FEATURE ARTICLE

Cytokine-Release Syndrome: Overview and Nursing Implications

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Cytokine-release syndrome is a symptom complex associated with the use of many monoclonal antibodies. Commonly referred to as an infusion reaction, it results from the release of cytokines from cells targeted by the antibody as well as immune effector cells recruited to the area. When cytokines are released into the circulation, systemic symptoms such as fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea can result. In most patients, the symptoms are mild to moderate in severity and are managed easily. However, some patients may experience severe, life-threatening reactions that result from massive release of cytokines. Severe reactions occur more commonly during the first infusion in patients with hematologic malignancies who have not received prior chemotherapy; severe reactions are marked by their rapid onset and the acuity of associated symptoms. Massive cytokine release is an oncologic emergency, and special precautions must be taken to prevent life-threatening complications. This article will present an overview of the etiology and management of cytokine-release syndrome in patients receiving monoclonal antibodies to better prepare oncology nurses to safely care for such patients.

Monoclonal antibodies (MOABs) have become an integral part of treatment plans for patients with a variety of malignant and nonmalignant disorders. With the widespread use of MOABs, a potentially serious and even fatal cluster of symptoms known as cytokine-release syndrome has been observed. This article will describe cytokine-release syndrome in patients receiving MOABs and provide oncology nurses with the information necessary to identify and protect patients at risk for life-threatening reactions.

Cytokines

Cytokines are a group of polypeptide proteins that are produced and secreted by most cells in the human body. Examples include interleukin (IL), interferons (IFNs), tumor necrosis factor (TNF), and hematopoietic growth factors, also known as colony-stimulating factors (CSFs). Cytokines that are secreted by lymphocytes are referred to as lymphokines; those that are secreted by monocytes or macrophages are termed monokines. Cytokines that bind to target cells causing other immune effector cells to be attracted to the area are called chemokines (National Cancer Institute, 2005).

Cytokines act as chemical messengers, facilitating communication among cells. In humans, cytokines coordinate responses among the innate and acquired immune systems and organs. Cytokines serve many functions, including promotion or inhibition of cell growth, activation of lymphocytes and other immune effector cells, mediation for the destruction of cells targeted by MOABs, and mediation of the inflammatory response (see Figure 1). Cancer cells also produce and secrete cytokines (Ekmekcioglu, Grimm, & Kurzrock, 2006; Oldham, 2003). IL, IFN, and TNF are families of cytokines that are integrally involved in mediating the inflammatory response. Systemic effects of cytokine activation can include fever, fatigue, hypotension, increased insulin production, and shock (Oldham, 2003). Because of their immunostimulatory effects, cytokines such as...
IL-2, IFN, and TNF have been used with varying success in the treatment of viral infections, autoimmune diseases, and cancer. Common to all of the agents are side effects that mimic those seen when naturally occurring cytokines are activated during the inflammatory response, such as fever, chills, headache, nausea, fatigue, and hypotension (Rieger, 2001b; Yeung & Escalante, 2006).

**Cytokine-Release Syndrome**

MOAbs are immunoglobulin molecules in which the fragment-antigen binding or variable region has been engineered genetically to target a specific cell surface antigen, protein receptor, or circulating growth factor. When a MOAB binds to an antigen on the target cell, chemokines recruit monocytes, macrophages, cytotoxic T cells, natural killer cells, and complement to the area. The immune effector cells bind to the fragment crystallizable or constant portion of the antibody, targeting the cell for destruction by phagocytosis and cytolysis. In addition, binding of the antibody to the antigen may block a critical growth receptor or may directly trigger apoptosis (Roskos, Davis, & Schwab, 2004; Schmidt & Wood, 2003; Weiner, 1999). When the cell is destroyed, cytokines are released into the circulation from the targeted cell as well as immune effector cells that have been recruited (see Figure 2). The constellation of associated symptoms is known as cytokine-release syndrome (Dillman, 2003).

Cytokine-release syndrome has been observed with the use of several MOAbs and often is referred to as infusion reaction. Typical symptoms of cytokine-release syndrome include fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, tongue and throat swelling, and dyspnea, which usually are mild to moderate in severity (Roskos et al., 2004). In addition to cytokine release, some of the symptoms may be related to physiologic clearance of antigen-antibody immune complexes by the reticuloendothelial system in the lungs, liver, and spleen (Byrd et al., 1999; Dillman, 2003; Wing et al., 1996; Winkler et al., 1999). Side effects generally occur within the first two hours of initiation of infusion and usually are managed easily with temporary cessation of infusion, ad-

ministration of histamine blockers, and infusion rate reduction (Dijulio, 2001).

