Chemotherapy-Induced Hypersensitivity Reactions

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This article has been chosen as being particularly suitable for reading and discussion in a Journal Club format. The following questions are posed to stimulate thoughtful critique and exchange of opinions, possibly leading to changes on your unit. Formulate your answers as you read the article.

1. Is this article research-based? Can we assess the level of evidence being presented?
2. Which drugs that we administer on a regular basis are likely to cause hypersensitivity? What is our rate of hypersensitivity reactions?
3. How structured is our patient assessment with regard to hypersensitivity risk factors? What changes can we make?
4. Do we educate patients regarding symptoms of hypersensitivity reactions?
5. What is our process for accessing emergency supplies if hypersensitivity reactions occur?

At the end of the session, take time to recap the discussion and make plans to follow through with suggested strategies.

Purpose/Objectives: To assist clinical nurses in understanding the complex nature of chemotherapy-induced hypersensitivity reactions as well as effectively preventing or managing these reactions.

Data Sources: Published articles and abstracts, pertinent book chapters, computerized databases.

Data Synthesis: Most available chemotherapy drugs can cause hypersensitivity reactions, but certain drug groups frequently are associated with these reactions (e.g., asparaginases, taxanes, platinum compounds, epipodophyllotoxins). Preventing hypersensitivity reactions is the primary goal; however, understanding the principles of managing these reactions is critical because hypersensitivity reactions can occur despite using appropriate prevention strategies.

Conclusions: Chemotherapy-induced hypersensitivity reactions are potentially life-threatening. Nurses working with chemotherapy drugs must understand which drugs are associated with a high risk of causing hypersensitivity reactions and must be prepared to attempt to prevent or manage reactions.

Implications for Nursing: The potentially life-threatening nature of hypersensitivity reactions to chemotherapy requires that nurses have a plan to manage them. This may include a written policy on staff education and training, appropriate equipment, and medications.

Key Points . . .

- All chemotherapy drugs have the potential to cause hypersensitivity reactions.
- Groups of chemotherapy drugs that have a high risk of causing hypersensitivity reactions include asparaginases, taxanes, platinum compounds, and epipodophyllotoxins.
- Skin testing, desensitization procedures for certain chemotherapy drugs, and premedication before chemotherapy administration can aid in the prevention of hypersensitivity reactions.
- Successful management of patients experiencing hypersensitivity reactions includes having a plan that guides nurses and encompasses the education and training needs of staff as well as appropriate equipment and medications for the specific setting of care.

The term "hypersensitivity" has been used widely in the cancer literature in recent years. Some authors use the term to refer to allergic reactions, and others use it to refer to infusion-related side effects, such as fever, chills, and rigors, seen with many of the newer targeted therapies. A hypersensitivity reaction is defined in this article as an exaggerated immune response that results in local tissue injury or changes throughout the body in response to an antigen or foreign substance. Most hypersensitivity reactions

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coincide with chemotherapy drug administration, and almost all are associated with parenteral drug administration. Some hypersensitivity reactions may be the result of a non–immune-mediated release of histamine or cytokines, because many patients can tolerate reexposure to the drug if it is readministered slowly after pretreatment with steroids and antihistamines (Shepherd, 2003). Generally, the mechanism of action for most of these reactions is not known because it has not been evaluated or has been evaluated only in a single patient.

Most of the available chemotherapy drugs have the potential to cause hypersensitivity reactions; however, the overall incidence of hypersensitivity reactions to chemotherapy drugs is only about 5% (Weiss, 2001). Some drugs cause hypersensitivity reactions frequently enough for this adverse effect to be a major treatment-limiting toxicity. Figure 1 lists the limited number of drugs that are considered to be associated frequently with hypersensitivity reactions, including asparaginases, taxanes, platinum compounds, and epipodophyllotoxins (Shanholtz, 2001; Zanotti & Markman, 2001). Most of the other drugs cause such reactions only sporadically. In many cases, hypersensitivity reactions are associated with a specific chemotherapy drug. Occasionally, excipients (i.e., substances used as a diluent or vehicle for a drug), such as Cremophor® EL (BASF Aktiengesellschaft, Ludwigshafen, Germany) in paxlitaxel solutions, may be responsible for hypersensitivity reactions. Reaction rates also may vary depending on which form of the drug is used; for example, the pegylated form is a chemical derivation of the drug that allows for an extended half-life and the potential for reduced toxicity (Shepherd, 2003).

