

OBJECTIVES:

To review the current evidence regarding hypersensitivity reactions related to the administration of biological drugs in the management of cancer, and to provide the nurse with appropriate interventions related to the management of hypersensitivity reactions.

DATA SOURCES:

Review articles and research studies from the medical and nursing literature.

CONCLUSION:

Current evidence is available regarding the types of reactions that are associated with the administration of biological drugs in the management of cancer. Medical and nursing studies that review the most effective management of hypersensitivity reactions related to the administration of biological drugs. A review of “best practice” is offered in this article regarding the management of hypersensitivity reactions related to the administration of biological drugs.

IMPLICATIONS FOR NURSING PRACTICE:

Nurses play a key role in the early identification of hypersensitivity reactions. Management of hypersensitivity reactions must be rapid for optimal patient outcomes.

KEYWORDS:

Hypersensitivity, biological therapy, nursing care

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HYPERSENSITIVITY REACTIONS TO BIOLOGICAL DRUGS

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THE USE of biological drugs, including interferon, interleukin, and monoclonal antibodies (MOABs), is becoming increasingly common for the treatment of a variety of cancers. The use of many of these drugs is improving the therapeutic outcomes related to many cancers, but they also carry some risk that a patient may experience an adverse infusion-related reaction during or shortly after the administration of the drug. Most reactions can be described as hypersensitivity reactions to the given biologic drug. Hypersensitivity reactions result from interactions between a pharmacologic drug and the immune system.¹ Adverse drug reactions are common; however, distinguishing the mechanism of action of the reaction can be difficult based on the variety of presenting signs and symptoms that may be demonstrated.

Most biological drugs have the potential to cause hypersensitivity reactions. Because many of these drugs are relatively new in the field of cancer care, there is no reported overall incidence rate of hypersensitivity reactions related to the administration of biological drugs. The incidence of hypersensitivity reactions reviewed in this article is based on individual biological drugs.

Understanding and managing hypersensitivity reactions are critical when caring for patients receiving biological drugs, as these reactions can be life-threatening. A thorough understanding of those drugs that have a high risk of causing hypersensitivity reactions is critical to the early identification of hypersensitivity reactions, which is crucial to optimal patient outcomes. Nursing management of hypersensitivity reactions related to the administration of biological drugs is based on the medical and pharmacy literature. No studies were identified that show nursing research-based evidence regarding outcomes related to the management of hypersensitivity reactions. Thus, a compilation of “best practices” is offered regarding the management of hypersensitivity reactions related to the administration of biological drugs.

DEFINITIONS AND CLASSIFICATIONS

The terms “drug reaction,” “drug allergy,” and “drug hypersensitivity” are often used synonymously in the literature and in clinical practice. *Drug reaction* includes all adverse drug events

Table 1.
Gell and Combs Classification of Types of Hypersensitivity Reactions^{1,5-7}

Type	Mechanism	Signs and Symptoms	Timing
Type I	Immunoglobulin E-mediated drug-immunoglobulin complex binds to mast cells with release of mediators of reaction (eg, histamine)	Fever, rashes, nausea, vomiting, flushing, diarrhea, dyspnea, urticaria, angioedema, bronchospasm, back pain, feeling of impending doom, anaphylaxis	Minutes to hours after drug administration
Type II	Antibody-mediated reaction (specifically IgG or IgM) resulting in antibody-antigen complexes; complexes activate pathways in the immune system to cause inflammation	Hemolytic anemia/hemolysis, neutropenia, thrombocytopenia	Variable
Type III	Drug-antibody mediated reaction through which immune complexes form in the circulation and deposit in various tissues, associated with an immune system response	Fever, rash, arthralgias, nephritis, vasculitis, urticaria, lymphadenopathy, serum sickness	1 to 3 weeks after drug administration
Type IV	Delayed reaction that involves the activation of T-cells in the immune system; the T-cells recognize the antigen and destroy the targeted cells	Graft rejection, granuloma formation, allergic contact dermatitis	2 to 7 days (or longer) after cutaneous drug exposure

related to drug administration, regardless of etiology. Drug reactions can be classified into immunologic and non-immunologic etiologies.¹ The majority of drug reactions are caused by predictable or sometimes unpredictable, non-immunologic effects. One example of a predictable non-immunologic drug reaction is the occurrence of dry mouth from the administration of antihistamines. Immune-mediated reactions account for approximately 5% to 10% of all drug reactions, and include drug allergy and drug hypersensitivity reactions.^{2,3}

Drug allergy is a reaction specifically mediated by the immune system and the immunoglobulin, IgE. *Drug hypersensitivity* is defined as an immune-mediated response to a drug in a sensitized patient.^{1,4} The Gell and Coombs classification system of hypersensitivity reactions describes the predominant immune mechanisms that lead to the clinical symptoms of drug hypersensitivity (Table 1). The four identified types of reactions include: type I is an immediate, IgE-mediated reaction; type II is an antibody-mediated reaction (IgG or IgM) that is cytotoxic in nature; type III is an immune-complex mediated reaction; and type IV is a cell-mediated or delayed type reaction.^{1,5-7}

Cytokine release syndrome is a drug reaction that has been described related to drugs directed against immune system targets, such as anti-CD3 and anti-CD20 antibodies. This syndrome is believed to be secondary to the release of cytokines,

such as the inflammatory mediators tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interferons, as tumor antigen-expressing cells are targeted and destroyed.⁸ *Cytokine release syndrome* is a hypersensitivity reaction that does not fit the Gell and Combs classification system of hypersensitivity reactions.

