Biphasic and Delayed Hypersensitivity Reactions: Implications for Oncology Nursing

Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP®, and Deanna Sanchez Yamamoto, RN, MS, CS, ANP, AOCNP®

Oncology nurses are well versed in the administration of chemotherapy and management of associated side effects. The side effects range from mild and easily managed to severe and potentially dose limiting, such as hypersensitivity reactions (HSRs). Although severe HSRs are not common and can be seen with any agent, some treatments or medications are associated with much higher risks, such as monoclonal antibodies. Anaphylaxis usually is uniphasic in nature; however, 20% of reactions are biphasic, with symptoms resurfacing after initial resolution of the original reaction. Some reactions can be delayed, occurring after repeated infusions or presenting days to weeks after the original drug administration. For specific patients, a protracted period of anaphylaxis may occur beyond 24 hours. This article describes the proposed pathophysiology for biphasic and delayed HSRs, as well as management strategies for anaphylaxis. Case reports will illustrate patient presentations for biphasic and delayed HSRs. Oncology nurses must be aware of the risk for HSRs and understand the difference in presentation for biphasic and delayed anaphylactic reactions.

Hypersensitivity reactions (HSRs) may occur with any medication, but the incidence in the literature varies; generally, HSRs are believed to occur in 5% of patients receiving oncology drugs (Weiss, 2001). However, specific agents carry much higher risks and have been associated with fatal reactions (see Table 1). Monoclonal antibodies, in general, are associated with a higher risk for HSRs and are seen increasingly in nononcology settings as well as in the treatment of patients with cancer. Although many of the reactions occur with the first dose of therapy, patients may react in later infusions; therefore, clinicians and oncology nurses must be alert to the possibility of reaction. Patients who develop significant HSRs may not be able to receive necessary therapy because of the risk of worsening reactions or even death (Castells, 2008; Ciesielski-Carlucci, Leong, & Jacobs, 1997; El-Shanawany, Williams, & Jolles, 2008).

Most HSRs occur immediately or shortly after drug administration and are called uniphasic reactions. Uniphasic reactions usually respond to medical management; however, some patients will develop a resurgence of the initial symptoms (i.e., symptoms appear to have improved but redevelop 30 minutes to several hours later) despite treatment of the original reaction, which then is called a biphasic reaction. Several commonly used chemotherapy agents increase the risk for HSRs with continued and repeated use (termed delayed reactions), thus limiting the agents’ effectiveness in specific patients. In particular, platinum agents can cause patients to develop increased incidences of HSRs with multiple courses of therapy.

At a Glance

- Biphasic hypersensitivity reactions (HSRs), although uncommon, may occur in patients with cancer and can have significant sequelae.
- Risk factors for biphasic HSRs with specific monoclonal antibodies include comorbid cardiac and pulmonary conditions.
- Delayed cutaneous reactions and serum sickness have been linked to specific patients receiving monoclonal antibodies.

(El-Shanawany, Williams, & Jolles, 2008). Because carboplatin is an effective therapy for ovarian cancers in initial and recurrent disease therapies, patients who develop moderate to severe HSRs may not be able to receive a beneficial therapy. Oxaliplatin, a useful agent in the treatment of patients with colorectal cancer in the adjuvant and metastatic setting, also is known for late-onset HSRs, often