High Potential
- L-asparaginase
- Taxanes
  - Paclitaxel
  - Docetaxel
- Platinum compounds
  - Cisplatin
  - Carboplatin
  - Oxaliplatin
- Epipodophyllotoxins
  - Etoposide
  - Teniposide

Occasional Potential
- Anthracyclines
  - Doxorubicin
  - Daunorubicin
  - Idarubicin
  - Epirubicin
- Mercaptopurine
- Azathioprine

Rare Potential
- Bleomycin
- Chlorambucil and melphalan
- Cyclophosphamide and ifosfamide
- Cytarabine and fludarabine
- Dacarbazine
- Dactinomycin
- Fluorouracil
- Hydroxyurea
- Methotrexate
- Polyethylene glycol-modified E. coli asparaginase
- Vincristine and vinblastine

Figure 1. Chemotherapy Drugs That Have Potential for Causing Hypersensitivity Reactions

Understanding and managing hypersensitivity reactions are critical when caring for patients receiving chemotherapy drugs because these reactions are potentially life-threatening. When possible, the first line of defense against hypersensitivity reactions is prevention, which is accomplished by understanding the drugs that place patients at risk for reactions, determining patients' responses to certain drugs via skin testing, and providing premedication before administering drugs thought to have the potential to cause hypersensitivity reactions. Hypersensitivity reactions can and do occur despite attempts to prevent them; therefore, having an emergency plan in place to manage them is necessary. The National Cancer Institute's *Common Terminology Criteria for Adverse Events v 3.0* (2003) is used primarily to grade reactions when testing drugs in clinical trials (see Table 1). Although these criteria delineate the grading of the toxicity of hypersensitivity reactions, no treatment algorithm based on that grading is provided.

Hypersensitivity Reactions

Four categories of hypersensitivity reactions have been identified: Type I is an immediate, immunoglobulin E- (IgE-) mediated reaction; type II is an antibody-mediated reaction that results in antibody-antigen complexes; type III is an immune complex-mediated reaction through which complexes form in the circulation and deposit in various tissues; and type IV is a cell-mediated or delayed-type reaction that involves activation of the T cells in the immune system (see Table 2).

Although clinical manifestations of types II, III, and IV reactions have been reported with the administration of a variety of chemotherapy drugs, chemotherapy-induced hypersensitivity reactions are primarily type I reactions (Zanotti & Markman, 2001). The antigen-specific IgE (the antigen is the chemotherapy drug, the drug's metabolite, or the vehicle in which the drug is dissolved) binds to mast cells and sensitizes them to the antigen. Subsequent exposure of the sensitized mast cell to the antigen or foreign substance causes a series of reactions that result in the degranulation of the mast cell and the release of mediators of the hypersensitivity reaction (Zanotti & Markman).

The signs and symptoms of immediate type I hypersensitivity reactions are a result of the effects of the mediators on target organs (i.e., the skin, lungs, cardiovascular system, and gastrointestinal tract) that lead to local reactions or systemic anaphylaxis. Type I hypersensitivity reactions may present as a local reaction and then progress to systemic anaphylaxis, or the initial presentation may be an acute life-threatening anaphylaxis. Symptoms of type I reactions include fever, nausea, vomiting, flushing, back pain, angioedema, maculopapular rash, dyspnea and bronchospasm, feelings of impending doom, and alterations in heart rate and blood pressure (Drain & Volcheck, 2001). Factors that influence the development and degree of anaphylaxis include the antigen's route of entry (e.g., anaphylaxis is more frequent with the IV route), the amount of antigen introduced, the rate of antigen absorption, and an individual's degree of hypersensitivity to the drug

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

Note. From "Common Terminology Criteria for Adverse Events v 3.0," by the National Cancer Institute, 2003. Retrieved June 8, 2005, from http://ctep.cancer.gov/reporting/ctc.html. Reprinted with permission.

(Labovich, 1999). Other examples of type I reactions are hay fever, allergic asthma, hives (i.e., urticaria), food allergies, and allergies to IV dye.

