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Management of Hypersensitivity Reactions: A Nursing Perspective

Oncology clinicians administer monoclonal antibodies (MoAbs) as part of the armamentarium against cancer. Nurses are skilled in the management of general treatment-related symptoms and are knowledgeable regarding the care of patients receiving these therapies. New therapies require expanded knowledge bases regarding unique and selective side effects, such as those seen with targeted therapy agents.

In general, the overall incidence of hypersensitivity reactions (HSRs) to most chemotherapy treatments is 5%, but certain agents carry much higher risks.[1] As a potential adverse event, HSRs may occur with almost any anticancer agent and can range in severity from mild to severe or even result in patient fatality. These reactions may present as acute or delayed, depending on the specific agent or class.[2] Although oncology nurses may be experienced in the management of HSRs with traditional chemotherapy agents, such as taxanes or platinum agents, certain MoAbs are associated with significant risks of HSRs as well. Specific MoAbs can result in immediate HSRs, which usually occur during the first infusion. As these therapies are becoming increasingly important in our treatments for cancer, awareness of the potential for HSRs with MoAbs and of the strategies used to manage them is vital for the practicing oncology professional.

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ABSTRACT

Infusion reactions occur commonly with the administration of monoclonal antibody therapy and can vary in severity. Oncology nurses have experience in hypersensitivity reactions with different chemotherapy agents, but with the increased use of monoclonal antibody therapy in the treatment of various cancers, knowledge of specific risk and management of reactions with these therapies is important. Anaphylactic reactions are mediated by IgE and anaphylactoid reactions are not; monoclonal antibody reactions are also considered to be associated with cytokine release syndrome, which has a specific constellation of symptoms associated with it. Infusion reactions, while common, have the potential to be distressing and frightening to oncology nurses. These challenging occurrences also can increase hospitalization costs. Strategies to manage reactions have included patient desensitization, alteration of infusion rates, skin testing, and the use of premedication. Baseline comprehensive assessments, including allergy history, are important in reducing or preventing hypersensitivity reactions. Clinical pathways or established guidelines can help to familiarize staff with appropriate responses to infusion reactions and nurses should be aware of the variety of symptoms which can indicate infusion or hypersensitivity reactions. Oncology nurses should understand the management of hypersensitivity and anaphylaxis; the Oncology Nursing Society and the American Heart Association have both published guidelines to assist practicing health-care professionals with the management of this potentially fatal adverse event. Knowledge of emergency drugs and mechanism of action is vital. Nurses should be aware of appropriate emergency response as well as management of delayed or biphasic hypersensitivity reactions. Oncology nurses should be well-prepared for these often common events.

Scope of the Problem

Reactions may be associated with the immunogenicity of the mouse protein of the drug, as in the case of MoAbs (see Figure 1). Although the immunoconjugates are used less frequently, the six unconjugated MoAbs are an integral

part of therapies used to treat common cancers.[3] Monoclonal antibodies have induced fatal reactions in rituximab (Rituxan), rare instances have occurred with trastuzumab (Herceptin; some noted up to 24 hours after the dose was given prompting a label change in 2000), and less than 1% of the doses associ-

ated with bevacizumab (Avastin) were noted to be fatal in the clinical trials.[4] Cetuximab (Erbix) has produced fatal infusion reactions in less than 0.1% of patients. Panitumumab (Vectibix) has not produced a fatal infusion reaction as of this writing; however, a fatal case of angioedema occurring several days after drug administration has recently been reported (personal communication, Dr. Volker Wagner, Amgen, Inc).

Because infusion reactions can be fatal for some patients, it is not surprising that oncology nurses are frightened of having patients experience one.[5] Oncology nurses surveyed at the 2005 annual meeting of the Oncology Nursing Society (ONS) depicts attitudes and beliefs of oncology nurses and how they experience infusion reactions.[6] This is the first time oncology nurses have been assessed for the impact of infusion reactions on patients and clinicians in inpatient and outpatient settings.

The results show that infusion reactions are common, that rituximab and paclitaxel were the most common cause of infusion reactions, and that the reactions are emotionally difficult for both staff and patients. The authors point out that 52% of the respondents felt that infusion reactions were very draining and frightening, and that 88% of outpatient nurses and 62% of inpatient nurses felt that reactions were frightening to other patients. Additionally, 42% of the nurses surveyed felt that physicians do not adequately inform patients about the risks of infusion reactions, which points out the importance of patient education regarding potential for HSRs with cancer therapies. The study authors recommended that further awareness of infusion reaction management and education of patients and clinicians are needed.[6]

Schwartzberg et al conducted a retrospective chart review of severe infusion reactions with commonly administered monoclonal antibodies.[7] This review shows that most reactions occur during the first cycle of therapy and that many of the patients (22%) needed hospitalization related to the event, with some patients subsequently discontinuing treatment of cetuximab because of their reactions.