CLINICAL IMPLICATIONS

Adverse drug reactions caused by immunologic and non-immunologic causes are a major cause of morbidity and mortality. Adverse drug reactions complicate 5% to 15% of therapeutic drug courses.⁹ Factors that increase the risk of general adverse drug reactions (Table 2) include

Table 2.
Risk Factors for Adverse Drug Reactions^{1,10-15}

Asthma
Liver disease
Female gender
Renal insufficiency
Use of beta blockers
Infection with herpes virus
Route of drug administration
Systemic lupus erythematosus
Infection with human immunodeficiency virus
Previous hypersensitivity to chemically-related drug

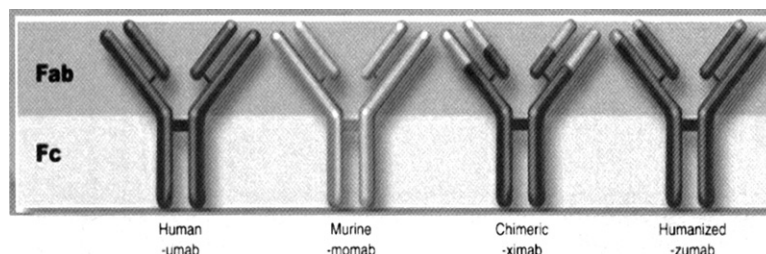


FIGURE 1. Types of monoclonal antibodies. (Reprinted with permission from the Oncology Nursing Society, “Chemotherapy and Biotherapy Guidelines and Recommendations for Practice,” Ed. 2, 2005.)

female gender,¹⁰ renal insufficiency, liver disease, infection with human immunodeficiency virus,¹¹ and infection with herpes.¹² Factors that increase the risk of hypersensitivity reactions include those risk factors already mentioned as well as asthma,¹³ use of beta blockers,¹³ systemic lupus erythematosus,¹⁴ previous hypersensitivity to a chemically related drug, and the route of drug administration. Topical, intramuscular, and intravenous administrations of medications are much more likely to cause hypersensitivity reactions than oral administration of medications.¹⁵

There are four types of MOABs, and their make-up plays a role in their influence on the development of hypersensitivity reactions (Fig 1). Murine (or mouse) MOABs are derived from mice. Murine antibodies have the highest risk of causing hypersensitivity reactions because they are antibodies completely developed from another species. Murine MOAB are usually named with the suffix “-momab,” such as ibritumomab tiuxetan (Zevalin; Biogen Idec, Cambridge, MA). The three other types of MOABs are “engineered” using more human and lesser amounts of murine components. Chimeric antibodies are made up of about 7 % to 9% murine antibody: the long arm of the antibody (the Fc portion) is human antibody and is fused to the “Y” section of the antibody (the Fab portion). Chimeric antibodies are usually named with the suffix “-ximab,” such as rituximab (Rituxan; Genentech, Inc, South San Francisco, CA, and Biogen Idec) and still place the patient at risk for developing hypersensitivity reactions. Humanized MOABs contain only 2% to 5% murine antibody (located on the Fab section of the antibody) and as such have the potential to cause hypersensitivity reactions, but to a lesser degree than murine and chimeric MOABs. Humanized antibodies are usually named with the suffix “-zumab,” such as alemtuzumab (Campath; Gen-

zyme Corp, Cambridge, MA). Fully humanized antibodies have been engineered to contain only human antibody gene sequences, and are usually named with the suffix “-umab” (eg, adalimumab [Humira; Abbott Laboratories, Abbott City, IL]). Humanized antibodies have much less risk of causing hypersensitivity reactions as they have no murine component.^{16,17}

Drug reactions can be mild and bothersome to life-threatening in nature. Identifying, understanding, and managing these reactions is critical when caring for patients receiving biotherapy agents because these agents are capable of causing adverse drug reactions, including hypersensitivity reactions. The first line of defense against hypersensitivity reactions is prevention. Prevention of hypersensitivity reactions is achieved by understanding the drugs that place patients at risk for reactions and by providing premedications for patients receiving drugs thought to have the potential to cause hypersensitivity reactions. It is critical to have an emergency plan in place to manage hypersensitivity reactions when they occur. The National Cancer Institute uses a “Common Terminology Criterion for Adverse Events v 3.0” (2003) to grade drug reactions (Table 3).¹⁸ This criterion is used primarily when testing drugs in clinical trials, and does not have a treatment algorithm based on the grading criteria.