Chemotherapy Drugs Frequently Associated With Hypersensitivity Reactions

L-asparaginase

L-asparaginase is a bacterial polypeptide protease derived from *Escherichia coli* (i.e., E. coli) and primarily is used to treat acute lymphoblastic leukemia. L-asparaginase frequently is associated with potentially life-threatening hypersensitivity reactions. Overall, rates of hypersensitivity reactions related to L-asparaginase are estimated at 10%–20% (Weiss, 2001). The clinical manifestations of hypersensitivity reactions to the drug suggest a type I reaction. Anaphylaxis related to L-asparaginase is more common with IV than intramuscular administration and with intermittent (i.e., weekly or monthly) than continuous (i.e., daily) schedules. IV administration is associated with a hypersensitivity reaction rate of 6%–43% (Stone, DiPiro, Davis, Meyer, & Wray, 1998). For this reason, L-asparaginase usually is given by the intramuscular or subcutaneous routes, which are associated with lower reaction rates (Shepherd, 2003). Retreatment with L-asparaginase usually is associated with an increased risk of reaction. In a study by Muller et al. (2001), 24% of 76 children with acute lymphoblastic leukemia developed hypersensitivity reactions during reinduction treatment.

Because of the frequency of hypersensitivity reactions to this drug, especially when it is given by IV, skin testing before the first dose and whenever an interval of one week or longer has elapsed between doses is recommended (Shepherd, 2003; United States Pharmacopeial Convention, Inc., 2000). Intradermal skin testing is not entirely reliable, so clinicians must be sensitive to the possibility of hypersensitivity reactions with each administration of the drug. Anaphylaxis medications and emergency equipment should be readily available, and patients should be monitored for approximately one hour whenever a test dose or full dose of the drug is given. A positive reaction to a test dose results in a wheal or erythema appearing within an hour after administration. No data exist regarding the benefits of pretreatment with steroids and antihistamines.

Three alternative approaches can be taken for treating patients who are sensitive to L-asparaginase and are unable to continue treatment with the drug. Patients can be given L-asparaginase derived from *Erwinia carotovora,* a parasitic bacterium immunologically distinct from E. coli. When 20 of 21 patients who had severe reactions to E. coli L-asparaginase were switched to *Erwinia carotovora* L-asparaginase, 18 were able to complete the course of therapy (Larson, Fretzin, Dodge, & Schiffer, 1998). Another approach is switching to a polyethylene glycol-modified E. coli asparaginase (i.e., PEG-asparaginase). Patients who are allergic to the native form of L-asparaginase also may be allergic to PEG-asparaginase; however, the use of skin testing before administration of PEG-asparaginase infrequently is mentioned in the literature and the possibility of patients having hypersensitivity reactions to this preparation should be noted. In a recent study by Muller et al. (2000), PEG-asparaginase was given as part of a reinduction protocol to 70 patients, four of whom already had experienced hypersensitivity reactions during induction therapy. No incidents of hypersensitivity occurred (Muller et al., 2000), compared

Table 2. Types of Hypersensitivity Reactions

Type	Mechanism of Action	Signs and Symptoms
I	Immediate immunoglobulin E-mediated reaction	Fever, nausea, vomiting, flushing, back pain, angioedema, maculopapular rash, dyspnea and bronchospasm, feelings of impending doom
II	Antibody-mediated reaction resulting in antibody-antigen complexes that form and activate pathways in the immune system to cause inflammation	Hemolysis
III	Immune complex-mediated reaction through which immune complexes form in the circulation and deposit in various tissues, where they trigger an immune system response	Vasculitis, nephritis, arthritis
IV	Delayed reaction that involves the activation of T cells in the immune system; the T cells recognize the foreign substance (antigen) and destroy the targeted cells.	Graft rejection, contact dermatitis, granuloma formation

Note. Based on information from Ream & Tunison, 2001; Thomas, 2004.

to the 30% incidence seen with E. coli L-asparaginase at reinduction. Finally, desensitization to E. coli L-asparaginase may be attempted in some cases of positive reaction to a test dose of the drug. A desensitization protocol may be based on escalating doses of the drug or switching from a bolus IV or intramuscular dose to a slow, continuous infusion (*Physician's Desk Reference,* 2001; Rodriguez, Baumgarten, Fengler, Soumpasis, & Henze, 1995).

Taxanes

Paclitaxel and the newer semisynthetic taxane, docetaxel, primarily are used to treat breast cancer, non-small cell lung cancer, and gynecologic cancers. Two to four percent of all patients treated with paclitaxel and 2% of patients treated with docetaxel experience severe anaphylactic reactions (Shepherd, 2003). Clinical manifestations of these reactions are consistent with a type I hypersensitivity reaction and include flushing, urticaria or rash, hypotension, angioedema, and dyspnea or bronchospasm. Severe reactions can cause cardiopulmonary collapse and death. Most severe reactions to paclitaxel occur with the first or second dose and are not preceded by a minor reaction. The onset of the reaction usually occurs within minutes of beginning a drug infusion.