It is also interesting to note that al-

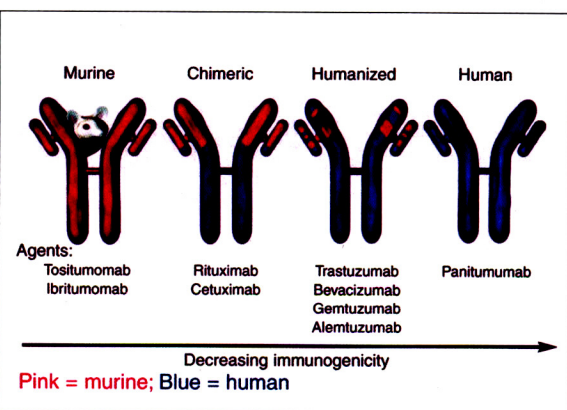


Figure 1: Immunogenicity of Monoclonal Antibodies—Reprinted, with permission, from the Institute for Medical Education and Research, Inc. (IMER).

though patients received pretreatment, many still had HSRs after or during infusion. Although the majority of reactions were limited to patients receiving rituximab and cetuximab (chimeric antibodies), some patients reacted to

bevacizumab, a humanized and fairly well-tolerated MoAb. Few of these patients (8%) received test doses to predict HSRs. The hospitalized patients usually required oxygen, steroids, fluid resuscitation, and/or antihistamine therapy.

Table 1

Premedications and Black Box Warnings for Monoclonal Antibodies*

Drug	Black Box Warning	Mechanism of Action	Premedication Recommendation
Ibritumomab tiuxetan	Yes	Targeted against CD20+ cells	Acetaminophen and diphenhydramine
Tositumomab	Yes	Targeted against CD20+ cells	Acetaminophen and diphenhydramine
Rituximab	Yes	Targeted against CD20+ cells	Acetaminophen and diphenhydramine
Cetuximab	Yes	EGFR inhibitor agent	H ₁ antagonist
Bevacizumab	No	Anti-VEGF agent	None required
Trastuzumab	Yes	Targeted against HER2/neu+ cells	None required
Gemtuzumab ozogamicin	Yes	Targeted against CD33+ cells	Diphenhydramine and acetaminophen initially, then 2 more doses of acetaminophen
Panitumumab	Yes	EGFR inhibitor agent	None required

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*Based on information from package inserts.

EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor.

Table 2

Elements of Baseline Comprehensive Assessment*

Patient Characteristic	Comments
Allergy history	Personal history of allergy to foods, bee stings, etc
Personal history of drug allergy	Previous reactions to other agents, including penicillins
Repeated use of the agent	Platinum agents
Gender	Identified as potential risk factor for patients on rituximab
Age	Identified as potential risk factor for patients on rituximab
Primary tumor type	Identified as potential risk factor for patients on rituximab
Geographic location	Identified as potential risk factor for patients on cetuximab
Race	Identified as potential risk factor for patients on cetuximab

*Based on information from Kang,[4] Gobel,[8] O'Neil,[9] Lenz,[10] Azmi,[20]

with some receiving epinephrine during the reactions or H₂ blockers.[7]

The researchers concluded that these events are challenging for both patients and practices, with cost of hospitalization substantial, and recommended that clinical pathways and directives would benefit clinicians in preparing a planned approach to HSRs. These strategies could be used to help identify patients at higher risk for HSR and to instruct clinical staff in the optimal approach to the management of patients with infusion reactions or HSR.

