Managing Drug Infusion Reactions: Focus on Cetuximab Monoclonal Antibody Therapy

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J.S. is a 54-year-old African American man originally from North Carolina who now lives in Boston, MA. He was diagnosed with stage IV colon cancer two years ago; his past medical history is remarkable only for intermittent asthma related to seasonal allergies. J.S.’s tumor responded to treatment with FOLFIRI ( folinic acid, 5-FU, irinotecan) and bevacizumab but recently has progressed. A new regimen is planned containing irinotecan and cetuximab (Erbitux™ [Imclone Systems, Inc. and Bristol-Myers Squibb]), a chimeric monoclonal antibody created from multiple types of protein (mouse [murine] and human). The nurse in the outpatient oncology clinic spent time with J.S. last week, describing the treatment and focusing on possible side effects of this monoclonal drug therapy (rare allergic reaction, common skin rash, and less common, diarrhea) and self-care management measures.

J.S. comes into clinic today to begin treatment. The nurse’s baseline examination reveals a temperature of 98.2°F, heart rate 76 and regular, blood pressure 110/70, respiratory rate 14, and oxygen saturation 98% on room air. His breath sounds are clear. His skin is smooth, unblemished, and without rash. He is premedicated with diphenhydramine and acetaminophen as ordered. The nurse stays with J.S. during initiation of cetuximab infusion. She monitors him closely during this time because cetuximab is known to produce a severe infusion reaction in about 3% of patients overall; of these, 90% occur during the first infusion (Bristol-Myers Squibb Company, 2007). Immediately after beginning the drug, J.S. complains of feeling uneasy, and shortly thereafter, develops wheezing with shortness of breath.

Etiology

Infusion reaction is a term used to describe a range of patient responses to the infusion of certain chemotherapy or biotherapy agents, from localized allergic responses, such as fever and flu-like symptoms, to sudden death related to cytokine release (Lim, Koh, & Tan, 1999). According to the National Cancer Institute ([NCI], 2006), symptoms may overlap among allergic or hypersensitivity reactions (HSRs) that are mediated by mast cells and the immune system and cytokine-release syndrome.

Symptoms related to cytokine-release syndrome are common with monoclonal antibodies and develop soon after the initiation of the infusion, usually resolving within 24 hours. Signs and symptoms of cytokine-release syndrome include fever, arthralgias and myalgias, lethargy, headache, hyper or hypotension, nausea, pruritis, rash, rigors, chills, tachycardia, tumor pain, urticaria, and vomiting. Similarly, grades 1 and 2 allergic reactions may include transient flushing or rash, fever to 100.4°F, urticaria, and dyspnea; grade 3 is symptomatic bronchospasm; and grade 4 is anaphylaxis with stridor, hypotension, nausea, and vomiting (NCI, 2006).

True HSRs rarely occur on the patient’s first exposure to a drug, whether chemotherapy or biotherapy agent. A HSR is an immune reaction mediated by immunoglobin E (IgE), an antibody that forms in response to initial exposure to the antigen (drug). IgE antibodies coat mast cells, which are inflammatory cells. When the patient is reexposed to the same drug, the IgE antibodies cause the mast cells to rupture, releasing histamine, prostaglandins, and leukotrienes, as well as cytokines, into the bloodstream and surrounding tissue. The presence of these substances can lead to histamine-induced vasodilation of arteries, resulting in hypotension with compensatory tachycardia, which can lead to cardiac ischemia, arrhythmias, or cardiac arrest; mucosal constriction of the bronchi, resulting in wheezing, stridor, bronchospasm, laryngeal edema, or even respiratory arrest; cutaneous effects, including flushing, urticaria, generalized pruritis, or angioedema; gastrointestinal effects, including nausea, vomiting, diarrhea, or cramping; and neurologic effects, including head-
ache, weakness, and a feeling of anxiety or impending doom.