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Table 1. Selected Agents and Risk for Serious Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLASS</th>
<th>RISK FOR SEVERE REACTION</th>
<th>HSR BLACK BOX WARNING</th>
<th>PREMEDICATION AND ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52</td>
<td>Not available</td>
<td>Yes</td>
<td>Give antihistamine and acetaminophen prior to dosing and withhold infusion for grade 3 or 4 HSRs.</td>
</tr>
<tr>
<td></td>
<td>humanized mAb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Humanized VEGF mAb</td>
<td>Less than 1%</td>
<td>No</td>
<td>Not specified; stop for severe infusion reactions.</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Chimeric EGFRI mAb</td>
<td>3%</td>
<td>Yes</td>
<td>Give H_{2} antagonist; reduce infusion rate by 50% for grade 1 or 2 infusion reactions; permanently discontinue for serious infusion reactions. Patients should be observed for one hour after infusion.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Platinum</td>
<td>Not specified</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Taxane</td>
<td>1%–3%</td>
<td>Yes</td>
<td>Give oral corticosteroids for three days, starting one day before administration.</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Humanized mAb</td>
<td>Less than 1% fatal; 8% for all events</td>
<td>Yes</td>
<td>Give diphenhydramine and acetaminophen one hour before drug, then give two more doses of acetaminophen (one every four hours) as needed. Giving methylprednisolone prior to drug may ameliorate infusion-related symptoms.</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan</td>
<td>Anti-CD20–directed radiotherapy mAb</td>
<td>Not specified</td>
<td>Yes</td>
<td>May use acetaminophen and diphenhydramine prior to administration of rituximab, an essential component of the ibritumomab regimen.</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Epothilone</td>
<td>1%</td>
<td>No</td>
<td>Administer H_{1} and H_{2} antagonists one hour before infusion and observe for HSR. In case of severe HSR, infusion should be stopped and aggressive supportive treatment started. If patient experiences HSR in one cycle, ixabepilone must be premedicated in subsequent cycles with corticosteroid in addition to H_{1} and H_{2} antagonists; consider extension of infusion time.</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Platinum</td>
<td>2%–3%</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Taxane</td>
<td>2%–4%</td>
<td>Yes</td>
<td>Give corticosteroids, diphenhydramine, and H_{2} antagonists; paclitaxel should not be rechallenged if patient experiences severe HSR.</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Fully human EGFRI mAb</td>
<td>Less than 1%</td>
<td>Yes</td>
<td>Not specified; reduce infusion rate by 50% or the duration of infusion in patients experiencing a mild or moderate reaction; immediately and permanently discontinue the drug in patients experiencing severe infusion reactions.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric anti-CD20 mAb</td>
<td>Less than 10%</td>
<td>Yes</td>
<td>Give acetaminophen and antihistamine prior to dosing; consider resumption of infusion at a minimum 50% reduction in rate after symptoms have resolved. Fatal reactions within 24 hours of infusion have occurred.</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>Anti-CD20–directed radiotherapy mAb</td>
<td>6%</td>
<td>Yes</td>
<td>Give acetaminophen and diphenhydramine 30 minutes prior to drug; reduce rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in rate.</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Humanized HER2-neu–targeted mAb</td>
<td>Less than 1%</td>
<td>Yes</td>
<td>Not specified; decrease the rate of infusion for mild or moderate HSRs; interrupt infusion in patients with dyspnea or clinically significant hypotension; discontinue for severe or life-threatening HSRs. Some fatal events occurred hours to days after serious infusion reaction.</td>
</tr>
</tbody>
</table>

EGFRI—epidermal growth factor receptor inhibitor; HSR—hypersensitivity reaction; mAb—monoclonal antibody; VEGF—vascular endothelial growth factor


Oncology nurses are familiar with the management of HSRs. Most institutions and practice settings have policies and procedures in place to manage the acute onset of an anaphylactic uniphasic reaction. Published algorithms and guidelines also help direct clinicians in the management of HSRs (Polovich, Whitford, & Olsen, 2009). However, the management of biphasic or delayed HSRs can be a potential problem in the oncology setting.
setting as well. Although several studies have reported on bi-
phasic and delayed reactions (Liang & Carson, 2008; Gleich & 
Leiferman, 2009) with chemotherapy agents, little information 
exists in the oncology nursing literature. As a result, this article 
discusses the pathophysiology of biphasic and delayed reactions 
and presents case reports.

Pathophysiology

**HSR, drug reaction, and allergic reaction** all describe adverse drug reactions and often are used interchangeably (Gobel, 
2007). **Hypersensitivity** refers to an immune-mediated response in a patient receiving an allergy-producing drug (Shepherd, 
2003). HSRs can present as localized reactions or develop into 
systemic anaphylaxis.

The current belief is that anaphylaxis is mediated immuno-
logically with immunoglobulin E (IgE)-mediated reactions com-
pared to reactions that are not IgE mediated (previously believed 
before to be anaphylactoid) (Gleich & Leiferman, 2009). Anaphylaxis is 
described by the Joint Task Force of the American Academy of 
Allergy, Asthma, and Immunology as a severe, potentially fatal, 
systemic allergic reaction occurring after contact with 
an allergy-producing substance (Sampson et al., 2006). The Na-
tional Cancer Institute (NCI) Common Terminology Criteria for 
Adverse Events defines anaphylaxis as an acute inflammatory re-
action caused by the release of histamine and related substances 
that trigger an HSR immune response and may lead to significant 
symptoms or death (Gobel, 2007; NCI Cancer Therapy Evalua-
tion Program, 2009) (see Figure 1 and Table 2).

To date, the exact mechanism of action for HSRs is unclear, 
although most chemotherapy agents are believed to cause a type I 
HSR mediated by IgE. True anaphylaxis is differentiated from 
other reactions because of the severity of the systemic reac-
tion, which results from exposure to a substance to which an 
individual has become sensitized (El-Shanawany et al., 2008). 
Physiologically, anaphylaxis is caused by the release of mediators 
by mast cells and peripheral basophils during degranulation of 
the cells (El-Shanawany et al., 2008). Although massive amounts 
of histamine and heparin from the cells cause a variety of physi-
cal symptoms (e.g., urticaria, development of rash, shortness of 
breath, peri orbital or facial edema, gastrointestinal symptoms) 
during the reaction (Gobel, 2005), other substances are released 
as well, including cytokines and chemokines (e.g., interleukin, tu-
mor necrosis factor-α, leukotrienes) and kinins (e.g., bradykinin) 
(El-Shanawany et al., 2008). Monoclonal antibodies can produce 
infusion reactions that are related to the antibody-antigen inter-
action or cytokine-release syndrome, producing increased levels 
of various interleukins, interferons, and tumor necrosis factor 
(Dillman & Hendrix, 2003). The reactions usually are manageable 
with pharmacologic interventions such as additional histamine 
blockers (Gobel, 2007; Lenz, 2007) and adjustment of infusion 
rate and occur within minutes to several hours after the start of 
administration of the antibody. Severe syndromes have caused 
fatal outcomes, often in patients with high numbers of circulat-
ing cells bearing the target antigen and significant comorbidities 
(Dillman & Hendrix, 2005).

