Clinical Oncology, 25,* 3644–3648.

Osterborg, A., Kipps, T.J., Mayer, J., Stilgenbauer, S., Williams, C.D., Hellmen, A., . . . Wierda, W.G. (2008). Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: Results from the planned interim analysis of an international pivotal trial [Abstract]. *Blood, 112,* 126.

Peereboom, D.M., Donehower, R.C., Eisenhauer, E.A., McGuire, W.P., Onetto, N., Hubbard, J.L., . . . Rowinsky, E.K. (1993). Successful retreatment with taxol after major hypersensitivity reactions. *Journal of Clinical Oncology, 11,* 885–890.

Piro, L.D., White, C.A., Grillo-Lopez, A.J., Janakiraman, N., Saven, A., Beck, T.M., . . . Jain, V. (1999). Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. *Annals of Oncology, 10,* 655–661.

Reff, M.E., Carner, K., Chambers, K.S., Chinn, P.C., Leonard, J.E., Raab, R., . . . Anderson, D.R. (1994). Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood, 83,* 435–445.

Rieger, P.T. (2001). Biotherapy: An overview. In P.T. Rieger (Ed.), *Biotherapy: A comprehensive review* (pp. 3–37). Sudbury, MA: Jones and Bartlett.

Riley, J.K., & Sliwkowski, M.X. (2000). CD20: A gene in search of a function. *Seminars in Oncology, 27*(6, Suppl. 12), 17–24.

Saif, M.W. (2006). Hypersensitivity reactions associated with oxaliplatin. *Expert Opinion on Drug Safety, 5,* 687–694. doi: 10.1517/14740338.5.5.687

Salar, A., Casao, D., Cervera, M., Pedro, C., Calafell, M., Abella, E., . . . Besses, C. (2006). Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. *European Journal of Haematology, 77,* 338–340. doi: 10.1111/j.1600-0609.2006.00713.x

sanofi-aventis U.S. LLC. (2008). *Taxotere® (docetaxel) injection concentrate* [Package insert]. Bridgewater, NJ: Author.

sanofi-aventis U.S. LLC. (2009). *Eloxatin® (oxaliplatin powder for solution*) [Package insert]. Bridgewater, NJ: Author.

Schulz, H., Bohlius, J.F., Trelle, S., Skoetz, N., Reiser, M., Kober, T., . . . Engert, A. (2007). Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: A systematic review and meta-analysis. *Journal of the National Cancer Institute, 99,* 706–714. doi: 10.1093/jnci/djk152

Sehn, L.H., Donaldson, J., Filewich, A., Fitzgerald, C., Gill, K.K., Runzer, N., . . . Connors, J.M. (2007). Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood, 109,* 4171–4173.

Shan, D., Ledbetter, J.A., & Press, O.W. (2000). Signaling events involved in anti-CD20-induced apoptosis of malignant human B cells. *Cancer Immunology, Immunotherapy, 48,* 673–683.

Siano, M., Lerch, E., Negretti, L., Zucca, E., Rodriguez-Abreu, D., Oberson, M., . . . Ghielmini, M. (2008). A phase I–II study to determine the maximum tolerated infusion rate of rituximab with special emphasis on monitoring the effect of rituximab on cardiac function. *Clinical Cancer Research, 14,* 7935–7939. doi: 10.1158/1078-0432.CCR-08-1124

Sliesoraitis, S., & Chikhale, P.J. (2005). Carboplatin hypersensitivity. *International Journal of Gynecological Cancer, 15,* 13–18.

Solomon, S., & Komanduri, K. (2001). The immune system. In P.T. Rieger (Ed.), *Biotherapy: A comprehensive review* (pp. 39–63). Sudbury, MA: Jones and Bartlett.

Tam, C.S., O'Brien, S., Wierda, W., Kantarjian, H., Wen, S., Do, K.A., . . . Keating, M.J. (2008). Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood, 112,* 975–980. doi: 10.1182/blood-2008-02-140582

Vial, T., & Descotes, J. (1995). Immune-mediated side-effects of cytokines in humans. *Toxicology, 105,* 31–57.

Weiss, R.B. (1992). Hypersensitivity reactions. *Seminars in Oncology, 19,* 458–477.

Zanotti, K.M., & Markman, M. (2001). Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Safety, 24,* 767–779.

Journal Club Discussion Questions

This article has been identified as appropriate for a journal club. When you read this article, think about how you and your practice address infusion reactions. See the Evidence-Based Practice column in the February 2009 *Clinical Journal of Oncology Nursing* (Vol. 13, No. 1, pp. 109–112) on how to implement and participate in journal clubs. Photocopying of this article for discussion purposes is permitted.

1. What is the clinical practice question the authors are trying to address?
2. Is the purpose of the article described clearly?
3. Is the literature review comprehensive, and are major concepts identified and defined?
4. What percentage of your patient population receives agents that may cause infusion reactions?
5. What is your protocol for preventing and managing infusion reactions?
6. Have any of your patients experienced infusion reactions? What was that like and what was done to manage it?
7. How do you manage the patient when rechallenged?
8. How do the author's recommendations compare to your current practice?
9. What practice change recommendations will you make based on the evidence presented in this article?