CLINICAL MANIFESTATIONS

Hypersensitivity reactions may present with involvement of any organ system, including systemic reactions such as anaphylaxis. The signs and symptoms of Type I hypersensitivity reactions are a result of mediators on target organs (eg, the skin, lungs, or cardiovascular system) that lead to local reactions or systemic anaphylaxis.

Table 3.
National Cancer Institute Common Terminology Criteria for Adverse Events¹⁸

Adverse Event	Short Name	Grade				
		1	2	3	4	5
Allergic reaction/hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; drug fever >38°C (>100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death

The antigen-specific IgE binds to mast cells and sensitizes them to the antigen (Fig 2). Subsequent exposure of the sensitized mast cell to the antigen causes a series of reactions that result in the degranulation of the mast cell and the release of mediators of the hypersensitivity reaction.¹⁹ Symptoms of type I reactions include fever, nausea, vomiting, flushing, rashes, urticaria, angioedema, bronchospasm, back pain, shortness of breath, and alterations in heart rate and blood pressure.²⁰ Patients often express a feeling of impending doom during an anaphylactic reaction.²¹ Anaphylactic reactions are potentially life-threatening, primarily because of airway and circulatory collapse. Factors that influence the development and severity of anaphylaxis include the antigen's route of entry (more frequent with IV administration), the amount of antigen introduced, the rate of antigen absorption, and an individual's degree of hypersensitivity to a drug (related to risk factors for the development of a hypersensitivity reaction).²²

Type 2 hypersensitivity reactions may result in hemolytic anemia, neutropenia, and thrombocy-

topenia. Type 3 hypersensitivity reactions can also result in urticaria, but it is more common with type I hypersensitivity reactions.¹ Other more common reactions associated with type III hypersensitivity reactions include fever, rash, arthralgias, lymphadenopathy, vasculitis, glomerulonephritis, and serum sickness. Type IV hypersensitivity reactions are associated with contact dermatitis, graft rejection, and a maculopapular drug rash.

Cytokine release syndrome is related to elevated levels of cytokines and histamines as tumor antigen-expressing cells are destroyed. The effects occur after administration of MOABs, interferon, and immune-response modifiers. These elevated cytokine levels are associated with a variety of clinical symptoms including fever, chills, rigors, nausea, vomiting, dyspnea and hypotension.²³ Cytokine release syndrome can present almost identically to type I reactions, and can progress to anaphylaxis or anaphylaxis-like reactions.

Epidermal growth factor receptor (EGFR) expression and/or signal transduction pathway are upregulated in many human cancers. The anti-

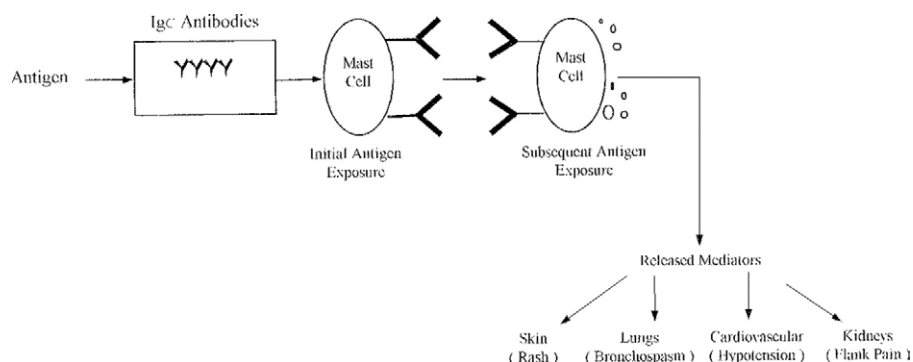


FIGURE 2. Type 1 hypersensitivity reactions.

EGFR antibodies, such as cetuximab, bind to the EGFR and inhibit its activation. Based on this mechanism of action, the most common side effect of these therapies is acneiform rash.²⁴⁻²⁷ The rash typically begins during the first week of therapy and resolves spontaneously after termination of therapy. Similar cutaneous side effects have been observed in studies investigating the low-molecular-weight tyrosine kinase inhibitors gefitinib and erlotinib, which also inhibit EGFR signaling.^{28,29} These cutaneous skin reactions are not hypersensitivity reactions to the drugs; they are manifestations of the mechanism of action of EGFR inhibition. It is critical to understand the mechanism of action of this side effect and not to discontinue therapy (depending on the severity of the rash) because clinical trials have reported that the tumor response to these drugs correlates with the severity of the skin lesions.^{30,31}

BIOOTHERAPY DRUGS ASSOCIATED WITH HYPERSENSITIVITY REACTIONS AND CYTOKINE RELEASE SYNDROMES

Interferon

Alfa interferon. There are a variety of alfa interferons available to treat a variety of cancers as well as other diseases. Common infusion-related side effects related to interferon alfa-2a is the frequent onset of chills, fever, rigors, and tachyphylaxis (decrease in severity and occurrence after successive treatments).^{32,33} These symptoms are often described as “flu-like symptoms” that generally occur 1 to 2 hours after a dose and may persist for 18 hours.³⁴ Prophylactic treatment with acetaminophen tends to blunt the severity of these side effects.