Most hypersensitivity reactions are uniphasic, occurring 
within a short period after drug administration. For some 
patients, reactions can be biphasic with an initial reaction to 
the drug or allergen that responds to therapy for the reac-
tion, followed by a resurgence of the original hypersensitivity 
symptoms. Delayed hypersensitivity reactions may occur with 
repeated administration of certain agents, such as platinum 
therapies; however, significantly delayed reactions in the form 
of cutaneous reactions have occurred with specific agents, such 
as monoclonal antibody agents.

**Types of Hypersensitivity Reactions**

**Uniphasic Reactions**

Anaphylaxis reactions can range from mild to moderate to life-
threatening, with a variety of physical symptoms encompassing 
the respiratory, cardiovascular, gastrointestinal, and central ner-
vous system (Brazil & MacNamara, 1998). The reactions can 
be immediate and uniphasic in nature versus biphasic (characterized 
by recurrence of original symptoms) and usually are IgE mediated 
(Kemp, 2008; Lieberman, 2005). Oncology nurses are familiar 
with the uniphasic reaction, which usually occurs while the treat-
ment is being administered, and symptoms resolve within hours 
of treatment (Lieberman, 2005). Infusion reactions to monoclonal 
antibodies also can occur as an acute or delayed reaction (Cheifetz 
& Mayer, 2005). Although anaphylaxis usually is considered a sys-
temic and immediate hypersensitivity reaction, the symptoms can 
occur three to four hours after infusion of a specific agent (Kang & 
Saif, 2007). Any chemotherapy or monoclonal antibody agent has 
the potential to cause an acute anaphylactic reaction.

**Biphasic Reactions**

Researchers interested in late-phase responses investigated 
immediate versus delayed reactions and determined that a biph-
asic response could be present in patients with an anaphylactic 
reaction and that the responses were IgE mediated (Dolovich et
Biphasic reactions are reported to occur in 1%-23% of patients and are characterized by initial symptoms of hypersensitivity that respond to therapy, with a recurrence from 1-72 hours after the apparent resolution of the symptoms (Brady, Lubey, Carter, Guertler, & Lindbeck, 1997; Lieberman, 2005). Why biphasic responses occur is not known, but several possible mechanisms are reported in the literature. Previously, the biphasic response was believed to occur because of inadequate initial treatment of the original reaction, causing a resurgence of initial symptoms (Popa & Lerner, 1984). Tole and Lieberman (2007) proposed several pathogenic mechanisms, such as a secondary influx of cells into the site of the reaction; however, histologic studies do not support this finding. Oral administration also has been postulated as a method of administration more likely to produce a biphasic reaction, but this has not been shown in published studies (Tole & Lieberman, 2007). In addition, researchers have proposed a biphasic wave of histamine release from mast cells as the causative factor or even the late response as a result of activation of secondary inflammatory pathways following the initial HSR (De Souza, Short, Warman, Maclennan, & Young, 2004; Tole & Lieberman, 2007).

The following biphasic cases mostly are related to food allergies, insect stings, and immunotherapy injections. Three patients experiencing reactions to rabies vaccine, immunotherapy, and yellow-jacket sting had improvement of their symptoms after appropriate treatment but developed symptom resurgences 3.5–4 hours later (Popa & Lerner, 1984). The patients all had specific IgE antibodies against the specific allergen. Another study reported that 20% of study participants developed recurrent symptoms of hypotension and respiratory distress after intervals of one to eight hours without symptoms, despite three patients receiving glucocorticoids as therapy for the reaction (Stark & Sullivan, 1996). Stark and Sullivan (1996) cautioned that patients should be followed carefully, even after abatement of the original symptoms.

A retrospective review over a 4.5-year period discovered that 2 of 67 cases of anaphylactic reactions were biphasic; again, intervals between symptoms ranged from 26–40 hours after initial symptoms (Brady et al., 1997). A prospective study reported by Ellis and Day (2007) demonstrated a 19% incidence of biphasic reactions (20 of 103 patients) seen in the emergency room and inpatient services. The range of time from the original presentation to the resurgence of symptoms was 2–38 hours. The authors determined that biphasic responses occurred in patients who received less epinephrine and corticosteroid medication, partially explaining the pathophysiology in some participants; in addition,

