Hypersensitivity reactions to chemotherapeutic agents can cause the discontinuation of first-line therapies. Chemotherapy desensitization is a safe, but labor-intensive, process to administer these important medications. A desensitization protocol can enable a patient to receive the entire target dose of a medication, even if the patient has a history of severe infusion reactions. In this article, the authors explain the pathophysiology of hypersensitivity reactions and describe the recent development of desensitization protocols in oncology. In part II of this article, which will appear in the April 2016 issue of the *Clinical Journal of Oncology Nursing*, the authors will give a detailed account of how a desensitization protocol is performed at an academic medical center.

At a Glance
- Chemotherapeutic and biotherapeutic drugs can cause severe, life-threatening hypersensitivity reactions; these reactions are most frequently associated with platinum agents, taxanes, and monoclonal antibodies, but all classes of chemotherapy and biotherapy require vigilance.
- Oncology nurses must be familiar with the signs and symptoms of hypersensitivity reactions and know how to respond to such reactions.
- Studies have demonstrated that complex desensitization protocols designed by allergists can allow patients to receive chemotherapeutic and biotherapeutic drugs, even if they initially experienced a severe hypersensitivity reaction.

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Hemotherapy desensitization is a procedure that enables a patient to receive a treatment that he or she is allergic to and otherwise would be unable to tolerate. With close supervision, using intricate protocols designed by allergists and oncologists, desensitization can be performed safely. These protocols provide a regimen for incrementally increasing the dose of a medication until the full target dose is reached. This article describes hypersensitivity reactions and reviews the literature regarding chemotherapy desensitization. In part II of this article, the authors will provide a practical guide for the nursing care of patients undergoing chemotherapy desensitization based on the existing literature as well their own experience at the University of California, Los Angeles (UCLA).

Infusion Reactions

*Infusion reaction* is a term used to describe adverse reactions that occur during or immediately after administration of the medication. Infusion reactions may be allergic or a nonallergic irritant effect. In general, most infusion reactions are mild in severity (grade 1 or 2) and usually represent irritant effects of the medication. In many cases, these are anticipated, such as during the first infusion of taxanes or monoclonal antibodies. Most infusion reactions can be managed with temporary interruption of the therapy and symptom management with steroids, antihistamines, antiemetics, and possibly anxiolytics. Generally, the infusion is completed without progression to a severe reaction, albeit at a slower rate and with greater reliance on supportive medications (Vogel, 2010).

Hypersensitivity Reactions

*Hypersensitivity reactions* are a subgroup of adverse drug reactions that are unexpected and characterized by objectively reproducible signs and symptoms at doses that are normally tolerated. Immediate hypersensitivity reactions appear within one hour of the infusion. The symptoms of an immediate hypersensitivity reaction can include urticaria, rhinitis, angioedema, bronchospasm, or anaphylactic shock. Delayed hypersensitivity reactions can occur anytime thereafter.
examples include maculopapular rashes and Stevens-Johnson syndrome (Romano, Torres, Castells, Sanz, & Blanca, 2011).

Most immediate hypersensitivity reactions are immunoglobulin E (IgE)-mediated and represent classic allergic reactions. IgE molecules are allergic antibodies, which can circulate freely in blood or tissues or function as cell surface receptors on B cells, mast cells, eosinophils, and basophils. Hypersensitivity reactions are governed by allergen-specific helper T subtype 2 (Th2) cells. In response to allergens, Th2 cells secrete cytokines, which stimulate B cells to differentiate into IgE-producing plasma cells (Porth, 2005). See Figure 1 for an illustration of an allergic reaction.

Hypersensitivity reactions can involve any organ system; systemic allergic reactions are called anaphylaxis. In addition to urticaria, angioedema, and bronchospasm, patients may experience nausea, vomiting, fever, flushing, back pain, dyspnea, or alterations in heart rate or blood pressure. Individuals who have experienced anaphylaxis also may describe a sense of impending doom. Anaphylactic reactions can be life-threatening because of airway compromise and circulatory collapse (Gobel, 2007). The National Cancer Institute has developed terminology for grading adverse reactions, which are presented in Table 1. Anything greater than grade 2 is a true allergic reaction.