Interferon beta (1A and 1B). The flu-like symptoms of chills, fever, rigors, and diaphoresis are also seen with the beta interferons. These symptoms occur regardless of dose, route, or schedule of the drug given. The symptoms generally occur within 1 to 2 hours after a dose and may persist for 18 hours, and tend to lessen with continued dosing.³⁴

Interferon gamma. As with the interferon beta drugs, the flu-like symptoms of chills, fever, rigors, diaphoresis, and night sweats occur with all routes of administration of the drug. Prophylactic treatment with acetaminophen also tends to blunt the severity of these side effects.

Interleukin

Aldesleukin. The flu-like symptoms of chills, fever, and rigors are common and expected with the use of aldesleukin. These symptoms generally occur 2 to 4 hours after the administration of the drug. The chills and fevers can generally be minimized by around-the-clock administration of acetaminophen. The rigors associated with aldesleukin are often successfully treated with the intravenous administration of meperidine or a comparable opioid.

Denileukin diftitox. Acute hypersensitivity reactions were reported to have occurred in 69% of patients treated with denileukin diftitox in clinical trials.^{35,36} Reactions were characterized by (in order of frequency) hypotension, back pain, vasodilatation, shortness of breath, rash, chest pain or tightness, tachycardia, dysphasia or laryngismus, syncope, and/or anaphylaxis. Anaphylaxis occurred only 1% of the time in clinical trials.^{35,36}

Flu-like symptoms occurred more often than acute hypersensitivity reactions in clinical trials with denileukin diftitox.^{35,36} Symptoms primarily include fever and chills, asthenia, and nausea and vomiting. These symptoms can be experienced hours to days after the infusion and respond to symptom management.

Monoclonal Antibodies

Alemtuzumab. Alemtuzumab is a humanized MOAB that targets the CD52 antigen present on most normal human lymphocyte cells, as well as malignant T-cell and B-cell lymphocytes. Reactions that have been observed with the administration of alemtuzumab include rigors (most frequent symptom), fever, nausea, vomiting, hypotension, rash, urticaria, dyspnea, and pruritis.^{33,37} Because of the frequency of reactions, premedication with oral diphenhydramine and acetaminophen is used to prevent or minimize these symptoms, especially recommended with the initial dose of alemtuzumab and with each dose increase.

Bevacizumab. Bevacizumab is a recombinant humanized MOAB targeted against vascular endothelial growth factor. Infusion-related side effects are generally mild and self-limited and include fever, chills, rigors, and myalgias.³⁸ These reactions are more common with the first treatments with the drug. Slower infusion time of the drug reduces the incidence of the infusion-related symptoms.³³ Premedication with acetaminophen and diphenhydramine is generally not necessary

unless a patient develops infusion-related symptoms.

Cetuximab. Cetuximab is a chimeric MOAB targeted against EGFR. Flu-like symptoms have occurred in approximately 15% of patients treated with cetuximab, including fever and chills.³⁹ Hypersensitivity reactions have also occurred with symptoms including hypotension, urticaria, stridor, dyspnea, hoarseness, and bronchospasm. Most of the reactions, whether the flu-like symptoms or a hypersensitivity reaction (including anaphylaxis), occur during the first infusion.⁴⁰

Gemtuzumab ozogamicin. Gemtuzumab ozogamicin is a recombinant humanized MOAB that is combined with the cytotoxic antibiotic calicheamicin. A symptom complex of fever, chills, nausea, vomiting, headache, and hypotension is commonly observed following the first infusion of this drug. These symptoms generally occur immediately after the 2-hour infusion of the drug, but may occur within 24 hours after the completion of the infusion. Patients are less likely to experience these symptoms with subsequent infusions.⁴¹ Anaphylaxis and other severe hypersensitivity reactions have been reported associated with gemtuzumab ozogamicin infusions.^{41,42}

Ibritumomab tiuxetan. Ibritumomab tiuxetan is a murine-derived MOAB directed against CD20-positive cells. Patients are pretreated with the anti-CD20 antibody rituximab. The most common infusion-related reactions include fever, chills, and rigors. These symptoms are generally observed with the first infusion and the incidence decreases with subsequent infusions. Other reported reactions that are symptomatic of hypersensitivity reactions include nausea and vomiting, hypotension, hypertension, bronchospasm, throat irritation, dizziness, and angioedema.⁴³ Anaphylaxis and other hypersensitivity reactions have been reported in less than 1% of patients treated with ibritumomab tiuxetan.⁴⁴ Premedication with acetaminophen and diphenhydramine is recommended to prevent hypersensitivity reactions to both the rituximab and the ibritumomab tiuxetan.