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
<td>Transient flushing or rash</td>
<td>Intervention or infusion interruption not indicated</td>
<td>Prolonged (e.g., not rapidly responsive to symptomatic medication or brief interruption of infusion)</td>
<td>Life-threatening consequences Urgent intervention indicated</td>
</tr>
<tr>
<td></td>
<td>Drug fever lower than 38°C (100.4°F)</td>
<td>Responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics)</td>
<td>Recurrence of symptoms following initial improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention not indicated</td>
<td>Prophylactic medications indicated for 24 hours or fewer</td>
<td>Hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>—</td>
<td>—</td>
<td>Symptomatic bronchospasm, with or without urticaria</td>
<td>Life-threatening consequences Urgent intervention indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parenteral intervention indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allergy-related edema and angioedema; hypotension</td>
<td></td>
</tr>
<tr>
<td>Cytokine-release syndrome</td>
<td>Mild reaction Infusion interruption not indicated</td>
<td>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids)</td>
<td>Prolonged (e.g., not rapidly responsive to symptomatic medication or brief interruption of infusion)</td>
<td>Life-threatening consequences Pressor ventilator support indicated</td>
</tr>
<tr>
<td></td>
<td>Intervention not indicated</td>
<td>Prophylactic medications indicated for 24 hours or fewer</td>
<td>Recurrence of symptoms following initial improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>Mild, transient reaction Infusion interruption not indicated</td>
<td>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids)</td>
<td>Prolonged (e.g., not rapidly responsive to symptomatic medication or brief interruption of infusion)</td>
<td>Life-threatening consequences Urgent intervention indicated</td>
</tr>
<tr>
<td></td>
<td>Intervention not indicated</td>
<td>Prophylactic medications indicated for 24 hours or fewer</td>
<td>Recurrence of symptoms following initial improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</td>
<td></td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Asymptomatic</td>
<td>Moderate arthralgia</td>
<td>Severe arthralgia or arthritis</td>
<td>Life-threatening consequences Pressor ventilator support indicated</td>
</tr>
<tr>
<td></td>
<td>Clinical or diagnostic observations only</td>
<td>Fever, rash, and urticaria</td>
<td>Extensive rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention not indicated</td>
<td>Antihistamines indicated</td>
<td>Steroids or IV fluids indicated</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. National Cancer Institute Grading Criteria for Adverse Events**

**Note.** Based on information from National Cancer Institute Cancer Therapy Evaluation Program, 2009.

NSAID—nonsteroidal anti-inflammatory drug

al., 1973).
no biphasic reactions occurred when patients had originally re-
sponded to the treatment for anaphylaxis within 30 minutes (Ellis
& Day, 2007). In general, the literature reported an incidence of
biphasic anaphylaxis of 20% in all patient populations (Douglas,
Specific cases of biphasic reactions in the oncology literature are
sporadic but do exist.

**Biphasic Reactions in the Oncology Literature**

In one case report, a 48-year-old woman with breast cancer
who underwent a sentinel lymph node biopsy experienced a
biphasic anaphylactic reaction after injection of the blue dye used
for the biopsy procedure. After injection of 1% isosulfan blue dye,
the patient became hypotensive with systolic blood pressures in
the 30–40 mmHg range and desaturation of her oxygen levels
(Liang & Carson, 2008). After surgery was halted, the patient
was placed in the Trendelenburg position and given oxygen; the
development of hives also was noted. Medical therapy consisted
of IV fluids, epinephrine, dexamethasone, and diphenhydramine.
After stabilization of her blood pressure, the patient was put on
an epinephrine drip and transferred to the intensive care unit
for observation and management. After a two-hour period, the
patient experienced a second hypotensive episode with blood
pressure dropping to 65 mmHg (Liang & Carson, 2008).

A possible biphasic or delayed hypersensitivity reaction in the
form of angioedema was reported in 2008 after the administra-
tion of panitumumab in an older woman (Gleich & Leiferman,
2009). Although the patient experienced angioedema six days
after the original infusion of the monoclonal antibody and re-
covered, subsequent administration with the fourth dose of the
drug caused facial swelling to reoccur with a fatal result (Gleich
& Leiferman, 2009).

First used in 1998 for metastatic HER2-positive breast cancer,
trastuzumab has received approval for adjuvant treatment as
well. Although mild infusion reactions were noted in the clinical
trials, a “dear doctor” letter in 2000 informed clinicians that 62
postmarketing reports of serious adverse events had occurred,
with some fatal results (Genentech, Inc., 2006; U.S. Food and
Drug Administration [FDA], 2000). Infusion reactions were more
severe than those seen in the original clinical trials, and se-
veral fatalities occurred within 24 hours or more of the infusion.
Whether the later events represent a biphasic or delayed response
is unclear, but some patients seemed to improve after the initial
HSR event, with a small number suffering subsequent deteriora-
tion and then dying at home (FDA, 2000). Of note, patients with
preexisting pulmonary compromise were considered at higher
risk. Rituximab received a labeling change in 1998 regarding
infusion-related events resulting in fatalities in a small number of
patients. In some cases, initial HSR symptoms worsened over
time; for others, an initial improvement occurred with clinical
deterioration, following a biphasic pattern (American Society of
Health-System Pharmacists, 1998). Again, comorbid cardiac and
pulmonary conditions may have played a role.

