

# Chemotherapy and Biotherapy-Induced Hypersensitivity Reactions

## ABSTRACT

Nearly all chemotherapy and biotherapy drugs used in cancer treatment today can cause hypersensitivity reactions. Certain groups of drugs frequently associated with these reactions include the asparaginases, taxanes, platinum compounds, epipodophyllotoxins, and the monoclonal antibodies. Recognizing and managing hypersensitivity reactions are critical when caring for patients receiving these drugs because the reactions are potentially life-threatening. A thorough understanding of the drugs is necessary to assist the nurse in prevention, early recognition, and timely management.

or foreign substance.<sup>1-3</sup> Most hypersensitivity reactions occur during or within hours of a chemotherapy or biotherapy drug administration; however, occasionally a reaction may occur 1 to 2 days after administration.<sup>2</sup>

## INCIDENCE OF HYPERSENSITIVITY REACTIONS

The exact incidence of hypersensitivity reactions to chemotherapy and biotherapy drugs is unknown. Although severe reactions are rare, with an incidence of less than 5%, the incidence of mild-to-moderate reactions is estimated to occur in approximately 5% to 15% of patients receiving chemotherapy or biotherapy drugs.<sup>4,5</sup>

For some drugs, a hypersensitivity reaction occurs frequently enough for this adverse effect to be a major treatment-limiting toxicity. These drugs include asparaginases, taxanes, platinum compounds, epipodophyllotoxins, procarbazine, and the monoclonal antibodies (MoAbs).<sup>3</sup> Nitrosoureas are the only class of chemotherapy drugs that has never been documented to cause a hypersensitivity reaction.<sup>6</sup>

An increased risk of hypersensitivity reactions is known to occur with drugs that are proteins such as L-asparaginase, drugs prepared in antigenic diluents such as taxanes and epipodophyllotoxins, heavy metal compounds such as cisplatin and carboplatin, and biologic agents.<sup>6</sup> Intravenous (IV) administration, higher drug dosages, and short intervals between exposures also increase the risk of a reaction. Additional risk factors associated with an increased incidence of hypersensitivity reactions include age, history of prior anaphylaxis to foods, antibiotics, insect bites, radiocontrast media, history of allergies, and female gender.<sup>3,7</sup>

Recognizing and managing hypersensitivity reactions are critical when caring for patients receiving chemotherapy and biotherapy drugs because the reactions are potentially life threatening. A thorough understanding of the drugs that have a high risk of causing a hypersensitivity reaction is necessary to assist the nurse in prevention, early recognition, and timely management.

Nearly all chemotherapy and biotherapy drugs used in cancer treatment today can cause hypersensitivity reactions. These reactions range in severity from mild flushing and itching to anaphylaxis, and in rare cases, death. The term *hypersensitivity reaction* is often used interchangeably to refer to allergic reactions as well as to acute infusion reactions such as fever, nausea, and chills associated with monoclonal antibodies. A *hypersensitivity reaction* is defined as an exaggerated or inappropriate immune response that may be localized or systemic and results in local tissue injury or changes throughout the body in response to an antigen

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## CHARACTERISTICS OF HYPERSENSITIVITY REACTIONS

There are 4 categories of hypersensitivity reactions that have been identified. Type I is an immediate immunoglobulin E (IgE)-mediated reaction, type II is an immunoglobulin G (IgG) or immunoglobulin M (IgM) antibody-mediated reaction resulting in antibody-antigen complexes, type III is an immune complex-mediated reaction, and type IV is a cell-mediated or delayed hypersensitivity reaction.