Strategies for Prevention of Hypersensitivity Reactions

Factors that determine the development and severity of anaphylaxis include the antigen's route of entry, the amount of antigen introduced, the rate of absorption for the antigen, and the individual's degree of hypersensitivity to the drug (Table 2).[8] Strategies to reduce or prevent HSRs include obtaining a comprehensive allergy history, the use of premedication, skin testing, desensitization, alteration of infusion rates, and knowledge of specific patient groups at risk—including awareness of the potential for geographic differences in the allergic response rate for spe-

cific medications, including MoAbs.[8] When conducting patient education sessions prior to administration of drug therapy, nurses should be cognizant of general allergy history and increased risk for patients scheduled to receive cetuximab in certain geographic areas, including North Carolina and Tennessee.[9] Data have also shown that certain risk factors with rituximab may predict higher HSRs, including age, gender, and primary tumor type.[4]

Premedications are recommended with MoAbs as well as chemotherapy agents. Although there is no evidenced-based standard for a premedication protocol, these medications often include the use of H₂ blockers, such as diphenhydramine, acetaminophen, and less frequently, corticosteroids, depending on the agent (Table 1).[8,10] Most MoAbs contain a black box warning for infusion-related reactions, with the exception of bevacizumab. Premedication is recommended for most agents, although it is not necessary with bevacizumab, panitumumab, or trastuzumab.

Assessment and Management of HSR

The National Cancer Institute (NCI) Common Terminology Criteria for Ad-

verse Events (CTCAE) v3.0 describes HSRs in terms of both an allergic reaction and the cytokine release syndrome more specific to MoAb reactions (see Table 2 in the article by Cmelak and colleagues that begins on page 18 of this supplement). The symptoms seen with cytokine release syndrome are related to the elevated levels of cytokines and release of histamine as tumor antigen-expressing cells are damaged.[8] There are a myriad of symptoms that could indicate a possible acute infusion reaction. Cytokine release syndrome can produce fevers, chills, and rigor, as well as those symptoms typically seen with acute hypersensitivity reactions.[8]

Hypersensitivity symptoms may include pruritus, urticaria, rigors, chills, headache, arthralgias or myalgias, pain at tumor site, gastrointestinal symptoms (including nausea), or respiratory symptoms (ranging from cough to dyspnea or bronchospasm).[10] Patients may describe a feeling of impending doom.[8] As edema of the upper or lower airway proceeds, patients may develop stridor or wheezing.[11] Cardiovascular symptoms may include changes in blood pressure or tachycardia. As vasodilation occurs, hypovolemia ensues, with increased capillary permeability producing intravascular collapse.

There are several existing guidelines for the management of HSRs (Figure 2). The ONS has established guidelines that are available as part of the ONS Chemotherapy and Biotherapy Guidelines and Recommendations for Practice.[12] The ONS recommends that clinical management of localized HSRs should entail patient observation and evaluation of symptoms, such as urticaria. Pharmacologic management may include the administration of diphenhydramine, cimetidine, and/or corticosteroids as ordered by the physician or according to standing protocols. Vital signs should be monitored at least every 15 minutes for 1 hour as deemed necessary. Thorough documentation of the episode, including any therapies administered, should be completed according to the policy of

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Management of Hypersensitivity Reaction

Localized Reaction

Patient observation and evaluation of symptoms
Consider administration of diphenhydramine, cimetidine, and/or corticosteroids per physician order
Vital signs every 15 min for 1 h or as deemed necessary
Thorough documentation

Anaphylaxis

Cease chemotherapy infusion immediately, maintaining IV line with normal saline or other appropriate solution for aggressive fluid resuscitation
Nurse should stay with patient while another staff member notifies physician and emergency staff
Place patient in supine or Trendelenburg position if possible; assess and maintain airway, breathing, and circulation
Monitor vital signs every 2 min until patient is stable, then every 5 min for 30 min, then every 15 min thereafter
O₂ should be administered at a high flow rate
Anticipate need for CPR
Accurate documentation of event is crucial

Pharmacologic Management of Anaphylaxis

For moderate reactions, IM administration of epinephrine (1:1000 0.3–0.5 mg q15–20 min as needed (IM preferred over SQ); monitor closely
For severe, epinephrine IV (1:10,000) 0.1 mg over 5 minutes or 1–4 µg/min; monitor closely and avoid fatal overdose
Corticosteroids: High dose given IV early in course of treatment useful for delayed reactions (biphasic); benefit noted 4–6 h later
H₁ blockers: Antihistamines such as diphenhydramine 25–50 mg IM or IV slowly
H₂ blockers: Cimetidine (or other) 300 mg orally, IM, or IV
Patients with bronchospasms need inhaled albuterol (β-adrenergics) or inhaled ipratropium for patients on β-blockers
Patients on β-blockers have higher incidence/severity of anaphylaxis and a paradoxical response to epinephrine
Consideration of glucagon and ipratropium is appropriate

Figure 2: Management of Hypersensitivity Reactions—Based on information from the American Heart Association,[11] the Oncology Nursing Society,[12] and Sampson.[19]

the institution.