**Protracted and Delayed Reactions**

Protracted HSRs can last 24 hours or longer, despite appro-
priate medical management. Patients with protracted reactions
usually require hospitalization with continuous medical treat-
ment and observation along with supportive care measures
(Brazil & MacNamara, 1998).

Delayed reactions can occur with many medications. In the
oncology setting, platinum agents are responsible for the most
frequently seen delayed HSRs. In most cases, oxaliplatin and car-
boplatin are the offending agents (Williams & Markman, 2009).
The incidence of HSRs increases as patients receive multiple cycles
of therapy. Two large reviews reported incidences of 17%–27% hy-
persensitivity in patients who received more than seven courses of
carboplatin therapy (Markman et al., 1999; Polyzos et al., 2001).

In a series of 124 patients receiving oxaliplatin, HSRs were seen
after 2–17 cycles of therapy, with nine patients experiencing a
moderate to severe reaction (Brandi et al., 2003). A study of 247
patients who received oxaliplatin showed an incidence of 11.7%
hypersensitivity, with grade 3 or 4 events in 1.6% of the patients
(Kim, Bradley, Tai, & Budman, 2009). In a large, retrospective trial
of 1,224 patients who received an oxaliplatin-containing regimen,
308 platinum-naïve patients developed HSRs that were validated
with the patients receiving a rechallenge with the drug (Polyzos
et al., 2009). The reactions developed after the first five courses,
with a median course number of nine (range = 1–24); although
mild reactions occurred in 63% (n = 194) of patients, severe re-
actions occurred in 37% (n = 113) within minutes of drug infusion
(Polyzos et al., 2009).

Although delayed HSRs typically seen with oxaliplatin occur
after exposure to the drug over time after the sixth, seventh, or
eighth cycle of therapy with an immediate onset of symptoms, a
case report detailed a different response. An 81-year-old woman
with metastatic colorectal cancer was treated with oxaliplatin (for
the first time) and capecitabine (a drug she had received before
successfully) (de Vries, Mattijssen, & van Sorge, 2006). Informa-
tion regarding premedications for the infusion was not available
in the case report; however, the patient developed significant
respiratory symptoms with stridor and peripheral cyanosis 20
hours after the initial infusion of oxaliplatin. Medical therapy
consisted of dexamethasone, cleomastine, oxygen, and bron-
chodilator therapy, and she had a complete recovery within 15
minutes. Three weeks later under strict observation, the patient
received a second dose of oxaliplatin after premedications with
steroid and antihistamines. Infusion time was lengthened (six
hours), and the patient exhibited no hypersensitivity symptoms
at the time of infusion. About 20 hours later, the patient exhibited
identical respiratory symptoms and the oxaliplatin therapy was
deemed unsafe to continue, despite tumor response (de Vries et
al., 2006).

As mentioned, delayed reactions can take several different
forms (from full anaphylaxis to cutaneous eruptions), but
cutaneous reactions occur frequently. Severe cutaneous drug
reactions are the most common type of adverse drug reaction
and can vary from drug-hypersensitivity syndrome to serum
sickness to toxic reactions, such as Stevens-Johnson syndrome
(Knowles & Shear, 2007). The reactions can occur with many
agents that patients with cancer may be prescribed, such as
sulfonamides, allopurinol, carbamazepine, and antiseizure
medications (Mockenhaupt et al., 2007). Because the reactions
can occur within a delayed timeline, recognition and manage-
ment are important. Delayed cutaneous reactions can occur
with monoclonal antibody treatment as well (Hellerstedt &
As rituximab therapy is given increasingly in the oncology and nononcology settings, serum sickness and cutaneous reactions have been reported. Patients can present with malaise, fever, headache, myalgias, arthralgias, a variety of maculopapular skin rashes, and rarely proteinuria or renal toxicity (Dillman & Hendrix, 2003). The first reported case of serum sickness (a delayed reaction) after rituximab therapy occurred in 2001. A 45-year-old man with refractory autoimmune polyneuropathy was treated with four weekly infusions of the monoclonal antibody and presented with a fever and severe arthralgias (D’Arcy & Mannik, 2001). The patient was presumed to have serum sickness secondary to the therapy and was given pulse corticosteroids. His symptoms were gone within 48 hours after methylprednisolone, and subsequent examination of his serum confirmed antibodies against rituximab (D’Arcy & Mannik, 2001).

