The Essentials of Chemotherapy-Induced Infusion Reactions

Eric Scott Zetka, PharmD

Almost all systemic agents used in cancer therapy can cause infusion-related reactions. Hypersensitivity or infusion reactions to platinum compounds are acquired, whereas reactions to taxanes and monoclonal antibodies usually occur during the first few minutes of the first infusion. By understanding the symptoms and treatment of infusion reactions, healthcare team members can provide timely and appropriate treatment and positively impact patient care.

Mechanism of Infusion-Related Hypersensitivity

The mechanism by which infusion-related hypersensitivity reactions (HSRs) occur varies among agents (Lenz, 2007). Most reactions to chemotherapy agents are consistent with type 1 hypersensitivity, an allergic reaction to re-exposure to an antigen or allergen. These reactions are caused by the immunoglobulin (Ig) E-mediated release of histamines, leukotrienes, and prostaglandins (Ream & Tunnison, 2001), which can result in urticaria, rash, angioedema, bronchospasm, and hypotension (Zanotti & Markman, 2001). HSRs to platinum compounds, such as carboplatin and oxaliplatin, generally are associated with type 1 IgE-mediated hypersensitivity (Gowda, Goel, Berdzik, Leichman, & Javle, 2004). Chemotherapy drugs such as paclitaxel and docetaxel manifest reactions that are clinically similar to type 1 hypersensitivity; however, research indicates these reactions may actually be related to an immune effect or other mechanism (Lenz, 2007). Cremophor EL (polyoxyethylated castor oil), found in paclitaxel (but not in docetaxel), also has been shown to induce histamine release and hypotension and may play a part in HSRs. The albumin-bound form of paclitaxel does not contain polyoxyethylated castor oil and has been associated with little to no incidence of severe HSRs (Gradishar, 2006). The exact mechanism responsible for infusion reactions to monoclonal antibodies is not known, but like the taxanes, these reactions are unlikely to be solely type 1 IgE-mediated HSRs (Lenz, 2007). Despite the different possible mechanisms underlying hypersensitivity, the associated clinical signs and symptoms overlap. Mild-to-moderate reactions (grades 1 and 2) are characterized by flushing, rash, fever, rigors, chills, dyspnea, and mild hypotension. Severe reactions (grades 3 and 4) are associated with bronchospasms and hypotension requiring treatment, cardiac dysfunction, anaphylaxis, and other symptoms (Lenz, 2007). Although many symptoms overlap, if a patient develops urticaria, repetitive cough, wheezing, and tightness in the throat, one should suspect anaphylaxis (Sampson et al., 2006).

The National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer therapy clinical trials and other clinical oncology settings. The CTCAE distinguishes between infusion-related reactions and acute infusion reactions induced by cytokine release (National Cancer Institute Cancer Therapy Evaluation Program, 2010) (see Table 1).

Depending on the agent, hypersensitivity may be seen almost immediately on exposure, or may occur after repeated exposures. Reactions to platinum drugs (e.g., cisplatin, oxaliplatin) usually occur after multiple treatments (Polyzos et al., 2001). Reactions caused by taxanes (e.g., paclitaxel, docetaxel) usually occur within the first hour of the first or second treatment (Zanotti & Markman, 2001). Although rare with most chemotherapy agents, anaphylaxis can be seen with platinum drugs and taxanes. The most common signs and symptoms of anaphylaxis are:

- Cutaneous: flushing, itching, hives, angioedema (usually of face, eyelids, or lips)
- Respiratory: cough, sudden nasal congestion, shortness of breath, wheezing, throat tightening, change in voice quality, hypoxia
- Cardiovascular: faintness, tachycardia, hypotension, loss of consciousness
- Gastrointestinal: nausea, vomiting, abdominal cramping, diarrhea
- Neurologic: sense of doom, tunnel vision, dizziness, seizure

Reactions to monoclonal antibodies such as rituximab and cetuximab usually
occur with the first treatment. However, 10%-30% of reactions to monoclonal antibodies are delayed. Those delayed reactions can occur during later infusions, emphasizing the importance of close observation of the patient following administration (Lenz, 2007).

Prevention

Although anticipating all possible infusion-related reactions is inconceivable, several factors have been associated with increasing likelihood of reaction, including repeated exposure to agents (e.g., platinum drugs), prior infusion reaction to drugs in the same class, and a history of multiple drug allergies regardless of class (Zanotti & Markman, 2001).

The incidence of HSRs to carboplatin was 27% in patients with gynecologic cancers receiving seven or more courses of carboplatin, compared with only 1% in patients who received fewer than seven courses (Markman et al., 2000). Conversely, almost 95% of all reactions to taxanes occur rapidly during the first or second infusion, with up to 80% of patients developing symptoms within the first 10 minutes of the infusion (Lenz, 2007). Similarly, infusion-related reactions to monoclonal antibodies occur primarily during the first cycle.

Knowledge of the key difference in the time of symptom onset among agents is integral to early identification of HSRs. A thorough nursing history, including assessment for prior drug allergies and assurance of adequate premedication, can reduce the risk of infusion-related reaction. Premedication with antihistamines, corticosteroids, or both has been shown to reduce the likelihood and severity of infusion reactions (Lenz, 2007). One example of a standard premedication regimen includes dexamethasone, diphenhydramine, and an H2 antagonist such as ranitidine. In some cases, such as with cetuximab, premedication can be discontinued if no infusion reaction occurs after the first treatment (Timoney et al., 2006).