Panitumumab. Panitumumab is the first fully human anti-EGFR MOAB available for treatment of cancer. In the pivotal trial of this MOAB, 3% of patients (43/1,336) experienced an infusion reaction and 1% of patients (6/1,336) experienced severe infusion reactions.⁴⁵

Rituximab. Rituximab is chimeric MOAB directed against CD20-positive cells. Because of the high rate of infusion-related reactions, it is recom-

mended that patients be premedicated with acetaminophen and diphenhydramine before each dose of rituximab. The most common symptoms associated with rituximab infusions are fever, chills, and rigors. These reactions are most common with the first infusion of the drug and decrease in incidence with subsequent infusions.⁴⁶ Infusion-related reactions generally resolve with slowing or stopping the infusion and symptomatic treatment of the patient (eg, acetaminophen, diphenhydramine, and intravenous saline). More severe reactions that are symptomatic of hypersensitivity reactions include nausea, vomiting, flushing, pruritis, dyspnea, rhinitis, urticaria, bronchospasm, angioedema, hypotension, and throat irritation.⁴⁷ These reactions occur in approximately 10% of patients treated with rituximab.⁴⁸

Tositumomab. Tositumomab is an iodine-1131 murine MOAB directed against CD20-positive cells. Because of the frequency of mild to moderate infusion-related reactions, it is recommended that patients be premedicated with acetaminophen and diphenhydramine before any infusion with tositumomab (dosimetric and radiolabeled). The most common symptoms related to tositumomab infusions are fever, chills, and rigors. Infusion-related symptoms generally resolve with slowing of the infusion. More severe reported reactions include wheezing, rhinitis, dyspnea, bronchospasm, and hypotension.⁴⁹

Trastuzumab. Trastuzumab is a recombinant humanized MOAB targeted against the human EGFR 2 protein (*Her-2*). The most common reported infusion-related symptoms are fever and chills. Other reported reactions include rash, rigors, nausea, vomiting, dizziness, dyspnea, and hypotension. The infusion-related symptoms occur most frequently with the first infusion of the drug and decrease in incidence with subsequent infusions. Symptoms can generally be managed with the administration of acetaminophen, diphenhydramine, and an opioid for the rigors. Severe or anaphylactic reactions have occurred, but are rare.^{33,34}

PREVENTION OF HYPERSENSITIVITY REACTIONS TO BIOTHERAPY DRUGS

Recognition of High-Risk Patients

Just like chemotherapy drugs, most biotherapy drugs have the potential to cause hypersensitivity

reactions. In addition to being aware of the general factors that increase the risk of adverse drug reactions, it is important to be aware of the type of drug to be administered. For example, the infusion-related symptoms of fever, chills, and rigors are very common with the administration of the interferons and interleukins. Patients receiving these drugs should be monitored closely for the occurrence of these symptoms. Teaching patients about the signs and symptoms to report helps to identify the symptoms early and to treat them appropriately. Knowledge of when patients are most likely to experience reactions helps the nurse to anticipate reactions and the management of the reactions. Reactions are most common during the first infusion of most of the MOABs, particularly the murine and chimeric antibodies.

A thorough history including the patient's allergy history will provide data about previous allergies to the drug, as well as to other drugs. Obtaining and recording baseline vital signs provides valuable data to determine if a hypersensitivity reaction has occurred. Ensuring that premedications to prevent hypersensitivity reactions and cytokine release syndrome are ordered and given, when appropriate, are also critical to prevent reactions to these drugs.

Premedication Regimens

There is no standard premedication regimen that has been published (based on research) that prevents hypersensitivity (and cytokine release syndrome) related to the administration of biotherapy drugs. Medications commonly used to help prevent these reactions include histamine two antagonists (eg, diphenhydramine) and antipyretics (eg, acetaminophen). Premedications are generally ordered for those drugs thought to carry a high risk for a drug reaction, such as the MOABs with a high murine component, the interferons, or the interleukins. Regular dosing of antipyretics is often prescribed to minimize the fever and chills associated with the interferons and the interleukins.^{50,51} If the patient does experience a severe hypersensitivity reaction to a particular drug and the treatment plan calls for continued use of that drug, then corticosteroids may also be used as part of the premedication regimen.

Infusion Rate Titration

MOAB infusions are rate-dependent, especially with the first infusion of the drug. It has been shown in clinical trials that when these drugs are

given slower there is a lower incidence and a decreased severity of reactions to the drugs. Each MOAB has a specified infusion rate. One example of a well-established infusion rate protocol is for the infusion of rituximab. The initial infusion rate is 50 mg/hour; the rate is then increased by 50 mg/hour every 30 minutes if the patient tolerates the drug. The drug can be titrated to a rate of 400 mg/hour, based on the clinical response of the patient. If the patient tolerates the first infusion of the drug, the subsequent doses can be administered at an initial rate of 100 mg/hour, increased by 100 mg/hour to the maximum of 400 mg/hour.⁴⁶ If the patient experiences hypersensitivity reactions to the first infusion, the subsequent infusions are initiated at a rate of 50 mg/hour.