The ONS guidelines for the management of hypersensitivity and anaphylaxis calls for the cessation of chemotherapy infusion immediately, while maintaining an IV line with normal saline or other appropriate solution. The nurse should stay with the patient while another staff member notifies the physician and

emergency staff if needed. If the reaction occurs outside the hospital setting, the local emergency medical service should be notified. The patient should be placed in a supine position if possible and vital signs monitored every 2 minutes until the patient is stable, every 5 minutes for 30 minutes more, and every 15 minutes thereafter. Oxygen should be administered if needed, and the nurse should anticipate the need for CPR.[12] Emergency medications may include epinephrine, corticosteroids, and H₁ and H₂ blocker agents. Because

managing a hypersensitivity reaction can be frightening to staff, patients, and family members, nurses should provide emotional support. Accurate documentation of the event is essential.

The American Heart Association (AHA) has published guidelines for management of anaphylaxis and prevention of cardiopulmonary arrest.[11] In general, the guidelines call for oxygen at a high flow rate, administration of corticosteroids, H₁ and H₂ blocker agents. The AHA guidelines discuss the role of corticosteroids in the management of

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acute reactions, noting that this class of drugs is also important in the management of delayed symptoms (the biphasic response), which can occur 4 to 6 hours after the initial HSR.

For moderate and severe reactions, the recommendation is for intramuscular epinephrine (preferred over the sometimes erratic absorption of subcutaneous administration). The AHA also notes that patients taking beta-blocker medications have a higher incidence and severity of anaphylaxis and possible paradoxical response to epinephrine and recommend the consideration of glucagon (Glucagen) and ipratropium bromide for those patients. Aggressive fluid resuscitation is necessary with hypotension. Other possible considerations for pharmacologic treatment might be vasopressin for severely hypotensive patients, atropine sulfate (Sal-Tropine) for patients with relative or severe bradycardia, or glucagon for patients not responsive to epinephrine.[11]

Rechallenge or retreatment with an agent after nonsevere or non-life-threatening HSRs may be attempted, but requires a careful assessment of the potential risk-benefit ratio prior to therapy.[13] For some patients, pretreatment with premedication regimens may be used. Some therapies involve the use of desensitization or skin testing.[14-16] With specific MoAb therapies, such as rituximab, alteration of infusion rates has been useful in reducing reactions. Rechallenge after severe reactions is not recommended, and it is advisable to conduct rechallenge administrations in settings where optimal administration support is present, such as inpatient settings.[8,10]

Established Clinical Pathways for Management of HSRs

The importance of established clinical pathways or protocols for the management of HSRs cannot be overestimated. Standardized order sets can ensure clinician response and direct the medical management of the patient in an orderly fashion.[10,13] Oncology nurses should know the individual drugs with higher risk for HSRs. If no standing protocol exists in an institu-

tion, nurses should advocate for one.

Strategies to bolster knowledge and improve accurate responses to HSRs include having resuscitation protocols or algorithms printed on laminated cards available above the medicine cart or for use at the patient's bedside.[17] Mock HSR drills can educate staff and help ensure the knowledge base and the promotion of comfort levels for appropriate responses. Nurses practicing in outpatient settings may be required to call emergency medical services teams and staff should be familiar with protocols to contact these response teams.[8,17]

Prompt recognition of the signs and symptoms of HSRs is crucial for early intervention and optimal patient outcome. Oncology nurses should be assessing patients for heightened risk with a thorough baseline evaluation prior to drug administration. Emergency kits or anaphylaxis drug kits should be present or close by during drug delivery. Knowledge of emergency drug action is necessary and nurses should have a comfort level in the administration of emergency agents and cardiopulmonary resuscitation if needed. Rarely, patients may suffer from a delayed or biphasic HSR in which symptoms may return hours after the initial event.[11,18] Rechallenge may occur in some treatment settings, depending on the severity of the reaction and perceived clinical need for the drug. Oncology nurses should understand the strategies employed in patient rechallenge, including the role of drug titration protocols and skin testing.

Conclusion

Oncology nurses should be aware of the risk for HSRs. Knowledge of the appropriate emergency response is paramount. Severe hypersensitivity reactions are not common, but can be distressing to both nurses and patients. Some infusion reactions can be fatal.

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