Debate exists regarding whether hypersensitivity reactions related to paclitaxel are attributable to the drug itself or to its excipient, Cremophor EL. Cremophor EL can induce histamine release and hypotension in dogs (Lorenz et al., 1977). In one study, however, sensitized individuals demonstrated histamine release only with paclitaxel and not with Cremophor EL (Essayan et al., 1996). In addition, Cremophor EL is not an excipient for docetaxel, the excipient of which is polysorbate 80 (i.e., Tween® 80 [Merck KGaA, Darmstadt, Germany]), which also is associated with a high incidence of hypersensitivity reactions.

Because of the potential severity of hypersensitivity reactions, patients generally require pretreatment with steroids (e.g., dexamethasone or equivalent), antihistamines (e.g., diphenhydramine), and a histamine 2-receptor blocker. No standard prophylaxis regimen exists for pretreatment with these agents. One report noted that no increase in the hypersensitivity reaction rate occurred in 132 patients pretreated with only 10–20 mg of dexamethasone immediately before paclitaxel infusion (Koppler, Heymanns, & Weide, 2001). Pretreatment decreases the incidence of hypersensitivity reactions (Myers, 2000); however, Essayan et al. (1996) noted that 41% of patients who had hypersensitivity reactions to paclitaxel had received pretreatment. Another measure to help prevent these reactions is infusing paclitaxel over one to three hours and docetaxel over one hour. Infusion of the drugs over a shorter time may precipitate an unacceptable frequency of hypersensitivity reactions (Tsavaris & Kosmas, 1998).

Docetaxel is tolerated by most patients who have had reactions to paclitaxel, thereby extending the possibility for continued therapy. Nevertheless, docetaxel is associated with a 2% incidence of hypersensitivity reactions, so patients should be pretreated with steroids and antihistamines (Bernstein, 2000). No research has determined why patients may be able to tolerate docetaxel and not paclitaxel. Possible explanations may be the lack of cross-reactivity or that docetaxel is a semisynthetic taxane. Patients also may tolerate paclitaxel with appropriate desensitization. Most desensitization protocols require administering incremental doses of the drug and pretreating patients with steroids and antihistamines (Essayan et al., 1996; Fishman et al., 1999; Peereboom et al., 1993). These studies reported that all patients were desensitized successfully without further reaction.

Platinum Compounds

Platinum-alkylating drugs (e.g., cisplatin, carboplatin, oxaliplatin [the new-generation platinum analog]) are used to treat a variety of cancers, including gynecologic tumors, adenocarcinoma of the lung, and, most recently, metastatic colon cancer. Hypersensitivity to platinum compounds is a well-established phenomenon that was first reported among refinery workers inhaling complex salts of platinum (Cleare, Hughes, Jacoby, & Pepys, 1976). After prolonged exposure to the agents, some of the workers developed allergic reactions that included rhinitis, asthma, urticaria, conjunctivitis, and contact dermatitis. When platinum compounds were introduced as chemotherapy, they induced type I hypersensitivity reactions (Cleare et al.). These drugs are associated with a high risk of hypersensitivity reactions (10%–27%), which have occurred with all routes of administration, including IV, intraperitoneal, and intravesicular (Blumenreich et al., 1982; Denis, 1983; Shukunami, Kurokawa, Kawakami, Kubo, & Kotsuji, 1999). Clinical studies have demonstrated that grades III and IV hypersensitivity reactions to oxaliplatin occur in less than 2% of cases (Sanofi-Synthelabo, Inc., 2003).

Hypersensitivity reactions associated with platinum compounds almost always develop after several courses of treatment (Markman et al., 1999; Stahl, Koster, & Wilke, 2001), suggesting sensitization during previous cycles. Symptoms generally occur within minutes of administration of the drug and are consistent with a type I hypersensitivity reaction. Symptoms may include fever, chills or rigors, hypotension, bronchospasm, tachycardia, facial edema, stridor or laryngospasm, and severe back pain caused by hemolysis (de Gramont et al., 2000; Ramanathan et al., 2003; Shepherd, 2003). More than 50% of patients who develop reactions to platinum compounds demonstrate at least moderately severe symptoms (Markman et al.). Delayed reactions to oxaliplatin also may occur (Sorich, Taubes, Wagner, & Hochster, 2004). 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 pruritis of the hands (Sorich et al.).