Many hypersensitivity reactions to chemotherapy drugs are consistent with type I reactions, although there have been case reports of types II, III, and IV. A type I reaction occurs following exposure to a foreign substance or antigen (the chemotherapy drug, the drug's metabolite, or the solution in which the drug is dissolved). This exposure results in the formation of IgE antibodies that attach to the receptors on tissue mast cells and peripheral blood basophils.<sup>6,8</sup> A subsequent exposure of the sensitized mast cell to the antigen causes a series of reactions resulting in the release of histamines, leukotrienes, prostaglandins, and other mediators. The signs and symptoms are due to the effects of the mediators on the skin, lungs, cardiovascular system, and gastrointestinal tract, and lead to local reactions or systemic anaphylaxis.<sup>6,9</sup> Symptoms of type I reactions include the following:

- *Cutaneous symptoms*: flushing, urticaria, pruritus, and/or angioedema (usually of face, eyelids, or lips)
- *Respiratory symptoms*: repetitive cough, sudden nasal congestion, dyspnea, chest tightness, wheeze, throat tightness, and change in voice quality (due to laryngeal edema)
- *Cardiovascular symptoms*: tachycardia and hypotension
- *Gastrointestinal symptoms*: nausea, vomiting, abdominal cramping, and diarrhea
- *Neurological symptoms*: feeling of "impending doom," tunnel vision, and dizziness<sup>10,11</sup>

Signs and symptoms highly suggestive of anaphylaxis include urticaria, repetitive cough, wheeze, and throat tightness or change in voice. Neck, trunk, abdomen, and axilla are sites where urticaria often appears first. These manifestations result from the release of mediators from the mast cells and basophils.<sup>12</sup>

A significant number of hypersensitivity reactions related to chemotherapy drugs, however, are considered anaphylactoid instead of anaphylactic. Anaphylactoid reactions differ from anaphylactic reactions in that no prior exposure to the drug or solution is necessary to cause the reaction. The drug itself, not the IgE antibodies, interacts directly with the mast cells and basophils causing the release of mediators. Anaphylactoid and anaphylactic reactions have identical signs and symptoms and are treated in the same manner.<sup>9,13</sup>

The mechanisms responsible for the hypersensitivity reactions caused by MoAbs remain unclear. Most reactions appear to be the result of antibody-antigen interactions resulting in the release of inflammatory cytokines. When released into the circulation, cytokines can produce a group of symptoms known as cytokine-release syndrome. Typical symptoms of cytokine-release syndrome include fever, chills, nausea, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, tongue and throat swelling, and dyspnea, which are mild to moderate in severity.<sup>14</sup> When massive cytokine release occurs, it may precipitate life-threatening infusion reactions. Since a cytokine-dependent mechanism does not depend on prior sensitization, cytokine-release syndrome most commonly occurs with the first infusion of a MoAb and lessens in frequency with subsequent infusions.<sup>9,14</sup> Side effects generally occur within the first 2 hours following initiation of the infusion and are usually managed with temporary cessation of the infusion, administration of histamine blockers, and infusion rate reduction.<sup>14</sup>

The National Cancer Institute Common Terminology Criteria for Adverse Events<sup>15</sup> (Table 1) distinguishes between allergic/hypersensitivity reactions and acute infusion reactions induced by cytokine release. Both types of reactions can vary in severity from grade 1 (mild) to grade 5 (fatal). Mild-to-moderate (grade 1 or 2) reactions are characterized by pruritus, flushing, rash, urticaria, fever, chills, dyspnea, and mild hypotension. Severe (grade 3 or 4) reactions are associated with angioedema, bronchospasm, and hypotension, and require immediate and urgent treatment.

## CHEMOTHERAPY DRUGS FREQUENTLY ASSOCIATED WITH HYPERSENSITIVITY REACTIONS

### Asparaginase

Asparaginase is an important component in the treatment of acute lymphoblastic leukemia and is the chemotherapy drug most likely to cause a severe hypersensitivity reaction. There are 3 formulations of asparaginase: the original *Escherichia coli* derivative, L-asparaginase; an *Erwinia chrysanthemi* derivative; and a form of *E coli* asparaginase that is attached to polyethylene glycol known as PEG-asparaginase. The incidence of hypersensitivity reactions is similar with L-asparaginase and *Erwinia*-derived products. The risk is 5% to 8% per administered dose and increases with the number of doses. By the fourth dose, up to 33% of patients experience an infusion reaction, consistent with an IgE-mediated reaction.<sup>16</sup> Another alternative is PEG-asparaginase, although hypersensitivity reactions can still occur.<sup>12</sup>