MANAGEMENT OF HYPERSENSITIVITY REACTIONS TO BIOTHERAPY DRUGS

Infusion Rate Titration

If an infusion-related reaction occurs when administering biotherapy drugs, stop the infusion until the symptoms improve. Once symptoms have improved (with appropriate symptom management), the infusion can be re-started at a slower infusion rate than was previously established. The published recommendation for rituximab-related infusions is that the infusion should be restarted at half the rate before the reaction.⁴⁶ If the patient experiences a severe hypersensitivity reaction, the infusion should be stopped and the symptoms appropriately treated.

Emergency Preparedness

Basic life support training is to be ensured in any setting of care that provides for the administration of biotherapy drugs. The initial steps in managing patients with potentially life-threatening reactions to biotherapy drugs are the same as those for a life-threatening reaction to any drug: managing and maintaining the patient's airway, breathing, and circulation. Emergency drugs and equipment should be available for the management of severe hypersensitivity reactions.

Pharmacologic Therapy and Equipment

The availability of oxygen and oxygen therapy equipment is vital to any setting of care that provides for the administration of biotherapy drugs, as even mild hypersensitivity reactions can progress to life-threatening reactions. Oxygen

Table 4.
Pharmacologic Therapy for the Management of
Moderate to Severe Hypersensitivity Reactions⁵³

- Adrenaline 1:1000 or 1:10,000
- Albuterol (aerolized)
- Aminophylline
- Atropine
- Calcium gluconate
- Crystalloid solutions (normal saline or lactated Ringer's solution)
- Corticosteroids
- Dopamine
- Famotidine
- Histamine 1 antagonist
- Histamine 2 antagonist
- Lidocaine
- Norepinephrine
- Ranitidine
- Sodium bicarbonate

therapy equipment that should be found in all settings of care includes oxygen tanks, nasal cannula oxygen tubing, and tubing with oxygen masks. Other essential respiratory equipment includes an ambu bag, oral airway, and suction apparatus if the patient becomes unconscious. Large-gauge intravenous catheters are recommended to enable administration of normal saline and emergency medications.

Mild or moderate hypersensitivity symptoms (eg, fever and chills) can generally be managed with acetaminophen, diphenhydramine, and intravenous saline infusion. Types 1 and 2 histamine blockers are used with hypersensitivity reactions that are not life-threatening and are progressing slowly, such as with rashes, urticaria, and angioedema. A combination of these drugs has been found to be more effective in treating these reactions than giving either of these drug types alone.⁵² Rigors are treated with the intravenous use of meperidine or a comparable opioid.

A number of drugs are required for the management of severe hypersensitivity reactions. Table 4 provides a comprehensive list of emergency medications to manage a severe hypersensitivity reaction.⁵³ Medications necessary for the first-line management of severe hypersensitivity reactions include adrenaline and crystalloid solutions (ie, normal saline and/or lactated Ringer's solution. Adrenaline helps to improve blood pressure, decrease angioedema and urticaria, and inhibits the inflammatory mediator release.⁵⁴ Adrenaline can

be given intramuscularly, subcutaneously, sublingually, intravenously (IV), or via the endotracheal tube. The route of administration generally depends on what is immediately available. For example, if the patient has an available IV the adrenaline can be given intravenously. But, if the patient does not have an IV or if there is difficulty starting an IV then the adrenaline can be given via the intramuscular or subcutaneous route.

Large volumes of crystalloid solutions, which are infused rapidly, may be required to help restore intravascular volume during a severe hypersensitivity reaction.⁵³ Intravascular volume shifts to the extravascular space during severe hypersensitivity reactions, thereby lowering the blood pressure.²⁰ Vasopressors may be required if the blood pressure does not respond to adrenaline and fluids alone. Dopamine is generally the vasopressor of choice. The dose of dopamine is weight-based and is adjusted based on the effect of the drug on the patient's blood pressure.²⁰

Close hemodynamic monitoring is critical during a hypersensitivity reaction to biotherapy drugs. During a severe hypersensitivity reaction vital signs are to be taken every 2 to 5 minutes while the patient is hemodynamically unstable, then every 15 minutes when the vital signs stabilize. Patients may need to be monitored closely for 24 hours if the reaction was severe.