No standardized prophylaxis protocols have been developed for platinum compounds. Most antiemetic regimens for platinum drugs include dexamethasone. Some prophylaxis against hypersensitivity reactions is recommended for patients who receive multiple courses of these agents (e.g., patients continuing treatment beyond four or five cycles of the drug). However, in a series of patients who received high-dose steroids and antihistamines immediately before reexposure to oxaliplatin, the majority (i.e., five of six) developed a hypersensitivity reaction of the same intensity as with a previous infusion of the drug (Brandi et al., 2003). Some data suggest that premedication followed by continuous six-hour infusions of oxaliplatin decreases the risk of hypersensitivity reactions (Brandi et al.; Dold et al., 2002; Sanofi-Synthelabo, Inc., 2003). For example, only one (1%) of 100 patients treated

with prolonged infusions in a study by Giacchetti et al. (2000) developed a hypersensitivity-like reaction.

Skin testing may be predictive of the development of hypersensitivity reactions to carboplatin. A trial using the intradermal injection of carboplatin identified patients who safely could be administered a seventh dose of carboplatin with a 99% negative predictive value (Zanotti et al., 2001). Patients who have hypersensitivity reactions to a platinum drug often have repeat reactions when rechallenged, even after pretreatment with steroids and antihistamines (Goldberg, Confino-Cohen, Fishman, Beyth, & Altaras, 1996). Some patients tolerate cisplatin if they have had a reaction to carboplatin and vice versa (Shlebak, Clark, & Green, 1995).

The success of desensitization protocols has been variable (Rose, Fusco, Fluellen, & Rodriguez, 1998; Zanotti et al., 2001). The report of a desensitization protocol that allowed for the successful retreatment of a patient who had experienced a severe hypersensitivity reaction to oxaliplatin recently was published (Bhargava, Gammon, & McCormick, 2004). This protocol (see Figure 2) combined a prolonged infusion time with serial dilutions of the drug.

Epipodophyllotoxins

The epipodophyllotoxins, etoposide and teniposide, are antimitotic drugs used to treat a number of cancers, including small cell lung, refractory testicular, neurologic, and hematologic cancers. Both drugs usually are administered over 30–60 minutes because of a 1%–2% potential of causing hypotension with rapid IV infusion.

Although these drugs are associated with a high risk of hypersensitivity reactions, the incidence rates vary significantly. Combined, etoposide and teniposide have a hypersensitivity reaction incidence of 6%–41% and an anaphylaxis incidence of 0.7%–14% (Kellie et al., 1991; O'Dwyer, King, Fortner, & Leyland-Jones, 1986). Hypersensitivity reactions related to these drugs generally occur during or shortly after drug administration. Clinical manifestations indicate type I hypersensitivity reactions with symptoms that include fever, chills, urticaria, dyspnea, and bronchospasm. Hypersensitivity reactions have been reported with the first infusion of the drug, and the risk of reaction increases with repeated exposures (Kellie et al.). Most reported hypersensitivity reactions to epipodophyllotoxins have been mild (Zanotti & Markman, 2001). No hypersensitivity reactions to oral etoposide have been reported.

Teniposide, like paclitaxel, is solubilized in the excipient Cremophor EL. No available data identify Cremophor EL as the causative agent in hypersensitivity reactions related to teniposide (Shepherd, 2003). In one study of children, histamine release occurred with the active drug but not with Cremophor EL (Nolte, Carstensen, & Hertz, 1988).

No standard prophylaxis regimen exists for preventing hypersensitivity reactions during treatment with etoposide or teniposide; however, Kellie et al. (1991) noted that rechallenge following a reaction to either of these drugs generally can be successful by administering a slow, graded infusion after pretreatment with steroids and antihistamines. These drugs have not been found to develop cross-reactivity, but because they are used to treat different cancers, they generally cannot be substituted for one another.

1. Prepare four serial dilutions based on the calculated total dose of oxaliplatin (i.e., 1:10,000, 1:1,000, 1:100, 1:10), each in 100 ml of 5% dextrose in water.
2. Administer the 1:10,000 dilution bag of oxaliplatin over one hour with careful monitoring.
3. Administer subsequent dilutions in the same manner.
4. Administer the final dose of the drug over two hours.
5. May premedicate patients with corticosteroids and antihistamines, depending on their reactions to the drug.