A case of significant delayed cutaneous reaction and possible serum sickness was reported in a 23-year-old woman receiving rituximab for lupus (Hellerstedt & Ahmed, 2003). Although on chronic steroids, the patient developed a lupus flare during pregnancy and she was started on rituximab in the postpartum period. She received her second dose and developed a fever and chills about 24 hours later. Within 48 hours after infusion, the patient developed a diffuse, pruritic rash with edema, arthralgias, and myalgias. Diarrhea, thrombocytopenia, and the presence of small aphthous ulcers also were noted. Her rash improved after a steroid bolus given in the emergency room. Within a 12-day period, her symptoms totally resolved. Although rituximab can cause acute symptoms of HSR, which often is believed to be related to cytokine-release syndrome, the patient’s reaction was considered to be more typical of serum sickness (which often occurs 8–13 days after exposure to an antigen) (Hellerstedt & Ahmed, 2003). A 36-year-old man with relapsed follicular lymphoma also was treated with rituximab and developed mucositis and fevers during cycle 2. During the third cycle, the patient developed a pruritic rash on his trunk and grade 2 mucositis. The rash began to spread and ulcerate; a clinical diagnosis of Stevens-Johnson syndrome was made and symptoms persisted after four months, although small improvements were noted (Lowndes, Darby, Mead, & Lister, 2002).

Delayed infusion reactions typical of serum sickness presentation have been reported with natalizumab, a monoclonal antibody used in the treatment of multiple sclerosis. In one patient series, 10% receiving the drug developed symptoms such as fever, headache, and arthralgias suggestive of serum sickness; all patients responded to steroid treatment (Hellwig et al., 2008). In addition, similar examples of serum sickness–like reactions have been reported with infliximab, a monoclonal antibody used in the treatment of Crohn disease and rheumatoid arthritis (Gamarra, McGraw, Drelichman, & Maas, 2006).

Case Studies

Case 1

A.F., a 72-year-old woman, was diagnosed with stage IVB mantle cell lymphoma in 2002. She received six cycles of R-CHOP (rituximab-cyclophosphamide, vincristine, doxorubicin, and prednisone) as her initial therapy with three additional cycles of rituximab, followed by radiation therapy with a good clinical response. A.F. did well until 2005, when she presented with an enlarged right parotid gland. A biopsy of the area revealed recurrent mantle cell lymphoma, and she received another three cycles of R-CHOP with a good response. A.F. did well again until 2007, when she presented with new right-sided parotid swelling and was diagnosed once more by biopsy with recurrent mantle cell lymphoma. She then was treated with six cycles of R-CVP (rituximab-cyclophosphamide, vincristine, and prednisone), but a positron-emission tomography (PET) scan showed only a partial response; she then received two cycles of bortezomib with no change in her condition. In 2008, A.F. received three more cycles of R-CVP, and monthly rituximab was initiated for maintenance therapy.

Several months later, A.F. developed a mild pruritic rash to the trunk and extremities. She did not have symptoms of fever or myalgia with the rash. A.F. was seen by her primary care physician and given a prescription for a low-potency topical steroid cream. When the rash failed to resolve in a week, A.F. was seen in the urgent care clinic and an oral antihistamine was added to her treatment regimen. The rash persisted, and A.F. presented to the oncology clinic with a progressive rash involving her trunk, arms, and legs (see Figure 2). A.F. had received her last rituximab infusion several weeks prior. A dermatology referral was generated; A.F. was seen in the dermatology clinic two days later. The differential diagnosis included possible paraneoplastic pemphigus, a heterogeneous autoimmune syndrome involving mucocutaneous tissue (Anhault et al., 1990; Nguyen et al., 2001). However, the clinical findings did not support this diagnosis. Because A.F. did not have fever or myalgias, a diagnosis of serum sickness related to rituximab was ruled out. A diagnosis of
delayed HSR, lichenoid dermatitis, secondary to rituximab, was made by the dermatology consultants, and A.F. was treated with a high-potency topical steroid ointment and oral doxepin for the pruritus. A subsequent restaging PET scan showed progression of her disease, and A.F. chose to discontinue her treatment.

This case illustrates the importance of awareness for the possibility of delayed cutaneous reactions secondary to rituximab and the length of time before a correct diagnosis could be made in A.F. Prompt referral to dermatology would have allowed for earlier diagnosis and treatment of this delayed cutaneous hypersensitivity reaction. Although A.F. developed progressive disease and ultimately stopped therapy, the treating physicians felt that A.F. could have been treated for the dermatologic symptoms with ongoing steroids and continued with her rituximab therapy if warranted clinically.

**Case 2**

F.C., a 63-year-old man, was admitted for his first cycle of treatment with a monoclonal antibody, rituximab, for his diagnosis of stage IV non-Hodgkin lymphoma. F.C. had a positive allergy history noted during his baseline evaluation for therapy and had reacted to an antibiotic previously, at which time he was diagnosed with a penicillin allergy. F.C. described a previous childhood history of seasonal allergies that had improved with adulthood. He also had mild coronary artery disease controlled with antihypertensives and aspirin therapy.