Anaphylaxis related to L-asparaginase is more common with an intermittent schedule versus a daily

**TABLE 1**

## National Cancer Institute Common Terminology Criteria for Adverse Events

| Adverse Event                                             | Short Name                | Grade 1                                                                        | Grade 2                                                                                                                                                                                    | Grade 3                                                                                                                                                                                                                                                              | Grade 4                                                   | Grade 5 |
|-----------------------------------------------------------|---------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|---------|
| Allergic reaction/hypersensitivity (including drug fever) | Allergic reaction         | Transient flushing or rash; drug fever < 38°C (<100.4°F)                       | Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C (≥100.4°F)                                                                                                                           | Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension                                                                                                                               | Anaphylaxis                                               | Death   |
| Cytokine-release syndrome/acute infusion reaction         | Cytokine-release syndrome | Mild reaction; infusion interruption not indicated; intervention not indicated | Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h | Prolonged (ie, not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) | Life-threatening; pressor or ventilator support indicated | Death   |

Abbreviations: IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.  
Adapted from the National Cancer Institute.<sup>15</sup>

schedule and with IV rather than intramuscular or subcutaneous administration. Up to 45% of patients who receive the drug via IV will have a reaction compared with 14% with intramuscular or subcutaneous administration. For this reason, L-asparaginase is usually given via the intramuscular or subcutaneous route.<sup>17</sup>

Because of the frequent occurrence of hypersensitivity reactions, intradermal skin testing, prior to the first dose and whenever an interval of 1 week or more has elapsed between doses, is recommended.<sup>18</sup> Skin testing can give both false-negative and false-positive results; therefore, nurses must be alert to the possibility of a hypersensitivity reaction with each dose.

For patients who develop a hypersensitivity reaction to the *E coli*-derived asparaginase, the *E chrysanthemi* derivative can be used. This drug is not available in the United States but is commercially available in Canada and Europe. The Food and Drug Administration, however, has authorized its distribution in the United States by OPi SA, Pharmaceuticals for Rare Diseases, on an individual basis for patients who have had a hypersensitivity reaction to the *E coli* form of the drug. Patients who react to one form of this drug have a reduced risk of reacting to the other bacteria-derived form. However, up to 25% of patients will cross-react, especially when multiple doses of the new drug are administered.<sup>19</sup>

Another alternative is polyethylene glycol-asparaginase, although hypersensitivity reactions can still occur.

### Taxanes

Paclitaxel and docetaxel are among the most widely used chemotherapy drugs. In initial clinical trials, hypersensitivity reactions developed in up to 30% of patients receiving paclitaxel. After the introduction of measures to reduce the incidence and severity of reactions, which included administration over 24 hours and premedication with antihistamines and corticosteroids, the rate of severe reactions decreased to 2% to 4%.<sup>20</sup> Prolonged infusions of more than 3 hours have been found to be unnecessary, and paclitaxel is being safely administered over 1 hour, as long as premedication is used.<sup>21</sup> Severe reactions, however, can still occur at a rate of approximately 2%, with mild reactions (rash, flushing) occurring in up to 40% of patients.<sup>19</sup> Most severe reactions to paclitaxel occur with the first or second dose, and onset is within minutes of initiation of the drug infusion.<sup>3</sup> To reduce the risk of severe hypersensitivity reactions with paclitaxel, premedication with a corticosteroid, a histamine-1 receptor (H<sub>1</sub>) antagonist, and a histamine-2 receptor (H<sub>2</sub>) antagonist administered via IV 30 minutes before initiating the infusion is recommended.<sup>22</sup>

Controversy exists regarding whether the hypersensitivity reactions with paclitaxel are due to the drug itself or to its diluent, Cremophor EL® (BASF Aktiengesellschaft, Ludwigshafen, Germany). Cremophor EL has been shown to cause hypersensitivity reactions when used as the diluent with nonantineoplastic drugs.<sup>23</sup> However, in one study, sensitized patients demonstrated histamine release only with paclitaxel and not with Cremophor EL.<sup>24</sup> In addition, docetaxel has a different diluent, polysorbate 80, yet produces a similar rate of hypersensitivity reactions as paclitaxel, approximately 2%. Therefore, patients receiving docetaxel should be pretreated with dexamethasone for 3 consecutive days, beginning the day before the infusion. This regimen is effective for reducing both the incidence and severity of hypersensitivity reactions and fluid retention.<sup>6</sup>

