Hypersensitivity Reactions to Oxaliplatin: Incidence and Management

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Gowda and colleagues reviewed 169 consecutive patients with esophageal or colorectal cancer who received oxaliplatin-based therapy over a 2.5-year period to identify the incidence of hypersensitivity reactions. Thirty-two patients (19%) experienced hypersensitivity; some patients experienced more than one symptom, including skin rash (13%), fever (3%), respiratory symptoms (3%), lacrimation/blurring of vision (1%), and laryngeal/glossal edema (0.6%).

Hypersensitivity Defined
In addition to the current review, there have been about a dozen case reports describing hypersensitivity reactions with oxaliplatin.[1] Hypersensitivity is broadly defined as a condition characterized by an exaggerated host response to the stimulus of a foreign antigen. Immediate hypersensitivity reactions (type I), also known as anaphylactic reactions, are initiated either by the combination of antigens with mast-cell-fixed cytophilic antibodies (primarily immunoglobulin [Ig]E), or complement activation (C3a, C4a, C5a) by antigen-antibody complexes that contain complement-fixing antibodies. Mast cell release of pharmacologically active substances (histamine, bradykinin, and serotonin) leads to contraction of smooth muscles and dilation of capillaries in various organ systems. In sensitized patients, symptoms occur within minutes of antigen exposure, reach a peak within 1 hour, then rapidly recede. Affected systems include pulmonary (dyspnea, cough, rhonchi, wheezing), cardiovascular (rapid pulse, hypotension), mucocutaneous (itching, flushing, urticaria, angioedema, lacrimation, rhinorrhea), and gastrointestinal (difficulty swallowing, nausea, vomiting, diarrhea, cramps, bloating) functions. Non-IgE-mediated anaphylactoid reactions also occur, are clinically indistinguishable from anaphylaxis, and result from drug- or chemical-mediated release of histamine from mast cells and basophils (eg, excipients like Cremaphor EL, complex platinum salts, and modulators of arachidonic acid metabolism).

Idiosyncratic Reactions
Unique organ toxicities (eg, hepatotoxicity, torsades de pointes) that are seen in a minority of patients receiving a particular drug have also been referred to in the literature as idiosyncratic. These may be due to polymorphisms in the drug-metabolizing enzymes leading to altered metabolism and delayed clearance of toxic metabolites. For this discussion, idiosyncratic reactions will be defined as abnormal reactions to a drug that occur in a minority of patients at any dose, and are not related to the known pharmacologic properties of the drug or a metabolite. Such reactions have been referred to as type B reactions.[2-4] There is usually a delay between the start of the drug before the initial occurrence of the adverse reaction, suggesting an immune-based mechanism. Symptoms occur within minutes to several hours after drug exposure, and include flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, pruritus, nausea, and various types of rashes. While conversion of drugs to chemically reactive metabolites is thought to be a crucial first step leading to idiosyncratic drug reactions, the subsequent mechanisms have not been elucidated for most drugs; more than one pathway may be involved. The "hapten" hypothesis proposes that small molecules induce immune responses only if bound to macromolecules. For example, the demonstration that IgE antibodies recognize betalactam-modified proteins led to the strategy of skin testing for IgE-mediated allergic reactions to penicillin and other beta-lactam antibiotics. Many drugs form reactive metabolites, but the incidence of idiosyncratic drug reactions is very low (eg, acetaminophen). Possible explanations include the following: (1) the level of covalent binding of the reactive metabolite to the macromolecule is too low to trigger an immune response, (2) covalent binding to certain proteins may be more likely to cause idiosyncratic drug reactions than binding to other proteins, and (3) covalent binding of reactive
metabolites may be necessary but not sufficient to cause an idiosyncratic drug reaction. For most drugs associated with idiosyncratic drug reactions, however, the requirement for covalent binding of the reactive metabolites has not been proven. *Danger Hypothesis*

The "danger hypothesis" propose that a pivotal role of the immune system is to distinguish between harmless and dangerous challenges. In this model, the primary stimulus for the immune response comes from endogenous signals and is controlled by the damaged tissue itself. The first signal is provided by antigen-presenting cells after the antigen from the reactive metabolite-bound self-protein is processed and presented in the groove of the major histocompatibility complex class II. Signal 2 costimulatory signals are mediated by upregulation of signaling molecules on the antigen-presenting cell that interact with T-cell receptors. The antigen-presenting cells must receive the activating ("danger") signals released from stressed or damaged cells in order to result in T-cell activation. It has been proposed that cytokines such as tumor necrosis factor-alpha, interleukin (IL)-1-beta, and IL-6 may function as danger signals. However, preclinical studies have shown that stressed or dead cells can stimulate T cells in the absence of protein synthesis, suggesting that constitutively present proteins may also function in this capacity.[5] As discussed by Gowda, there have been reports of elevated tumor necrosis factor and IL-6 that parallel the onset of symptoms of "infusion reactions" in patients receiving oxaliplatin, whereas falling levels are associated with symptom resolution. **Conclusions**

The incidence of anaphylactic/anaphylactoid reactions with oxaliplatin is under 1%.[1] For IgE-mediated anaphylactic reactions, desensitization is certainly possible. There are anecdotal reports of successful desensitization to oxaliplatin after patients experienced anaphylaxis, but there are also reports that anaphylactic symptoms recurred in subsequent cycles despite several symptom-free cycles after desensitization.[1] In a review of hypersensitivity reactions with chemotherapy drugs, Shepherd concludes that desensitization is not uniformly successful for platinum anticancer agents.[6] The basis for oxaliplatin-associated idiosyncratic drug reactions is not clear, and the various reactions may be due to more than one mechanism. Prophylaxis with dexamethasone and histamine-1 and -2-receptor blockers may be successful in some patients with either anaphylactic or idiosyncratic drug reactions. Dose reduction and/or increasing the infusion duration may improve tolerance. This discussion highlights the fact that oxaliplatin-associated hypersensitivity reactions represent heterogenous symptom complexes with different potential etiologies. It will be helpful if future studies more fully characterize the hypersensitivity symptom complex to facilitate our understanding of the magnitude of the problem and the success of interventions.

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