Figure 2. Desensitization Protocol for Oxaliplatin

Note. Based on information from Bhargava et al., 2004.

Prevention of Hypersensitivity

Recognition of High-Risk Patients

All chemotherapy drugs have the potential to cause hypersensitivity reactions. Even a drug in a low-risk category carries the possibility of a reaction, and caution should be exercised when administering any chemotherapy drug. Careful review of patients' previous treatment with chemotherapy drugs and any reactions to these drugs is critical. Patients commonly are treated at more than one treatment center, such as physicians' offices and inpatient settings; therefore, eliciting a clear history of patients' previous treatment experiences helps to reduce the incidence of hypersensitivity reactions. The risk of anaphylaxis increases when drugs are given at high doses, given by IV, derived from bacteria (as with L-asparaginase), or given as crude preparations, such as those used in phase I studies (Gobel, 2005).

Although patients may react to the first infusion of a chemotherapy drug (e.g., paclitaxel), previous exposure is a risk factor for many chemotherapy drugs with a high potential for causing hypersensitivity reactions. The likelihood of hypersensitivity reactions increases with repeated exposure to L-asparaginase, platinum compounds, and epipodophyllotoxins (Kellie et al., 1991; Stahl et al., 2001). Even with the new platinum compound oxaliplatin, the same phenomenon has occurred (Brandi et al., 2003). Other risk factors for the development of hypersensitivity reactions include preexisting allergic reactions to agents such as foods, insulin, opiates, penicillins, bee stings (Grosen, Siitari, Larrison, Tiggelaar, & Roecker, 2000), blood products, and radiographic contrast media. A thorough health history, including allergic reactions to medications or any of the mentioned risk factors, should be recorded before chemotherapy is administered.

Skin Tests

Skin testing frequently is performed before administration of drugs that have a high likelihood of causing hypersensitivity reactions. This testing also may be done on patients with a history of drug allergies or exposure. Patients generally are given a small test dose of the drug intradermally. The recommended test dose for L-asparaginase is 0.1 ml intradermally of a 20 IU/ml dilution of the drug. Patients should remain under direct nursing supervision for at least the first 20 minutes after the test dose is given. Vital signs should be taken at baseline and every 15 minutes during the observation period (Polovich, White, & Kelleher, 2005). A positive test result is defined as a wheal or erythema appearing at any time within an hour after the test or if the patient develops systemic reactions, such as wheezing or shortness

of breath (Shepherd, 2003). This test is recommended before the first dose of the drug and when an interval of one week or longer has elapsed between doses. Emergency equipment and medications should be readily available during test dosing or any time that L-asparaginase is given because of the potential of hypersensitivity reactions.

In a trial by Zanotti et al. (2001), patients were given skin tests before their seventh dose of carboplatin to help predict hypersensitivity reactions to the drug using an intradermal 0.02 ml aliquot of the total dose of the drug (already mixed in the appropriate concentration). The skin test was read 5, 15, and 30 minutes after the dose was given. A positive test result was defined as the presence of a wheal at least 5 mm in diameter with surrounding erythema (Zanotti et al.).

Premedication Regimens

Although several premedication regimens exist, no standard premedication regimens have been developed to prevent hypersensitivity reactions to chemotherapy drugs. Medications commonly used to help prevent hypersensitivity reactions include corticosteroids, histamine 1 antagonists (e.g., diphenhydramine), histamine 2 antagonists (e.g., famotidine), and antipyretics (e.g., acetaminophen). Standard practice for patients receiving paclitaxel (Bristol-Myers Squibb Company, 2003) is premedication with a corticosteroid and an antihistamine, whereas premedication with a corticosteroid only is recommended for patients receiving docetaxel (Aventis Pharmaceuticals Inc., 2003). Patients often are able to tolerate a rechallenge of a taxane if they are pretreated with a corticosteroid and an antihistamine even if they previously have experienced hypersensitivity reactions (Thomas, 2004).

Desensitization Approaches

When patients experience hypersensitivity reactions to particular chemotherapy drugs that are considered to be vital components of their treatment regimens, formal desensitization protocols may be attempted. However, no standard desensitization protocols exist, and many of the published recommendations are based on case reports. The general principles of most desensitization protocols include treating patients with escalating small doses of the drug in dilution and prolonging the infusion time.