### Platinum Compounds

Most hypersensitivity reactions with platinum compounds (cisplatin, carboplatin, and oxaliplatin) are classic type I, IgE-mediated reactions. These drugs are associated with a high risk of hypersensitivity reactions, ranging from 10% to 27%, and have occurred with all routes of administration, including IV, intraperitoneal, and intravesicular.<sup>19</sup>

Reactions to platinum compounds typically occur only after multiple cycles of therapy. In one study, in patients with gynecologic cancers receiving 7 or more cycles of carboplatin, the incidence of hypersensitivity reactions was 27%, compared with only 1% in patients who received fewer than 7 cycles.<sup>25</sup> Morgan and colleagues<sup>26</sup> reported that 67% of patients receiving 10 cycles of carboplatin had hypersensitivity reactions. This is consistent with type I hypersensitivity reactions, which are associated with repeated exposure to the agent.

The overall incidence of reactions with carboplatin is approximately 12%.<sup>25</sup> With cisplatin, the incidence of infusion reactions is not as well reported. In early trials, incidence rates were between 5% and 20%.<sup>27-29</sup> Current studies, however, report an apparent decrease in the rate of infusion reactions. Possible reasons include the routine use of pretreatment corticosteroids and antihistamines, possibly suppressing any hypersensitivity reaction, and patients often require fewer cycles of cisplatin or carboplatin.<sup>19</sup>

The incidence rates of hypersensitivity reactions with oxaliplatin are between 10% and 13%. The average number of cycles prior to a reaction is 7 or more.<sup>30</sup> No reactions with the first infusion of oxaliplatin have been reported.<sup>19</sup> Most hypersensitivity reactions with oxaliplatin occur at the beginning of the infusion; however, they may occur at any time during the infusion. Regardless of whether a reaction is immediate or delayed, early symptoms of hypersensitivity reactions to oxaliplatin may include erythema of the hands and face accompanied by pruritus of the hands.<sup>31</sup>

### Procarbazine

Procarbazine has been known to cause hypersensitivity reactions since its initial use in the early 1960s. The most common reaction is characterized by a diffuse, pruritic, erythematous, and maculopapular rash, but urticaria, angioedema, and high fever have also been reported.<sup>32</sup> The incidence is uncertain, but reactions have been reported in 30% to 50% of patients treated for brain tumors and 5% to 10% of patients with Hodgkin's lymphoma.<sup>33,34</sup> Reasons for the variation in incidence may be the concomitant use of cytochrome P450 (CYP 3A)-enhancing anticonvulsants in patients with brain tumors.<sup>35</sup> In addition, patients who receive procarbazine in the mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen for Hodgkin's lymphoma are already receiving a corticosteroid as part of the treatment regimen. Hypersensitivity reactions to procarbazine may still occur despite the corticosteroid therapy.<sup>19</sup>

### Epipodophyllotoxins

Etoposide and teniposide are used to treat a variety of different cancers; etoposide is most often used for pediatric malignancies and etoposide for cancers in adults. Overall, teniposide causes hypersensitivity reactions in approximately 6% of patients. In patients with neuroblastoma, however, the incidence of reactions can occur up to 13%.<sup>36</sup> Reactions may occur with any dose, including the initial dose, and can occur after only a few milligrams of the drug have been infused or several hours after administration. O'Dwyer and colleagues<sup>36</sup> reported that 32% of patients reacted with their first dose of teniposide.