CONCLUSION

The use of biologic drugs for the management of cancer is increasingly common. One of the side effects of many of the biologic drugs is that of hypersensitivity reactions. Hypersensitivity reactions can be mild and localized or severe and generalized, leading to the occurrence of anaphylaxis. Nurses are in a key position to identify hypersensitivity reactions early and thereby make a positive impact on patient outcomes. Several risk factors have been identified that increase the likelihood of a drug reaction (eg, female gender,¹⁰ renal insufficiency, and liver disease) as well as risk factors for the development of hypersensitivity reactions (eg, use of beta blockers,¹³ systemic lupus erythematosus,¹⁴ previous hypersensitivity to a chemically related drug, the route of drug administration, as well as the specific biologic drug used). In addition to knowing the risk factors that increase the likelihood of reactions, the nurse should ensure the administration of medications

for the prophylaxis for hypersensitivity reactions with many of the high-risk biologic drugs. Another strategy to prevent hypersensitivity reactions, particularly cytokine release syndrome, is titration of certain drugs (eg, rituximab), starting with a slow infusion rate and increasing the rate depending on the patient's reaction to the drug.

Nursing management of hypersensitivity reactions related to the administration of biologic drugs is similar to treating those reactions related to the administration of chemotherapy and other drugs. Nurses need to consider the formulation of

an emergency plan in any setting of care and the appropriate medications to treat hypersensitivity reactions. Nurses working with biologic drugs should consider the need for ongoing education regarding the management of hypersensitivity reactions related to the administration of biologic drugs. These reactions, especially moderate to severe reactions, can be frightening and highly anxiety-producing to patients and their families. Thus, the care of the patient and their family experiencing a hypersensitivity reaction needs to be delivered in a calm and confident manner.

REFERENCES

1. Riedl MA, Casillas AM. Adverse drug reactions: types and treatment options. *Am Fam Physician* 2003;68:1781-1790.
2. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. *JAMA* 1997;278:1895-1906.
3. Weiss RB. Miscellaneous toxicities. In: DeVita VT, Hellman S, Rosenberg SA, eds: *Cancer: principles and practice of oncology*. Ed 6. Philadelphia, PA: Lippincott Williams and Wilkins; 2001;2964-2976.
4. Shepherd GM. Hypersensitivity reactions to drugs: evaluation and management. *Mount Sinai J Med* 2003;70:113-125.
5. Gobel BG. Chemotherapy-induced hypersensitivity reactions. *Oncol Nurs Forum* 2005;32:1027-1035.
6. Ream M, Tunison D. Hypersensitivity reactions. In: Yasko JM, ed: *Nursing management of symptoms associated with chemotherapy*. Ed 5. Bala Cynwyd, PA: Meniscus Limited; 2001;271-282.
7. Thomas M. Treatment-related hypersensitivity reactions to antineoplastic agents. recognition, prevention, and management [Continuing education monograph and self-test]. Skillman, NJ: American Academy of Continuing Medical Education; 2004.
8. Winkler U, Jensen M, Mancke O, et al. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999;94:2217-2224.
9. Ditto AM. Drug allergy, part A: Introduction, epidemiology, classification of adverse reactions, immunochemical basis, risk factors, evaluation of patients with suspected drug allergy, patient management considerations. In: Grammer LC, Greenberger PA, eds: *Patterson's allergic diseases*. Ed 6. Philadelphia, PA: Lippincott Williams and Wilkins; 2002;295-334.
10. Barranco P, Lopez-Serrano MC. General and epidemiological aspects of allergic drug reactions. *Clin Exp Allergy* 1998;28 (suppl 4):61-62.
11. Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J Acquir Immune Defic Syndr* 1992;5:1237-1257.
12. Descamps V, Valance A, Edlinger C, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001;137:301-304.
13. Lang DM, Alpern MB, Visintainer PF, et al. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. *Ann Intern Med* 1991;115:270-276.
14. Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. *J Rheumatol* 1992;19:265-269.
15. Adkinson NF Jr. Risk factors for drug allergy. *J Allergy Clin Immunol* 1984;74:567-572.
16. Cheng JD, Rieger PT, von Mehren M, et al. Recent advances in immunotherapy and monoclonal antibody treatment of cancer. *Semin Oncol Nurs* 2000;16(suppl 1):2-12.
17. Rieger PT, Green M, Murray L. Monoclonal antibodies: Applications in solid tumors and other diseases. In: Rieger PT, ed: *Biotherapy*. Sudbury, MA: Jones and Bartlett; 2001;317-355.
18. National Cancer Institute. Common terminology criteria for adverse events v 3.0. 2003. Available at: <http://ctep.cancer.gov/reporting/ctc.html> (accessed December 18, 2006).
19. Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Safety* 2001;24:767-779.
20. Drain KL, Volcheck GW. Preventing and managing drug-induced anaphylaxis. *Drug Safety* 2001;24:843-853.
21. Lieberman P, Kemp SF, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115:S483-S523.
22. Labovich TM. Acute hypersensitivity reactions to chemotherapy. *Semin Oncol Nurs* 1999;15:222-231.
23. Yeung S, Escalante CP. Oncologic emergencies. In: Kufe DW, Pollock RE, Weichselbaum RR, et al. eds: *Holland-Frei Cancer Medicine*. Ed 5. Hamilton, Ontario: BC Decker Inc; 2000;2659-2670.
24. Busam KJ, Capodieci P, Motzer R, et al. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol* 2001;144:1169-1176.
25. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-345.
26. Monti M, Mancini LL, Ferrari B, et al. Complications of therapy and a diagnostic dilemma case. Case 2. Cutaneous toxicity induced by cetuximab. *J Clin Oncol* 2003;21:4651-4653.
27. Saltz LB, Meropol NJ, Loehrer PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that

expresses the epidermal growth factor receptor. *J Clin Oncol* 2004;22:1201-1208.