Severe infusion reactions occur rarely with the initial administration of cetuximab. Although pooled clinical trials show an overall severe infusion reaction of 3%, patients in the middle-southern United States actually have a significantly higher incidence of 15%–20%, particularly patients who have a history of allergies (Allen et al., 2007). Chung et al. (2007) studied patients in Nashville, TN, and found that some patients who experienced severe hypersensitivity reactions to cetuximab on initial treatment had preexisting cetuximab-specific IgE antibodies. How patients developed these antibodies is unclear; however, some patients did not, suggesting that they may have had an anaphylactoid reaction, which is different from an anaphylaxis reaction in that it is not IgE mediated. J.S. originally is from North Carolina and also has a history of seasonal allergic asthma. Anaphylactoid reactions manifest the same physiologic response as a HSR, but these reactions are not mediated by an immunologic response (e.g., IgE); instead, they are seen with the first exposure to the drug, as mast cells release the same vasoactive agents as with HSRs. Regardless of the etiology, the nurse’s role is to support the patient and prevent further progression of symptoms.

**Assessment**

The nurse immediately stops the cetuximab infusion, which is administered first in case a reaction occurs, and assesses J.S. The most important assessment features are airway patency, breathing, and circulation. Once these are assured, the nurses’ role is to provide patient comfort. Assessment findings reveal that J.S. can speak without difficulty, his respiratory rate is 22, and he is wheezing with high-pitched, music-like sounds on expiration but without stridor (crowning sound heard during inspiration and expiration that heralds airway closure). His oxygen saturation is 90% on room air, blood pressure is 90/70, and heart rate is 106 and regular. Fortunately, the nurse was at J.S.’s side and was able to stop the drug immediately when he developed symptoms; early intervention can arrest more serious and lethal sequelae.

**Management**

Regardless of the precipitating etiology, J.S. was experiencing vasodilatation with hypotension and airway narrowing related to contraction of the smooth muscle in the airway. Although his oxygenation was desaturating, he was able to talk and was not yet hoarse, indicating that he did not have angioedema of the larynx at this point. Tachycardia developed secondary to vasodilation, which stimulated catecholamine release. Early intervention is imperative to prevent serious and potentially fatal sequelae.

The drug (antigen) infusion has been stopped, so the effort is now to terminate the physiologic reaction (Sampson et al., 2006). First, the nurse places J.S. in the supine (or if the hypotension had been more significant, in the Trendelenburg position) to ensure adequate blood flow to vital organs and also administers oxygen via nasal prongs. The nurse has evidence-based standing orders that allow the administration of IV normal saline at 250 ml per hour, as well as anti-histamines to inactivate the high level of histamines in the blood, and steroids to reverse the inflammatory effect of mast cell contents. Following these orders, the nurse administers diphenhydramine 50 mg IV, a H1 antagonist, as well as ranitidine 50 mg IV, a H2 antagonist, followed by hydrocortisone 100 mg IV.

On reassessment, the nurse finds that J.S.’s wheezing has stopped, his oxygen saturation has increased to 98%, his blood pressure has risen to 106/80, and his heart rate has fallen to 90. He is no longer anxious but feels fatigued. If J.S. had not responded to rapid intervention with clearance of the airway and recovery of his blood pressure, epinephrine 0.2–0.5 ml of a 1:1,000 dilution would be given intramuscularly or subcutaneously and repeated every 10–15 minutes as needed up to 1 mg total dose of epinephrine. In addition, bronchodilators would have been required, such as nebulized albuterol 2.5–5 mg in 3 ml of normal saline, and vasopressors for vasocostriction of the arteries. If the patient was taking a beta-blocking agent, then IV glucagon would have been needed to overcome resistance to epinephrine. Although J.S. responded well to medication management, he was admitted to the hospital for observation for 24 hours to ensure that when the half-life of the rescue agents were reached, if a reoccurrence of the reaction occurred, he would be in a setting where additional rescue medications could be given.

**Conclusion**

Infusion reactions continue to challenge oncology nurses as they administer chemotherapy and biotherapy agents. The essential first step is to immediately stop the drug infusion to turn off the reaction.
allergic reactions, so that the patient may be monitored closely, the drug stopped, and interventions implemented immediately to prevent more serious sequelae if a reaction does occur. If these agents are being administered, it is very important to develop and have standing orders as well as rescue drugs available.

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References