Incidence of hypersensitivity reactions in patients treated with etoposide is estimated at 1% to 3%,<sup>19</sup> although in one study, the authors reported an incidence of 51%.<sup>37</sup> Most hypersensitivity reactions have occurred with the first or second dose of etoposide. No hypersensitivity reactions to oral etoposide have been reported.<sup>19</sup>

## BIOOTHERAPY AGENTS FREQUENTLY ASSOCIATED WITH HYPERSENSITIVITY REACTIONS

Biotherapy uses substances naturally produced by the immune system to stop the growth of or destroy cancer cells, whereas chemotherapy uses drugs to block cell replication or cause cell death in frequently dividing cancer cell populations. Biotherapy may be referred to as biological therapy or immunotherapy and includes targeted therapy. Targeted biotherapy is directed at an identifiable receptor on the surface of cancer cells. Biotherapies include MoAbs, angiogenesis inhibitors, tyrosine kinase inhibitors, cytokines (ie, interleukins,

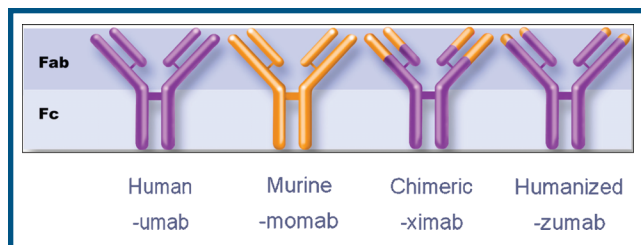


**Figure 1** Types of monoclonal antibodies. Reprinted with permission from Oncology Education Services, Inc.<sup>40</sup> Copyright 2003, Oncology Education Services, Inc.

interferons, colony-stimulating factors), and gene therapy. Hypersensitivity reactions have been reported for all types of biotherapy agents.<sup>19,38,39</sup>

### Monoclonal Antibodies

There are 4 types of MoAbs, and their structure is a factor in their impact on the incidence of hypersensitivity reactions (Figure 1).

- Murine MoAbs, or mouse MoAbs, are derived from mice and have the highest risk of causing hypersensitivity reactions because they are developed completely from another species. Murine MoAbs are usually named with the suffix “-momab.” Examples include ibritumomab tiuxetan and tositumomab.
- Chimeric MoAbs are composed of about 7% to 9% murine antibody, still placing the patient at risk for hypersensitivity reactions. Chimeric MoAbs are usually named with the suffix “-ximab,” such as rituximab and cetuximab.
- Humanized MoAbs contain only 2% to 5% murine antibody and have the potential to cause hypersensitivity reactions, but to a lesser degree than murine and chimeric MoAbs. Humanized MoAbs are usually named with the suffix “-zumab,” such as alemtuzumab or trastuzumab.
- Fully humanized MoAbs contain only human antibody gene sequences and are usually named with the suffix “-umab,” such as panitumumab. Humanized MoAbs have much less risk of causing hypersensitivity reactions.<sup>38</sup>

### Alemtuzumab

Alemtuzumab is a humanized MoAb that targets the CD52 antigen present on the surface of most B and T lymphocytes. Infusion reactions are frequent, up to 90%, because T lymphocytes are loaded with cytokines and normal CD52+ T cells are more plentiful than normal B cells. Reported reactions include rigors, the most frequent; fever; nausea; rash; dyspnea; hypotension; and hypoxia. Reactions are the most common in the first week of therapy and decrease with subsequent administration.<sup>41</sup>

### Bevacizumab

Bevacizumab is a humanized MoAb that targets vascular endothelial growth factor. Infusion reactions of any grade are reported in less than 3% of cases, most of which are mild to moderate in severity and include fever, chills, rigors, and myalgias. These reactions are more common with the first infusion.<sup>42</sup> The recommended administration schedule is a 90-minute infusion with the first dose, 60 minutes with the second dose, and 30 minutes with subsequent doses to reduce the incidence of infusion-related symptoms; however, a rapid infusion over 10 minutes for doses at 5 mg/kg does not appear to increase the incidence of reactions.<sup>43</sup>