After premedication with 50 mg of diphenhydramine and acetaminophen, the infusion of rituximab was started. About two hours into the infusion, F.C. complained of chest tightness. Blood pressure was stable and pulse was slightly higher than baseline, increasing to 98 from 86. On examination, F.C. had a mild erythema on his trunk. No vesicles or hives were noted. His oxygen saturation was 94% on room air, and he noted that he had a moderate feeling of shortness of breath. The rituximab was halted and additional diphenhydramine was administered along with a 50 mg dose of hydrocortisone via IV. The chest symptoms resolved within 15 minutes and although resumption of the infusion was considered, the team decided that F.C. should be treated the next day in the hospital setting versus the clinic outpatient setting. F.C. was observed in the treatment area prior to discharge. About 60 minutes after infusion was halted, F.C. described new feelings of chest discomfort; his blood pressure had dropped from 130/90 to 90/70, and his heart rate had increased from 88 to 110. F.C.’s oxygen saturation was 90% on room air; oxygen therapy was administered by nasal cannula. F.C. received 100 mg hydrocortisone, and 50 mg of diphenhydramine was repeated via IV. Because F.C. described increased feelings of shortness of breath, a dose of epinephrine was delivered intramuscularly. F.C. noted that he had a moderate feeling of shortness of breath. The rituximab was halted and additional diphenhydramine was administered along with a 50 mg dose of hydrocortisone via IV. The chest symptoms resolved within 15 minutes and although resumption of the infusion was considered, the team decided that F.C. should be treated the next day in the hospital setting versus the clinic outpatient setting. F.C. was observed in the treatment area prior to discharge. About 60 minutes after infusion was halted, F.C. described new feelings of chest discomfort; his blood pressure had dropped from 130/90 to 90/70, and his heart rate had increased from 88 to 110. F.C.’s oxygen saturation was 90% on room air; oxygen therapy was administered by nasal cannula. F.C. received 100 mg hydrocortisone, and 50 mg of diphenhydramine was repeated via IV. Because F.C. described increased feelings of shortness of breath, a dose of epinephrine was delivered intramuscularly. The symptoms resolved once again, and F.C. stated that he felt better. However, this reaction was believed to be a possible biphasic reaction because it had occurred postinfusion; F.C. subsequently was hospitalized for observation and further administration of supportive therapy (e.g., oxygen, steroids) if needed.

This case points out important risk factors for HSR with rituximab and the need for a comprehensive baseline assessment prior to instituting therapy. F.C.’s risk factors were determined to be monoclonal antibody infusion, childhood history of allergies, medication allergies, advanced stage of lymphoma, and comorbidities (cardiac and possibly lung).

**Management**

Oncology nurses are familiar with the management of acute HSRs. The reactions occur at the onset of drug administration or soon thereafter, so nurses usually are present when symptoms of a reaction begin and manage patients accordingly.

However, biphasic and delayed reactions may occur when the patient is at home, and oncology nurses may not be aware of the reaction until it is reported at a subsequent visit or when a patient visits the emergency room. Delayed reactions may present as a cumulative exposure or delayed reactions, such as those seen with platinum agents, or as a cutaneous or serum sickness type of reaction. Patients also receive oral and IV contrast for scans, which can cause HSRs in some people.

Diagnostic criteria for an anaphylactic reaction include an acute onset of illness, with associated symptoms such as skin or mucosal involvement, respiratory symptoms, or changes in blood pressure (90 mmHg or less, or a 50% reduction in systolic blood pressure) (Gleich & Lieberman, 2009). Typical symptoms seen in acute anaphylactic reactions can be respiratory (e.g., shortness of breath, laryngeal edema), gastrointestinal (e.g., nausea and vomiting, diarrhea), cardiovascular (e.g., hypotension, tachycardia, arrhythmias), and cutaneous effects (e.g., rash, flushing, erythema, urticaria) (Ellis & Day, 2003; Polovich et al., 2009). Prompt recognition and management of acute anaphylaxis are important.

**Biphasic Reaction**

Although patients at risk for biphasic reactions cannot be readily identified, the previous review of studies points to possible causative factors, such as delay in initial administration of epinephrine or an inadequate amount of epinephrine administered with the first onset of HSR symptoms (Tole & Lieberman, 2007). Corticosteroid administration has been described as a way to prevent onset of recurrent symptoms, particularly as the peak action of this class of agents is about four to six hours after initial administration; however, the evidence is weaker for this as a causative factor (Tole & Lieberman, 2007). The method of administration for the HSR-producing agent has been examined as well, but biphasic reactions have occurred with oral, parenteral, and inhaled agents (Tole & Lieberman, 2007). In one study reported by Brazil and MacNamara (1998), biphasic reactions were higher in patients who required larger doses of epinephrine to control their original symptoms, leaving the authors to conclude that this factor may be a marker for prediction of a biphasic response. A 2008 report by Kemp described potential risk factors as severity of original phase, delayed or suboptimal doses of epinephrine during initial treatment, symptoms of laryngeal edema or hypotension during initial therapy, or a delayed symptomatic onset after exposure to the antigen. The European Resuscitation Council guidelines call for increased caution with patients who had severe reactions with slow onset caused by idiopathic anaphylaxis, reactions in patients with severe asthma or severe asthmatic component,
reactions with the possibility of continued absorption of allergens, or patients with a history of a biphasic reaction; the guidelines state that a patient who remains symptom-free for four hours after treatment for a reaction may be discharged (Soar et al., 2005).