Nursing Management

Patients must be closely monitored during the infusion and immediately afterward. Assessment of vital signs, particularly blood pressure, before, during, and after each infusion is imperative. Patients should be educated to inform the nurse if they feel any unusual symptoms not present when the infusion began. The Oncology Nursing Society guidelines for the management of hypersensitivity and anaphylaxis call for immediate cessation of chemotherapy infusion and maintaining an IV line with normal saline or other appropriate solution (Polovich, Whitford, & Olsen, 2009). The nurse should remain with the patient to monitor vital signs and clinical condition while another staff member notifies the physician and emergency staff as indicated. Detailed documentation of the event and accurate grading of the reaction are essential.

Interrupting the infusion and administering supportive care for symptoms may manage mild-to-moderate reactions. Some patients can be safely rechallenged with the drug following complete resolution of symptoms with administration of additional premedication and at a reduced infusion rate. If the reaction is severe, the infusion should be stopped, and treatment may need to be discontinued (Lenz, 2007).

Rechallenge with platinum agents generally is less successful than with taxanes, with about 50% of patients rechallenged with platinum agents experiencing recurrent HSRs despite premedication (Zanotti & Markman, 2001). Desensitization protocols modifying infusion times have been used successfully with platinum compounds (Lenz, 2007). Some of those protocols reinstate treatment at a low concentration and progressively increase the drug concentration by administering a succession of serial dilutions (i.e., 1:10, 1:102, 1:103, 1:104) over extended infusion times. The decision to rechallenge with any agent should be based on several factors, including the potential clinical benefit of additional treatment (Lenz, 2007).

Despite optimal premedication, infusion-related reactions still can occur. Any infusion suite that provides chemotherapy must be prepared to treat any HSRs without delay. Oncology nurses should be prepared for a reaction to occur during each administration (Zanotti & Markman, 2001). The nurse should remain with the patient following administration (Polovich, Whitford, & Olsen, 2009).

TABLE 1. National Cancer Institute’s Common Terminology Criteria

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>Mild, transient reaction;</td>
<td>Therapy or infusion interruption indicated</td>
<td>Prolonged (i.e., not rapidly responsive to</td>
<td>Life-threatening consequences; urgent</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>infusion interruption not</td>
<td>but patient responds promptly to symptomatic</td>
<td>symptomatic medication or brief interruption</td>
<td>intervention indicated</td>
<td>intervention indicated</td>
</tr>
<tr>
<td></td>
<td>indicated; intervention not</td>
<td>treatment (e.g., antihistamines, non-</td>
<td>of infusion); recurrence of symptoms</td>
<td>indicated but patient responds</td>
<td>indicated but patient responds</td>
</tr>
<tr>
<td></td>
<td>indicated</td>
<td>steroidal anti-inflammatory drugs, narcotics,</td>
<td>following initial improvement; hospitali-</td>
<td>promptly to symptomatic treatment (e.g.,</td>
<td>promptly to symptomatic treatment (e.g.,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV fluids); prophylactic medications indicated</td>
<td>zation indicated for clinical sequelae</td>
<td>antihistamines, non-</td>
<td>antihistamines, non-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 24 hours or less</td>
<td></td>
<td>steroidal anti-inflammatory</td>
<td>steroidal anti-inflammatory</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>Mild reaction; infusion</td>
<td>Therapy or infusion interruption indicated</td>
<td>Prolonged (i.e., not rapidly responsive to</td>
<td>Life-threatening consequences; urgent</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>interruption not indicated</td>
<td>but patient responds promptly to symptomatic</td>
<td>symptomatic medication or brief interruption</td>
<td>intervention indicated</td>
<td>intervention indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment (e.g., antihistamines, non-</td>
<td>of infusion); recurrence of symptoms</td>
<td>indicated but patient responds</td>
<td>indicated but patient responds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>steroidal anti-inflammatory</td>
<td>following initial improvement; hospitali-</td>
<td>promptly to symptomatic treatment (e.g.,</td>
<td>promptly to symptomatic treatment (e.g.,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>drugs, narcotics, IV fluids); prophylactic</td>
<td>zation indicated for clinical sequelae</td>
<td>antihistamines, non-</td>
<td>antihistamines, non-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medications indicated for 24 hours or less</td>
<td></td>
<td>steroidal anti-inflammatory</td>
<td>steroidal anti-inflammatory</td>
</tr>
</tbody>
</table>

Note. Based on information from National Cancer Institute Cancer Therapy Evaluation Program, 2010.
That can be accomplished by creating a preprinted order set, which can be initiated quickly based on the type of symptoms that present and the severity of those symptoms. At Sylvester Comprehensive Cancer Center, for example, the nursing and pharmacy departments collaborated to develop standing orders that include specific interventions for symptoms of hypersensitivity (see Figure 1). An HSR “emergency kit” including items needed for immediate stabilization of the patient, such as epinephrine, inhaled bronchodilators, and corticosteroids, as well as any other equipment required, should be readily available.

Conclusion

The risks for chemotherapy infusion-related reactions can be reduced by checking for prior history of allergies, ensuring appropriate premedication, and monitoring carefully during and immediately after infusion. By being aware of the signs and symptoms of HSRs, nurses and other healthcare team members can manage these reactions appropriately, optimizing patient safety and potentially enhancing efficacy of cancer treatment.

References


Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology, 117, 391–397.