### Cetuximab

Cetuximab is a chimeric MoAb targeting epidermal growth factor receptor. Ninety percent of reactions occur with the first dose. Infusion reactions can occur in up to 25% of patients, but only 3% to 4% are severe. O’Neil and colleagues<sup>44</sup> reported geographic differences with 22% of patients in Tennessee and North Carolina experiencing grades 3 to 4 hypersensitivity reactions. All the reactions occurred during the first 30 minutes of the first dose of cetuximab. Patients with a history of allergic disorders were significantly (29% vs 8%) more likely to experience a severe infusion reaction than individuals with no history of allergies. To decrease the risk of reaction for patients in high-risk geographic areas, cetuximab infusions should begin at 2.5 mL/min and be gradually increased to complete infusion over 2 hours. In addition, premedication with diphenhydramine is recommended before each infusion.<sup>42</sup>

### Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin is a humanized MoAb that targets the CD33 antigen expressed on myeloblasts in more than 80% of patients with acute myeloid leukemia. Infusion reactions of chills, nausea, vomiting, headache, and hypotension are common. Most reactions occur during the first infusion but may develop up to 24 hours after administration.<sup>45</sup> The overall incidence is about 30% during the first infusion, but about 10% of patients will develop a reaction with subsequent infusions.<sup>46</sup>

### Ibritumomab Tiuxetan

Ibritumomab tiuxetan is a murine antibody combined with the radioactive isotope yttrium 90 that targets the CD20 antigen on more than 90% of B-cell non-Hodgkin’s lymphoma cells. Patients are pretreated with rituximab.<sup>13</sup> Severe infusion reactions of angioedema, bronchospasm, hypotension, and hypoxia are rare, yet have been reported during or within 30 minutes to 2 hours after the first infusion.<sup>42</sup> Reactions of fever, chills, rash, nausea, vomiting,

and hypotension are seen in about 10% of patients and are generally observed with the first infusion. The incidence of reactions decreases with subsequent infusions.<sup>19,47</sup>

### Panitumumab

Panitumumab is a fully humanized MoAb that targets epidermal growth factor receptor. During clinical trials, 4% of patients experienced mild infusion reactions and less than 1% developed severe reactions.<sup>48</sup> As a result, routine premedication is not recommended prior to panitumumab infusion.<sup>42</sup>

### Rituximab

Rituximab is a chimeric MoAb that targets the CD20 antigen. Infusion reactions occur in the initial 30 minutes to 2 hours of the first infusion in 80% of patients. The frequency of reactions decreases with subsequent infusions to 30% during the fourth infusion and 14% with the eighth infusion.<sup>19</sup> Fever, chills, and rigors are the most common symptoms experienced. Other reactions include nausea, urticaria, pruritus, headache, bronchospasm, dyspnea, hypotension, and angioedema and affect approximately 10% of patients receiving rituximab.<sup>13</sup>

### Tositumomab

Tositumomab is an I-131 murine MoAb that targets the CD20 antigen. Infusion reactions are seen in 26% of patients receiving tositumomab. The most common symptoms are fever, chills, and rigors. More severe reactions include wheezing, dyspnea, bronchospasm, rhinitis, and hypotension. Infusion-related symptoms usually resolve with slowing of the infusion.<sup>49</sup>

### Trastuzumab

Trastuzumab is a humanized MoAb that targets the epidermal growth factor receptor 2 protein (HER2). Between 20% and 40% of patients have an infusion reaction during the initial administration of trastuzumab. Incidence declines with subsequent infusions. Most infusion reactions are mild and start shortly after initiation of the drug. The most common symptoms are fever, chills, nausea, headache, abdominal pain, and dyspnea. Other reactions include vomiting, dizziness, rash, rhinitis, and hypotension.<sup>50</sup>

## PREVENTION OF HYPERSENSITIVITY REACTIONS

Prior to initiation of treatment with any chemotherapy or biotherapy drug, a detailed history of allergies and previous drug treatment and any reactions is critical. A previous history of hypersensitivity reactions, even to structurally unrelated drugs, increases the patient's risk of subsequent reactions.<sup>4</sup>

Nurses need to have knowledge of the drugs being administered and the associated risk of hypersensitivity reactions with each agent. Prior to initiation of the infusion, a thorough baseline assessment needs to be conducted to include vital signs, oxygen saturations, lung sounds, cardiovascular status, and presence of any rashes. Patients must be informed of the potential side effects of the drugs, including the risk of a hypersensitivity reaction and the possible associated symptoms. It is essential that patients understand the importance of reporting any unusual symptoms including pruritus, flushing, chills, rigors, dyspnea, throat tightness, or restlessness.