Culprit Drugs

In oncology settings, hypersensitivity reactions are most commonly seen with the use of platinum, taxanes, L-asparaginase, procarbazine (Matulane®), and epipodophyllotoxins (Lee, Gianos, & Klausnermeyer, 2009). Because hypersensitivity reactions to these agents can be life-threatening, the nurse must be able to recognize and manage these events. Hypersensitivity reactions to taxanes most commonly occur during the first or second infusion (Lee et al., 2009). By contrast, with platinum agents, the risk of a hypersensitivity reaction increases with each new infusion cycle (Lee et al., 2009; Mezzano, Giavina-Bianchi, Picard, Caiado, & Castells, 2014). A comprehensive list of chemotherapy agents that can cause hypersensitivity reactions is presented in Table 2.

History of Desensitization

Classic drug desensitization protocols begin at 1/10,000 of the target dose, and subsequent doses are doubled or tripled until the goal dose is obtained. Until about a decade ago, most desensitizations involved antibiotics or aspirin. However, studies have demonstrated the safety and efficacy of protocols for medications in the treatment of cancer, specifically chemotherapy and monoclonal antibodies (Mezzano et al., 2014).

The groundbreaking work performed by Castells et al. (2008) was the largest study to demonstrate the safety and efficacy of desensitization protocols for chemotherapeutic agents. They examined 98 patients who underwent a total of 413 desensitizations. This study is unique because it successfully used the same protocol in hundreds of desensitizations involving four different chemotherapy agents: carboplatin (Paraplatin®), cisplatin (Platinol®), oxaliplatin (Eloxatin®), and paclitaxel (Taxol®). In 94% of desensitizations using a standardized 12-step protocol of increasing infusion rates and using more concentrated dilutions, patients were without any or experienced only mild reactions. The majority of reactions occurred within the initial desensitization attempt, during the last step of the final solution. No life-threatening reactions or deaths occurred. Most importantly, all of the patients were able to receive the full target dose (Castells et al., 2008).

TABLE 1: National Cancer Institute Terminology Criteria for Adverse Events for Grading Adverse Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild transient reaction; infusion interruption not indicated; intervention not indicated</td>
<td>Transient pruritus, nausea, dizziness</td>
</tr>
<tr>
<td>2</td>
<td>Therapy or infusion interruption indicated but responds promptly to systematic supportive care</td>
<td>Flushing responsive to antihistamines, emesis responsive to antiemetics</td>
</tr>
<tr>
<td>3</td>
<td>Prolonged despite supportive care and/or brief interruption of infusion; recurrence of symptoms following initial improvement</td>
<td>Urticaria that evolves into angioedema, persistent back or abdominal pain, recurrent cough</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Cardiovascular instability with tachycardia, hypotension, bronchospasm, dyspnea, fever, rigors, syncope, or throat tightening</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
<td>Anaphylaxis, myocardial infarction</td>
</tr>
</tbody>
</table>

The first publication to describe the use of a desensitization protocol specific to monoclonal antibodies was published by Brennan, Bouza, Hsu, Sloane, and Castells (2009). A series of desensitizations were used to mitigate acute infusion reactions to rituximab (Rituxan®), infliximab (Remicade®), and trastuzumab (Herceptin®). They performed the standard 12-step protocol in 23 patients, in a total of more than 105 desensitization procedures. All but one of the 105 desensitizations in the study was completed successfully. The incidence of hypersensitivity reactions was 29%, and 27 mild, 1 moderate, and 2 severe reactions occurred.

The study by Castells et al. (2008) validates that desensitization can be successful repeatedly for immediate hypersensitivity reactions to several chemotherapy agents, and the study by Brennan et al. (2009) demonstrates that desensitization can be performed successfully to administer monoclonal antibodies. Of note, the use of desensitization protocols for delayed hypersensitivity reactions is still investigational (Clayton, Madamba, Kong, & Braskett, 2014). Because most reactions in Castells et al. (2008) and Brennan et al. (2009) were mild, these studies demonstrate that desensitization protocols provide an extremely effective