Symptoms of cytokine-release syndrome most commonly are seen with the first infusion of an antibody and tend to subside with successive doses, unlike the symptoms associated with true allergic-type reactions that typically are more severe when patients are rechallenged (Dijulio, 2001; Dillman, 2003; Rieger, 2001a). This can be explained by the fact that the highest percentage of targeted cells are cleared rapidly with the first infusion, resulting in a decreased tumor burden and less cytokine release with subsequent infusions. Cytokine-release syndrome most commonly is associated with antibodies used to treat patients with hematologic malignancies such as leukemia and lymphoma but also may be seen in patients with solid tumors as well as nonmalignant conditions (Rieger, 2001a). Side effects appear to be more severe in patients who have not received prior chemotherapy, reportedly because of the higher cytokine levels seen in such patients (Byrd et al., 2003).

Cytokine-release syndrome after the administration of muro-mab-CD3 (Orthoclone OKT®3, Ortho Biotech Products, L.P., Bridgewater, NJ), an anti-CD3 MOAB used to prevent transplant rejection, has been well described. Binding of OKT3 to CD3+ T lymphocytes first results in T-cell activation, stimulating the production of cytokines, followed by T-cell destruction. When cytokines are released from the targeted T cells, symptoms of cytokine-release syndrome can occur. Most commonly, flulike symptoms have been reported. Changes in blood pressure, gastrointestinal disturbances, myalgias, pruritis, dyspnea, rash, and tachycardia have occurred less commonly (Liossis & Tsokos, 2005). The symptoms have been shown to correlate with detectable levels of TNF-α, IFN-γ, granulocyte macrophage-CSF, and several subtypes of the IL family (Jeyarajah & Thistlethwaite, 1993). Premedication with corticosteroids prior to administration of OKT3 has been recommended to lessen the severity of the side effects (Jeyarajah & Thistlethwaite; Norman, Chatenoud, Cohen, Goldman, & Shield, 1993).

Symptoms of cytokine-release syndrome, associated with measurable serum levels of TNF and IL-6 from targeted B and T lymphocytes, also have been reported in patients receiving alemtuzumab (Campath®, Berlex, Montville, NJ), a humanized anti-CD52 MOAB approved for use in patients with relapsed, fludarabine-refractory chronic lymphocytic leukemia (CLL). As a result, a fractionated dose-escalation schedule is recommended upon initiation of treatment. After premedication with acetaminophen and diphenhydramine, patients receive a total dose of 3
mg alemtuzumab over two hours on day 1 followed by 10 mg on day 2, and 30 mg on day 3, if tolerated. Subsequent doses of 30 mg are given on alternating days three times a week for a maximum weekly dose of 90 mg. The fractionated dosing reportedly helps to mitigate symptoms of cytokine release (Berlex, 2005; Press, Leonard, Coiffier, Levy, & Timmerman, 2001).

Infusion reactions are common in patients receiving rituximab (Rituxan®, Genentech BioOncology, South San Francisco, CA), a chimeric MOAB approved for the treatment of CD20+ B-cell non-Hodgkin lymphoma (NHL) as well as rheumatoid arthritis (RA). Side effects generally are mild to moderate in severity and are most common with the first infusion, despite routine premedication with acetaminophen and diphenhydramine. Symptoms usually are managed easily with temporary interruption of the infusion, readministration of histamine blockers, and infusion rate reduction once symptoms subside (Kosits & Callaghan, 2000). Rituximab-related cytokine-release syndrome also has been reported in patients with RA, but the incidence and severity are less than in patients with NHL (Hainsworth, 2003).

Radioimmunotherapy delivers targeted radiation to tumor cells by using a MOAB as a carrier for a radionuclide. Two products, I131 tositumomab (Bexxar®, GlaxoSmithKline, Research Triangle Park, NC) and Y90 ibritumomab tiuxetan (Zevalin®, Biogen Idec, San Diego, CA) have received regulatory approval for relapsed or refractory indolent or transformed B-cell NHL. Patients are pretreated with a cold (nonradioactive) antibody infusion prior to administration of the radiolabeled antibody to improve biodistribution. Patients who receive I131 tositumomab are pretreated with tositumomab, a murine anti-CD20 MOAB, whereas patients treated with Y90 ibritumomab tiuxetan receive the chimeric MOAB rituximab. With both agents, infusion reactions have occurred during administration of the cold antibody, although more commonly with rituximab than tositumomab. This may be because of the fact that murine MOABs are less effective in stimulating the human immune system than chimeric antibodies, recruiting fewer effector cells to the antigen-antibody complex, therefore resulting in less cytokine release (Dillman, 2002).