28. Raben D, Helfrich BA, Chan D, et al. ZD1839, a selective epidermal growth factor receptor tyrosine kinase inhibitor, alone and in combination as a new therapeutic strategy in non-small cell lung cancer. *Semin Oncol* 2002;29(suppl 4):37-46.

29. van Doorn R, Kirtschig G, Scheffer E, et al. Follicular and epidermal alterations in patients treated with ZD1839 (Iressa) an inhibitor of the epidermal growth factor receptor. *Br J Dermatol* 2002;147:598-601.

30. Perez-Soler R. Can rash associated with HER1/EGFR inhibition be used as a marker of treatment outcome? *Oncology* 2003;17:23-28.

31. Susman E. Rash correlates with tumour response after cetuximab. *Lancet Oncol* 2004;5:647.

32. Polovich M, White JM, Kelleher LO, eds. *Chemotherapy and biotherapy guidelines and recommendations for practice*. Ed 2. Pittsburgh, PA. Oncology Nursing Society: 2005.

33. Wilkes GM, Barton-Burke M, eds. *Oncology nursing drug handbook*. Sudbury, MA. Jones and Bartlett: 2005.

34. Fischer DS, Knobf MT, Durivage HJ, et al, eds, *The cancer chemotherapy handbook*. Ed 6. Philadelphia, PA: Mosby: 2003.

35. Foss FM, Bacha P, Osann KE, et al. Biological correlates of acute hypersensitivity events with DAB (389) IL-2 (denileukin diftitox, ONTAK) in cutaneous T-cell lymphoma: decreased frequency and severity with steroid premedication. *Clin Lymphoma* 2001;1:298-302.

36. Olsen ED, Duvic M, Frankel A, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001;19:376-388.

37. Osterborg A, Dyer MJS, Bunjes D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukaemia. *J Clin Oncol* 1997;15:1567-1574.

38. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2334-2342.

39. Clinical pharmacology. Cetuximab. 2006. Available at: <http://cpip.gsm.com> (accessed January 5, 2007).

40. Herbst RS, Langer CJ. Epidermal growth factor receptors as a target for cancer treatment: the emerging role of

IMC-225 in the treatment of lung and head and neck cancers. *Semin Oncol* 2002;29(suppl 4):27-36.

41. Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 2001;19:3244-3254.

42. Clinical pharmacology. Gemtuzumab ozogamicin. 2006. Available at: <http://cpip.gsm.com> (accessed January 5, 2007).

43. Wiseman GA, White CA, Witzig TE, et al. Radioimmunotherapy of relapsed non-Hodgkin's lymphoma with zevalin, a 90Y-labeled anti-CD20 monoclonal antibody. *Clin Cancer Res* 1999;5:3281s-3286s.

44. DeNardo G. Treatment of non-Hodgkin's lymphoma (NHL) with radiolabeled antibodies (mAbs). *Semin Nucl Med* 2002;35:202-211.

45. Vectibix (Panitumumab). Full prescribing information. Thousand Oaks, CA; Amgen Inc. 2007.

46. Rituxan (Rituximab). Full prescribing information. Genentech, Inc, South San Francisco, CA. 2002. Revised February 2002.

47. Maloney DG, McLaughlin P. Rituximab for the treatment of patients with B-cell non-Hodgkin's lymphoma. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Progress in oncology*. Boston, MA: Jones & Bartlett: 2001;204-227.

48. Plosker GL, Figgitt DP. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukemia. *Drugs* 2003;63:803-843.

49. Kaminski MS, Tuck M, Estes J, et al. Pivotal study of iodine I131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol* 2001;19:3918-3928.

50. Clinical pharmacology. Interferon alfa. 2006. Available at: <http://cpip.gsm.com> (accessed January 5, 2007).

51. Clinical pharmacology. Aldesleukin. 2006. Available at: <http://cpip.gsm.com> (accessed January 5, 2007).

52. Runge JW, Martinez JC, Caravati EM, et al. Histamine antagonists in the treatment of acute allergic reactions. *Ann Emerg Med* 1992;21:237-242.

53. Joint Task Force on Practice Parameters. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allerg Clin Immunol* 2005;3(suppl 2):S438-S524.

54. Brown AF. Therapeutic controversies in the management of acute anaphylaxis. *J Acc Emerg Med* 1998;15:89-95.