Emergency Preparedness

Because all chemotherapy drugs have the potential to cause hypersensitivity reactions, including several groups of drugs that have a high risk of causing such reactions, all settings of care that administer these drugs should have a basic emergency plan. The key components of this plan should include necessary equipment, appropriate and available emergency medications, and education and training of the staff caring for patients. No regulatory requirements currently exist to guide the prevention or treatment of hypersensitivity reactions. Therefore, obtaining orders for emergency drug procedures before drug administration, especially if a physician or nurse practitioner is not readily available during the drug administration, may be wise.

Equipment

Many physicians' offices are not equipped to provide advanced life support and rely on local emergency services for this level of care. However, providing basic life support (BLS) in the case of hypersensitivity reactions is critical because even a mild reaction can progress to a life-threatening anaphylactic reaction. All care settings in which patients receive chemotherapy drugs should have at least an oxygen tank, nasal prongs, and an oxygen mask available to manage respiratory symptoms. Other respiratory equipment that is critical in all settings of care includes an ambu bag, oral airway, and suction apparatus in case a patient becomes unconscious. Large-gauge IV catheters are recommended to enable administration of normal saline and emergency medications. A cardiopulmonary resuscitation (CPR) board is not necessary as long as the treatment chairs are low enough for a patient to be eased to the floor in case of loss of pulse.

Patients often are rechallenged with a drug to which they previously have experienced hypersensitivity reactions in an inpatient setting, which requires a higher level of emergency equipment and should have equipment for advanced life support, including a laryngoscope and related placement equipment, an endotracheal tube, and tracheostomy equipment. A CPR board and a defibrillator with electrocardiographic leads also are recommended.

Emergency Medications

Professionals in each setting of care must decide which equipment and emergency medications they deem necessary to successfully manage hypersensitivity reactions. Figure 3 provides a comprehensive list of emergency medications to manage a severe hypersensitivity reaction. Physicians' offices may choose to maintain medications for first-line management of hypersensitivity reactions. Types 1 and 2 histamine blockers are used when an allergic condition is not life-threatening and is progressing slowly, such as with angioedema and urticaria. Most care settings stock these medications because they often are used as prophylactic medications to prevent hypersensitivity reactions. A combination of these medications is preferred in the management of hypersensitivity reactions (Runge, Martinez, Caravati, Williamson, & Hartsell, 1992). Medications necessary for the first-line management of a severe hypersensitivity reaction include adrenaline and crystalloid solutions (i.e., normal saline and/or lactated Ringer's solution) in addition to oxygen. The care and maintenance of these medications are critical to the successful management of hypersensitivity reactions. These medications should be easily accessible and kept in the same location at all times.

- Adrenaline 1:1,000 or 1:10,000
- Normal saline and/or lactated Ringer's solution
- Histamine 1 antagonist
- Histamine 2 antagonist
- Dopamine
- Corticosteroids
- Aminophylline
- Albuterol (aerolized)
- Atropine
- Sodium bicarbonate
- Anticonvulsants
- Lidocaine
- Calcium gluconate

Figure 3. Emergency Medications for the Management of Severe Hypersensitivity Reactions

Education and Training

Because of the potential severity of hypersensitivity reactions related to the administration of chemotherapy drugs, staff members who administer these drugs at least should be trained in BLS. The American Red Cross and the American Heart Association require recertification every two years after passing a BLS course to maintain certification. In the midst of acute hypersensitivity reactions, immediate action is necessary to save lives. The initial steps in managing patients with potentially life-threatening reactions to chemotherapy drugs are the same as those for a life-threatening reaction to any drug: control of a patient's airway, breathing, and circulation (i.e., the ABCs of resuscitation). In acute care settings, consideration should be given to training staff in advanced life support. Ongoing education regarding the management of hypersensitivity reactions, including doses, routes, and mechanisms of action of emergency medications, is valuable. Every setting of care should have a written policy regarding the management of hypersensitivity reactions.

Management of Hypersensitivity Reactions

Whenever a hypersensitivity reaction is suspected, the first step in managing it is to stop infusion of the offending drug while maintaining patent vascular access. The ABCs of resuscitation then are followed based on a patient's symptoms. The airway is maintained first. If an adult patient becomes unconscious, the head should be tilted back and the chin lifted to open the airway. Oxygen therapy is initiated when breathing first becomes compromised. A patient who becomes hypotensive is placed in a supine position. CPR is initiated if necessary, and hemodynamic monitoring is done frequently until the patient becomes stable.