In the minority of patients with B-cell malignancies, severe and even fatal infusion reactions associated with massive cytokine release and tumor cell agglutination have occurred after the administration of rituximab (Biogen Idec & Genentech, Inc., 2006; Byrd et al., 1999; Morris & Holland, 2000; Yeung & Escalante, 2006). Severe infusion reactions can be distinguished from common infusion reactions by the rapidity of onset, usually within minutes of initiation of the infusion, and severity of symptoms. Most acute side effects occur after only 25–50 mg of the antibody has been infused (Winkler et al., 1999). Acute elevations in body temperature, rigors, dyspnea, bronchospasm, acute respiratory distress syndrome, hypoxemia, pulmonary infiltrates and edema, severe hypotension, loss of consciousness, and respiratory and cardiac arrest have been reported. Cardiopulmonary symptoms may be caused, in part, by deposition of immune complexes in vital organs and microvasculature obstruction (Byrd et al., 1999; Dillman, 2003; Greenberger, 2006).

Kunzmann, Ruediger, Hallek, Mueller-Hermelink, and Wilhelm (2001) reported autopsy findings in a patient with transformed diffuse large B-cell NHL who suffered a fatal cardiopulmonary arrest 13 hours after the initiation of treatment with rituximab. Because of the high number of circulating malignant lymphocytes, fractionated dosing was planned and the infusion was initiated at 2.5 mg per hour. However, after only 42.5 mg of rituximab was administered, the infusion was discontinued because of a severe infusion reaction that could not be controlled despite infusion rate reduction and administration of additional medications. On autopsy, the patient was found to have microvascular leukostasis in the brain, heart, and lung. The authors postulated that binding of the rituximab to the CD20 antigen caused formation of antigen-antibody immune complexes with resultant tumor cell agglutination and small vessel obstruction.

Detectable serum levels of TNF-α, IFN-γ, IL-6, and IL-8, as well as complement products, have been documented in patients experiencing cytokine-release syndrome (Byrd et al., 2001; Greenberger, 2006; Szlosarek & Balkwill, 2003; van der Kolk, Grillo-Lopez, Baars, Hack, & van Oers, 2001; Wing et al., 1996; Winkler et al., 1999). In patients experiencing a severe reaction, several laboratory values may be affected. The most significant observation reported is a transient decrease of platelets, which may decline by 50%-75% within 12 hours of initiation of rituximab infusion. In addition, decreases in hemoglobin and calcium have been reported (Byrd et al., 1999; Kunzmann et al., 2001; Maloney et al., 1997; Winkler et al.). Patients can experience mild elevations in liver enzymes, d-dimers, lactic dehydrogenase, creatinine, uric acid, and phosphorous (Byrd et al., 1999; Winkler et al.). The abnormalities have been attributed to immune-mediated cytolysis of targeted cells, with release of intracellular contents as well as a possible bystander effect (on neighboring, nontargeted cells) of the antibody on nontargeted cells such as platelets (Maloney et al.; Winkler et al.). For patients treated with rituximab, temporary declines in total white blood cell counts are expected because mature B lymphocytes, which are CD20+, also are targeted by the antibody. Occasionally, transient declines in neutrophils also are seen, which may be a bystander effect. Figure 3 outlines the laboratory abnormalities that have been observed in patients treated with rituximab who experienced cytokine-release syndrome.

Patients with lymphoma and leukemia who have circulating lymphocyte counts of 25,000/mm³ or higher are at greatest risk for developing massive cytokine release. The risk is most acute during the first infusion, when the circulating tumor burden is...
at its peak (Biogen Idec & Genentech, Inc., 2006; Byrd et al., 1999; Winkler et al., 1999). High circulating lymphocyte counts are common in CLL and may be seen in the blast variant of mantle cell lymphoma (MCL) and leukemic variants of other NHLs such as small lymphocytic lymphoma (SLL).

Massive cytokine-release syndrome is an oncologic emergency; special precautions are necessary for patients at high risk. For patients with circulating lymphocyte counts of 25,000/mm³ or higher, the addition of corticosteroids and histamine-2 receptor antagonists to the usual premedications is recommended. Hospitalization of such patients for inpatient administration of medication and close monitoring should be strongly considered. Allopurinol and hydration also have been suggested to prevent renal damage from rapid clearance of targeted cells (Byrd et al., 1999; Morris & Holland, 2000; Winkler et al., 1999; Yeung & Escalante, 2006). In addition, fractionated dosing has been employed in an attempt to reduce cytokine release during the first infusion when circulating malignant lymphocyte counts are highest. Byrd et al. (1999) developed a protocol for rituximab infusion in patients with high counts of circulating lymphocytes. On day 1, 100 mg in 1,000 cc of normal saline is infused (infusion rate not described) followed by the remainder of the infusion on day 2. Winkler et al. administered rituximab to patients at high risk for cytokine-release syndrome over three days using the fractionated dosing schedule described in Figure 4. Reduction of tumor burden by pretreating high-risk patients with chemotherapy or corticosteroids also has been suggested (Kunzmann et al., 2001; Morris & Holland, 2000; Petryk & Grossbard, 2000; Winkler et al.; Wood, 2001; Yeung & Escalante).

