CLINICAL Q&A

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Paclitaxel-Related Hypersensitivity Reactions and Monitoring Recommendations

QUESTION: We have observed an increase in the incidence of paclitaxel-related hypersensitivity reactions at our institution. Does any new information explain the etiology of these reactions? Should we change our standards for monitoring patients receiving paclitaxel infusions (e.g., begin placing patients on cardiac monitors)?

ANSWER: Factors to consider when investigating an increase of paclitaxel-related hypersensitivity reactions include an accurate patient history of allergic reactions to other medications, thorough admixture of the paclitaxel solution, the use of non-polyvinyl chloride (PVC) containers and tubing, and the use of standard premedication. Correspondence with Bristol-Myers Squibb Oncology, the company that manufactures paclitaxel (Taxol®), indicated that no increase in paclitaxel hypersensitivity reactions to date had been reported to them.

Symptoms associated with paclitaxel-related hypersensitivity reactions may include chest or back pain, flushing, dyspnea, pruritus, hypotension, hypertension, bronchospasm, urticaria, and diaphoresis (Greco, Thomas, & Hainsworth, 1999; Olson, Sood, Sorosky, Anderson, & Buller, 1998). These symptoms are treated by prompt recognition, stopping the infusion immediately upon recognition of any signs and symptoms of a reaction, and administering appropriate emergency medications. Typical medications used to treat hypersensitivity reactions include IV diphenhydramine; a corticosteroid, such as hydrocortisone or methyprednisolone; and subcutaneous epinephrine (Compton, 1997; Labovich, 1999; Mackan, 1995).

During clinical trials of paclitaxel, only 1% of patients experienced significant cardiotoxicity not related to rate of infusion or prior exposure to anthracyclines and not associated with hypersensitivity reactions (Bristol-Myers Squibb Oncology, 2002). The manufacturer's package insert recommendations do not advocate routine continuous cardiac monitoring during paclitaxel infusions unless patients have cardiac risk factors, such as underlying cardiac disease or damage. However, equipment that allows for continuous monitoring of heart rate, blood pressure, and oxygen saturation provides valuable information for all patients throughout infusion. In the event of an infusion reaction, diphenhydramine and a corticosteroid typically are administered immediately and, in most cases, are successful in reversing the symptoms associated with the reaction. The use of a cardiac monitor when administering subcutaneous epinephrine is not mandatory; however, the monitor becomes necessary when epinephrine is administered via IV.

Cremophor EL® (BASF Aktiengesellschaft, Ludwigschafen, Germany) (a diluent made up of polyoxyethylated castor oil) commonly is believed to be the primary cause of paclitaxel-related hypersensitivity reactions. However, debate about this issue still exists, as taxanes also have been found to induce histamine release without the presence of Cremophor EL (Zanotti & Markman, 2001). The incidence of reactions prior to use of the premedication regimen often used today range from 10%–16%. The standard regimen of IV diphenhydramine, a histamine antagonist (e.g., cimetadine, ranitidine, famotidine), and oral or IV dexamethasone has decreased the incidence to 1%–3% (Olson et al., 1998; Rowinsky & Donehower, 1995). Studies have shown that single-dose IV dexamethasone administered 30 minutes prior to a paclitaxel infusion produces comparable results to oral dexamethasone given 6 and 12 hours prior to infusion (Bookman, Kloth, Kover, Smolinski, & Ozols, 1997; Kintzel, 2001; Markman et al., 1999; Micha et al., 1998). Research also has shown that dexamethasone dose reduction for patients receiving weekly treatment with paclitaxel has not caused an increase in the incidence of hypersensitivity reactions (Koppler, Heymanns, & Weide, 2001).

Paclitaxel must be administered in non-PVC containers via infusion sets. Prolonged contact of Cremophor EL with PVC allows leaching of the plasticizer di-2-ethylhexylphthalate (DEHP) into the infusate and was associated with enhanced liver toxicity during animal trials. One incident of delayed hypersensitivity occurred during a patient's sixth cycle of treatment (24-hour infusion of paclitaxel delivered in four, six-hour bags) that was thought to be related to cumulative exposure to DHEP from the inadvertent use of PVC equipment. The patient's 24th bag had been mixed in a PVC container 10 hours prior to administration (Peters, Xynos, Ponsillo, & Zurnsteg, 1992).

Liau-Chu, Theis, and Koren (1997) described complications associated with a high cumulative dose of Cremophor EL and ethanol when mixed suboptimally. In this case, Cremophor EL was the diluent for high-dose cyclosporine (CSA) infusions (Liau-Chu et al.). A 24% incidence of hypersensitivity reactions was noted in the pediatric population (Theis et al., 1995). Incomplete admixture led to an inadvertent bolus of Cremophor El and ethanol at the beginning of the infusion. For this reason, paclitaxel infusions should be gently inverted several times after admixture and prior to administration to ensure that the paclitaxel, Cremophor El, and ethanol are distributed evenly.

Patients with a history of allergic reactions to the diluent Cremophor El (used in the admixture of medications, such as high-dose cyclosporine) are not candidates for therapy with paclitaxel. Patients who have experienced hypersensitivity to other drugs may be at increased risk and should be monitored carefully (Bristol-Myers Squibb Oncology, 2002).

An important part of the oncology nursing role is to recognize, treat, and report hypersensitivity reactions. Oncology nurses must be familiar with the facility policy for reporting and managing adverse events and alert the pharmacist should they occur. In ambulatory settings without an onsite pharmacy, nurses may report to the risk management department. Internal reporting mechanisms are important to facility quality assurance trending. Many institutions make external reporting a function of the pharmacy department; however, nurses also may report events directly. In the case of paclitaxel, Bristol-Myers Squibb Oncology has two options for reporting adverse events. An Adverse Event Reporting Form may be obtained by calling 800-426-7644 and selecting document code number 2000. The Bristol-Myers Squibb Worldwide Safety and Surveillance representative may be reached at 609-818-3737.

Patient and family education also is critical. Alerting patients and family members to the signs and symptoms of hypersensitivity reactions allows them to assist the nurse in early identification of a reaction so that

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