Premedication can help prevent or reduce the severity of hypersensitivity reactions. Medications commonly used include corticosteroids, H<sub>1</sub> antagonists (ie, diphenhydramine), H<sub>2</sub> antagonists (ie, cimetidine, famotidine, and ranitidine), and antipyretics (ie, acetaminophen). Premedications are recommended for drugs that have a high risk of reaction or for patients with a history of hypersensitivity reactions.<sup>3,12</sup> With administration of MoAbs, infusion at a slower rate can decrease the incidence and severity of reactions.

Hypersensitivity reactions are unpredictable and can occur at any time, despite preventive measures. Therefore, nurses need to be prepared for a reaction during each administration. Patients need to be observed for signs of restlessness, fidgeting, scratching, change in mood, and frequent changes in position. Patients may not interpret these signs as abnormal or associated with a potential hypersensitivity reaction.<sup>51</sup> Patients should be monitored closely during and immediately after all infusions. Vital signs should be monitored before, during, and after the infusion. The possibility of a delayed reaction should also be considered and monitoring continued as appropriate.

Standing orders should be available for immediate intervention if a reaction occurs. Emergency equipment and medication should also be readily available in all care settings, where chemotherapy and biotherapy drugs are administered. Oxygen therapy equipment, including nasal cannula and oxygen masks, an Ambu bag, oral airway, and suction apparatus in case the patient becomes unconscious are essential.<sup>5,47</sup>

## MANAGEMENT OF HYPERSENSITIVITY REACTIONS

Prompt intervention is critical if an acute hypersensitivity reaction occurs. Interventions are focused on counteracting the 3 physiologic processes of anaphylaxis: increased capillary permeability, vasodilatation, and smooth muscle contraction.<sup>4</sup>

- Stop the drug infusion.
- Maintain an IV line with normal saline or another appropriate solution.

- Stay with the patient. Have other staff notify the physician.
- Place patient in supine position to promote organ perfusion.
- Monitor vital signs every 2 minutes until stable, then every 5 minutes for 30 minutes, and then every 15 minutes.
- Maintain airway, provide oxygen if patient experiences respiratory difficulty, and monitor oxygen saturation.
- Administer emergency medications as ordered by physician (Table 2).
- Provide emotional support to the patient and his or her family.
- Document all interventions and the patient's response.<sup>4,7,51</sup>

In many instances, mild-to-moderate reactions will resolve after a brief interruption of the infusion and the administration of supportive medications. Most patients who experience a mild-to-moderate reaction during the first administration of the drug, such as taxanes and MoAbs, will tolerate resuming the infusion with medica-

tion and a slower rate after resolution of all symptoms. Retreatment is generally discouraged in patients who have a severe initial reaction, emphasizing the need for accurate grading of infusion reactions.<sup>5,12</sup>

Desensitization protocols allow patients to continue treatment with drugs that are vital to their regimen but have previously caused a hypersensitivity reaction. Intravenous and oral desensitization protocols are available for asparaginase, taxanes, platinum compounds, and MoAbs. Rapid desensitization protocols involve the gradual reintroduction of the medication, beginning at very low doses to full therapeutic doses, typically over a 4- to 14-hour interval.<sup>52</sup> A protocol successfully used for carboplatin and oxaliplatin desensitization includes a series of serial dilutions (1:10,000; 1:1000; 1:100; and 1:10) each prepared in 100-mL solution. Starting with the lowest dose, each dilution is infused over 60 minutes with careful monitoring of vital signs. A final solution containing 90% of the total dose in 500 mL is infused over 2 hours.<sup>5,53</sup>

Initial rapid desensitizations should be performed only in settings with close observation, and emergency personnel and resources are readily available.<sup>52</sup>