Adrenaline (i.e., epinephrine) is the first-line drug for a severe hypersensitivity reaction. The route of administration depends on what is immediately available. Adrenaline can be given intramuscularly, subcutaneously, sublingually, by IV, and via the endotrachial tube. In the case of hypersensitivity reactions related to chemotherapy drugs, IV access usually is available. IV fluids also should be initiated. Although no standard dose of adrenaline is recommended, a suggested protocol is 0.3–0.5 ml subcutaneously of a 1:1,000 aqueous epinephrine solution diluted in 10 ml of normal saline. This dose can be infused over 5–10 minutes, resulting in a total dose of 100 mcg. The dose may be repeated depending on a patient's condition (Drain & Volcheck, 2001). Adrenaline in a solution of 1:10,000 (in a commercially prefilled syringe) is administered by IV for severe bronchospasm, respiratory arrest, or cardiac arrest (Thomas, 2004). Adrenaline helps improve blood pressure, decreases angioedema and urticaria, provides for bronchodilation, and inhibits further inflammatory mediator release (Brown, 1998).

Large volumes of IV fluids may be required to help restore intravascular volume lost because of fluid shifting from the intravascular to the extravascular space. Generally, either normal saline and/or lactated Ringer's solution is infused rapidly to help maintain blood pressure. If large volumes of fluids are required, patients will require intensive monitoring to guide fluid volume status (Drain & Volcheck, 2001). Vasopressors may be needed if a patient's hypotension is not managed by adrenaline and fluids alone. Dopamine is generally the vasopressor of choice and should be given at a rate of 2–20 mcg/kg per minute and adjusted according to the effect on a patient's blood pressure (Drain & Volcheck).

Histamine antagonists may offer relief of symptoms in some patients but are not considered to be lifesaving. As previously stated, clinical trials have shown that the combination of a histamine 1 and histamine 2 antagonist is superior to either histamine antagonist alone (Runge et al., 1992). These medications may be given intramuscularly or by IV.

The role of corticosteroids in the management of hypersensitivity reactions is not entirely clear, although they are recommended as one of the emergency medications that should be available when these reactions occur. Anaphylaxis can be biphasic, and corticosteroids theoretically maintain their action on this late-phase reaction (Drain & Volcheck, 2001). For this reason, corticosteroids should be kept among the emergency medications in physicians' offices. Depending on the length of the ambulance ride to a medical facility, patients may experience a biphasic episode that, if not treated appropriately, may have tragic results. Patients with milder hypersensitivity reactions may benefit from oral prednisone or dexamethasone. If the IV route is required, methylprednisolone may be used. Other medications that should be available to manage hypersensitivity reactions include aminophylline, albuterol (aerosolized), atropine, and others as prescribed by physicians (Ream & Tunison, 2001).

Hemodynamic monitoring is observed closely in patients with hypersensitivity reactions. Vital signs are to be taken every two to five minutes until patients are stable and every 15 minutes thereafter. Patients may continue to be monitored closely for the next 24 hours if the reaction was severe, especially because of the possibility of a biphasic episode.

Summary

Hypersensitivity reactions related to the administration of chemotherapy drugs are potentially life-threatening events. Although any of the chemotherapy drugs has the potential to cause these reactions, certain groups of these drugs have a high risk of causing hypersensitivity reactions, including L-asparaginase, taxanes, platinum compounds, and epipodophyllotoxins. Predicting which patients will develop hypersensitivity reactions is not always possible, but skin testing can be performed with drugs that have a high level of suspicion for causing reactions. Testing generally is done before the first dose of L-asparaginase and whenever an interval of one week or longer has elapsed between doses. Test dosing also is done frequently before the seventh dose of carboplatin to help determine which patients may have hypersensitivity reactions to that dose. Several premedication regimens exist to help prevent hypersensitivity reactions to many chemotherapy drugs. Desensitization procedures, as well as gradual dose-escalation protocols, are available. A number of these procedures and protocols have been published, but many are based on only one or a few patients. Basic principles of resuscitation used in the management of hypersensitivity reactions are based on control of the airway, breathing, and circulation. In addition to the ABCs of resuscitation, first-line therapies for patients with severe hypersensitivity reactions are oxygen, adrenaline, and fluids.

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