Nursing Implications

Prior to administering any MOAB, nurses should be familiar with its toxicity profile, including the potential for acute and delayed infusion-related side effects. The need for specific premedications should be assessed. MOABs always should be administered piggy-back into the distal port of a main IV line and never should be given as an IV bolus. An infusion pump always should be used for administration. The first infusion should be administered slowly. Subsequent infusions may be given more rapidly as tolerated and per package instructions.

Observe patients closely and monitor vital signs frequently for any indications of severe infusion reactions, especially during the first hour. At the first sign of a reaction, the infusion should be stopped and IV access should be maintained with normal saline. That maneuver, combined with readministration of a histamine blocker, is sufficient to manage reactions for most patients. Once symptoms subside, usually within 30 minutes, the infusion can be restarted cautiously at half the rate and titrated as tolerated (DiJulio, 2001; Kosits & Callaghan, 2000). Administration schedules are antibody specific and are detailed in the manufacturers’ prescribing information approved by the U.S. Food and Drug Administration.

In addition to following that protocol for all patients, nurses must be able to identify and monitor patients at high risk for severe infusion reactions. Newly diagnosed, untreated patients with hematologic malignancies are more likely to develop acute infusion-related reactions; special precautions may be required to provide safe care to such patients. Nurses should be aware of patients’ diagnoses and circulating lymphocyte counts prior to antibody administration. Elevated circulating lymphocyte counts are common in patients with CLL, SLL, and MCL; such patients are at highest risk for life-threatening infusion reactions from massive cytokine release. Infusion rate reduction, fractionated dosing, steroid premedication, and hospitalization for inpatient administration may be necessary. Patients with preexisting cardiac and pulmonary dysfunction may be incapable of tolerating symptoms related to cytokine release. This could cause a decrease in oxygen saturation from deposition of immune complexes in the lungs. Such patients must be monitored carefully (Dillman, 2003).

In the case of severe infusion reactions, supplemental oxygen, corticosteroids, bronchodilators, and emergency medications may be required (Kosits & Callaghan, 2000). Patients who suffer severe reactions should be monitored for thrombocytopenia and transfused as indicated. Electrolyte abnormalities should be monitored and may require replacement.

Patient and Caregiver Education

Although most patients tolerate monoclonal infusions well, patients and their caregivers should be educated about the unique mechanism of action that could cause adverse reactions. They should be reassured that most infusion-related problems can be managed easily and that most patients tolerate treatment well with only mild or moderate infusion-related side effects.

Week 1, Day 1
- Start allopurinol 300 mg per day and continue through last infusion.
- Premedicate with acetaminophen 1,000 mg and diphenhydramine 50 mg.
- Mix 50 mg rituximab in 1,000 ml normal saline.
- Start infusion at 50 ml (2.5 mg) for one hour; if tolerated, increase the rate to 100 ml (5 mg) for a half-hour; increase rate by 50 ml every 30 minutes to a maximum infusion rate of 300 ml (15 mg) per hour as tolerated.
- Administer 2,000 ml normal saline concurrently.

Week 1, Day 2
- Premedicate with acetaminophen 1,000 mg and diphenhydramine 50 mg.
- Mix 150 mg rituximab in 1,000 ml normal saline.
- Start infusion at 50 ml (7.5 mg) for one hour; if tolerated, increase to 100 ml (15 mg) for a half-hour; increase rate by 100 ml every 30 minutes to a maximum of 300 ml (45 mg) per hour as tolerated.
- Administer 2,000 ml normal saline concurrently.

Week 1, Day 3
- Premedicate with acetaminophen 1,000 mg and diphenhydramine 50 mg.
- Mix remainder of total dose in 1,000 ml normal saline.
- Start infusion at 50 ml for one hour, then 100 ml for a half-hour, and increase every 30 minutes to maximum infusion rate of 300 ml per hour as tolerated.
- Administer 2,000 ml normal saline concurrently.

Figure 4. Rituximab First Infusion Fractionated Dosing Schedule

Note. Based on information from Winkler et al., 1999.
Explanations should be given that such reactions are expected and that they occur most commonly with the first infusion. Patients should be instructed to report any symptoms they are experiencing, especially during the first two hours of infusion. For high-risk patients, the rationale for inpatient administration and fractionated or rate-reduced dosing schedules should be discussed.

**Conclusion**

Cytokine-release syndrome is a common host reaction to many MOABs. Its management presents a new challenge for oncology nurses. An understanding of the principles related to cytokine release can help nurses identify patients at risk for severe symptoms to minimize the potential for life-threatening complications.

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**References**


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