**TABLE 2**

## Drugs Used in the Treatment of a Hypersensitivity Reaction of Anaphylaxis

| Drug                                                                                                                                                                                                     | Dosage/Route                                  | Action                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epinephrine                                                                                                                                                                                              | 0.1-0.5 mg (1:10,000) IV                      | Slow absorption of drug; counteracts effects of HSR: bronchodilation, peripheral vasoconstriction, increases cardiac contractility and heart rate                         |
|                                                                                                                                                                                                          | 0.2-0.5 mg (1:1,000) subcutaneous (preferred) |                                                                                                                                                                           |
| Antihistamines                                                                                                                                                                                           |                                               |                                                                                                                                                                           |
| H <sub>1</sub> antagonist:                                                                                                                                                                               |                                               | Reduce multiple histamine effects: inhibit respiratory, vascular, and GI smooth muscle constriction; decrease capillary permeability; manage urticaria                    |
| Diphenhydramine                                                                                                                                                                                          | 25-50 mg IV                                   |                                                                                                                                                                           |
| H <sub>2</sub> antagonist:                                                                                                                                                                               |                                               |                                                                                                                                                                           |
| Cimetidine                                                                                                                                                                                               | 300 mg IV                                     |                                                                                                                                                                           |
| Famotidine                                                                                                                                                                                               | 20 mg IV                                      |                                                                                                                                                                           |
| Ranitidine                                                                                                                                                                                               | 50 mg IV                                      |                                                                                                                                                                           |
| Aminophylline                                                                                                                                                                                            | 5 mg/kg IV over 30 min                        | Bronchodilation                                                                                                                                                           |
| Dopamine                                                                                                                                                                                                 | 2-20 mcg/kg/min IV                            | Increase cardiac output, blood pressure, and organ perfusion                                                                                                              |
| Corticosteroids                                                                                                                                                                                          |                                               |                                                                                                                                                                           |
| Dexamethasone                                                                                                                                                                                            | 10-20 mg IV                                   | Slow or halt the inflammatory process, decrease vascular permeability, block production of prostaglandins and leukotrienes, and enhance therapeutic effect of epinephrine |
| Hydrocortisone                                                                                                                                                                                           | 30-60 mg IV                                   |                                                                                                                                                                           |
| Methylprednisolone                                                                                                                                                                                       | 100-500 mg IV                                 |                                                                                                                                                                           |
| Abbreviations: GI, gastrointestinal; HSR, hypersensitivity reaction; IV, intravenous.<br>Data from Labovich, <sup>4</sup> Carr and Burke, <sup>51</sup> Polovich et al, <sup>7</sup> Myers. <sup>6</sup> |                                               |                                                                                                                                                                           |

## SUMMARY

Hypersensitivity reactions will continue to be a potential life-threatening side effect of cancer treatment. Although nearly all chemotherapy and biotherapy drugs have the potential to cause these reactions, certain groups of drugs, including asparaginases, taxanes, platinum compounds, epipodophyllotoxins, and MoAbs, have a high risk of causing a hypersensitivity reaction.

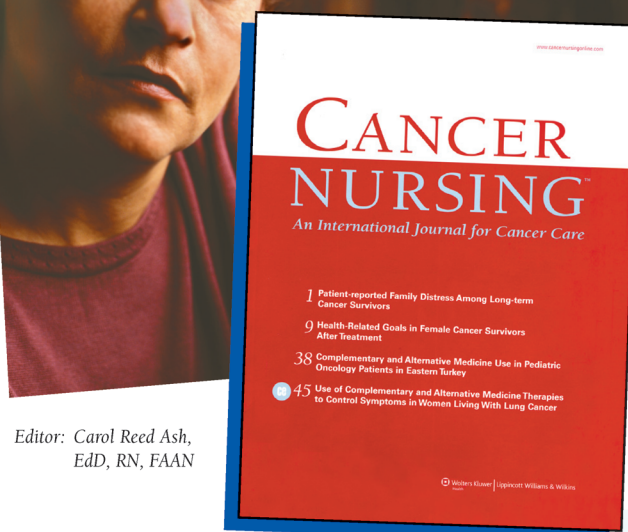
Nurses play a key role in the identification of patients at risk and prevention of hypersensitivity reactions with appropriate premedications. Early recognition of a hypersensitivity reaction and prompt intervention are critical to successful patient outcomes.

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