**Delayed Reactions**

The pathophysiology for delayed HSR development in patients receiving multiple cycles of therapy is not clear. The reactions develop over time, which suggests that patients become sensitized during previous cycles and that the reactions are IgE mediated (Brandi et al., 2003). Although identifying all patients receiving platinum agents who will develop a delayed HSR may not be possible, the more cycles a patient receives and the length of time between courses of therapy can help clinicians to predict patients at risk. Skin testing can help to identify patients who may react to platinum agents, and prevention of reactions by desensitization protocols may allow select patients to receive needed therapy with these agents (Bhargava, Gammon, & McCormick, 2004; Castells et al., 2008; Gammon, Bhargava, & McCormick, 2004). In a report by Castells et al. (2008), a universal 12-step protocol was successful for 98 patients who received 413 rapid desensitizations without significant adverse events. All patients were able to complete their target dose, and 94% had limited or no reactions; no deaths or codes occurred. However, all patients required one-on-one nursing care, and all patients were initially desensitized in the intensive care unit (Castells et al., 2008).

Delayed cutaneous reactions or serum sickness can occur within days or even weeks after the initial presentation; therefore, knowledge of potential reactions is crucial. Recognition of the clinical presentation of delayed or serum sickness reactions are essential for early diagnosis and treatment, usually involving administration of steroids (Gamarra et al., 2006). This requires diligent assessment of patients at risk as the presenting symptom complex can be varied and can include fever, rash, and arthralgias (Todd & Helfgott, 2007). Patients who call with these atypical symptoms after infusion of monoclonal antibodies should be assessed promptly. Patients with new signs of hypersensitivity skin reactions should be screened for exposure to other triggers, such as new lotions, soap detergents, dyes, additional prescription medications, mineral and vitamin supplements, and herbal remedies. In addition, steroids commonly are employed in the treatment of delayed cutaneous reactions.

**Nursing Implications**

Colwell et al. (2007) confirmed that infusion reactions significantly impact nurses. They surveyed 202 nurses attending the 2005 Oncology Nursing Society Congress meeting and asked questions regarding incidence, impact of reactions on patients, and whether or not the reactions were disrupting. Most nurses surveyed reported that grade 1 or 2 reactions were very or extremely disruptive to patients, and 30% of the nurses felt that the reactions were disruptive to themselves. The reactions were reported to interrupt nurses’ routines and took time away from other patients, often causing delays in the administration of chemotherapy for other patients in the clinic. Colwell et al. (2007) concluded that further awareness of optimal management of reactions and education of patients and clinicians is needed.

Patients should be educated regarding the types of symptoms that may indicate an impending HSR so that they will report signs earlier (Gobel, 2007; Viale, 2009). Oncology nurses must be aware of the strategies used to treat patients with HSRs, understanding that prompt and accurate treatment of the reaction may improve patient outcome. Mock HSR drills can help to educate staff and promote comfort levels for nurses responding to HSRs in patients receiving cancer therapies (Viale, 2009). Hospitals and clinics should have existing algorithms or policies and procedures in place to treat patients with HSRs or infusion reactions (Timoney, Eagan, & Sklarin, 2003). Risk of delayed infusion reaction increases as patients receive multiple platinum infusions, and nurses should be aware of the number of cycles a patient has received and anticipate reactions accordingly. Understanding the possibility of biphasic reactions is important. Patients who experience biphasic reactions will require additional intervention and monitoring and may need to be hospitalized. Adequate treatment given at the time of the original reaction may help to reduce the risk of biphasic reaction.

Delayed cutaneous reactions or serum sickness reactions may occur days after an infusion. As monoclonal antibodies are used more frequently in the oncology and nononcology settings, reactions may be seen more frequently. Increased awareness of this type of symptom complex is crucial. Oncology nurses should educate patients regarding the possibility of such reactions and encourage patients to report all unusual cutaneous symptoms, fevers, or arthralgias when they appear.

**Conclusion**

HSRs can occur with almost any agent given in the oncology setting. Acute uniphasic reactions are seen most commonly after infusion of chemotheraphy or monoclonal antibody treatments, and although rarely reported in the oncology setting, biphasic reactions may occur. Delayed reactions with platinum agents or delayed cutaneous reactions secondary to monoclonal antibody therapy may occur in patients with cancer as well. Oncology nurses should increase their awareness of possible biphasic or delayed HSR reactions. As monoclonal antibody treatments are seen more frequently in nononcology settings, nurses should understand the risk for atypical HSRs and the presenting symptoms. Although biphasic reactions may occur anywhere from 2–38 hours or even longer after drug administration, delayed reactions may present several weeks later. Understanding the phases of HSRs may aid oncology nurses in the recognition and management of biphasic and delayed HSRs in educating patients and families about this possibility.

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Biphasic and Delayed Hypersensitivity Reactions After Cisplatin/Paclitaxel

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