### TABLE 2. Chemotherapy Agents and Associated Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chance of Reaction</th>
<th>Description of Reaction</th>
<th>Prevention</th>
<th>Skin Test</th>
<th>Options After Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin (Paraplatin®)</td>
<td>1%–19.5% mostly after six to eight cycles</td>
<td>Urticaria or angioedema, bronchospasm, hypotension, rash</td>
<td>Skin test after sixth cycle; monitor subsequent cycles and after an interval of longer than two years between doses.</td>
<td>0.02 ml of undiluted carboplatin intradermal</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Cisplatin (Platinol®)</td>
<td>1%–5%</td>
<td>Mild to severe, to even lethal; urticaria or angioedema, bronchospasm, hypotension, rash</td>
<td>Skin test is not recommended nor validated.</td>
<td>—</td>
<td>Possible desensitization, but more experience is needed.</td>
</tr>
<tr>
<td>Docetaxel (Taxotere®)</td>
<td>30% during first or second dose</td>
<td>Dyspnea, hypotension, bronchospasm, urticaria, or rash</td>
<td>Premedicate with dexamethasone (Maxidex®) 16 mg per day for three days, starting the day prior to chemotherapy.</td>
<td>—</td>
<td>Substitute with paclitaxel (Abraxane®).</td>
</tr>
<tr>
<td>Epipodophyllotoxins</td>
<td>Teniposide (Vumon®) with 4%–6%, mostly grade 1 or 2; etoposide (Etopophos®) with less than 2%</td>
<td>Hypotension, dyspnea, bronchospasm</td>
<td>Slow infusion for 30–60 minutes</td>
<td>—</td>
<td>Rechallenge after premedication with antihistamines and steroids.</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>5%–8% but increases to 33% after fourth dose</td>
<td>Urticaria or angioedema, bronchospasm, hypotension; serious anaphylactic reactions occurring in less than 10% of patients</td>
<td>Skin test not validated; some experts assert that the skin test is of no use because of the high false-positive and false-negative.</td>
<td>Intradermal injection of 0.1 ml of a 20 IU/ml dilution of L-asparaginase</td>
<td>Desensitization or substitute with a different preparation (Escherichia coli, Erwinia, or polyethylene glycol).</td>
</tr>
<tr>
<td>Oxaliplatin (Eloxatin®)</td>
<td>0.5%–25%, usually after several cycles</td>
<td>Urticaria or angioedema, bronchospasms, hypotension, rash, hemolytic anemia, cytokine release syndrome</td>
<td>Skin testing reported to be 75%–80% accurate, but that is not validated.</td>
<td>European Academy of Allergy and Clinical Immunology recommends a skin test at 5 mg/ml for prick test and 0.5 mg/ml for intradermal test.</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Paclitaxel (Taxol®)</td>
<td>2%–4% if proper premedication is given; develops during first or second dose</td>
<td>Urticaria or angioedema, bronchospasm, hypotension</td>
<td>Premedication with antihistamines, steroids, and ranitidine (Zantac®)</td>
<td>—</td>
<td>Desensitization with standard 12-step program if rechallenge resulted in reaction; substitute with docetaxel.</td>
</tr>
<tr>
<td>Procarbazine (Matulane®)</td>
<td>6%–18%</td>
<td>Maculopapular rash, urticaria, cough, angioedema, or interstitial pneumonitis</td>
<td>No reliable prevention</td>
<td>—</td>
<td>Discontinue use.</td>
</tr>
</tbody>
</table>

Note. Based on information from Joerger, 2012; Lazaro et al., 2014; Lee et al., 2009; Pagani, 2010; Weiss et al., 1990.
and relatively safe treatment modality for patients with hypersensitivity reactions to desired therapies.

Conclusion

The success of these protocols has permitted the widespread availability of these interventions. The protocol at UCLA is adapted from the protocols used in the literature; a systematic approach toward chemotherapy desensitization began in 2012 and since has been used in more than 50 desensitization procedures. The center has performed chemotherapy desensitization to administer many agents, including oxaliplatin, carboplatin, and irinotecan (Camptosar®), and oral agents, such as temozolomide (Temodar®) and lenalidomide (REVLIMID®).

Part II of this article will describe the UCLA medical center’s desensitization protocol in detail and will explain nurses’ roles and responsibilities during each stage of the protocol.

References


Do You Have an Interesting Topic to Share?

Safety provides readers with information on potential hazards affecting patients with cancer and those caring for them. Length should be no more than 1,000–1,500 words, exclusive of tables, figures, insets, and references. If interested, contact Associate Editor David G. Glenn, RN, MS, at david.glenn@umaryland.edu.