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Gemtuzumab Ozogamicin

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Drug name: Gemtuzumab ozogamicin is manufactured as Mylotarg® (Wyeth Pharmaceuticals, Philadelphia, PA).

Classification: Monoclonal antibody-based chemotherapeutic agent

Indication: Gemtuzumab ozogamicin is indicated for the treatment of CD33 positive acute myeloid leukemia (AML) in patients 60 years of age or older in first relapse who are not candidates for cytotoxic chemotherapy. The CD33 antigen is expressed on more than 80% of patients with AML.

Action: This drug is comprised of an antibody, along with a cytotoxic antitumor antibiotic, colechiamicin. The antibody binds to CD33 antigen and is linked to the antitumor antibiotic calicheamicin. Calicheamicin has been shown to produce DNA strand breakage and induce apoptosis in exposed cells, although a necrotic (nonapoptotic) mechanism of cytotoxicity also has been suggested.

Metabolism: The drug causes hydrolytic release of calicheamicin derivative.

Excretion: Metabolites are found in human liver microsomes and cytosol (i.e., the part of the cell that contains organelles, such as mitochondrion, and is the site of many vital cellular functions) and in HL-60 promyelocytic leukemia cells.

Half-life: 45 hours (total calicheamicin) and 100 hours (unconjugated calicheamicin)

Effect on blood counts: Gemtuzumab ozogamicin induces severe myelosuppression. The median recovery of absolute neutrophil counts to 500 cells/mm^3 is 40.5 days after the first dose. Thrombocytopenia occurs in every patient and generally is severe. Median time to recovery of platelets to 25,000/mm^3 is 39 days after the first dose. Grades 3 and 4 anemia have been reported in up to 50% of patients.

Adverse reactions and effects: Adverse reactions include infusion-related reactions, infection and sepsis, tumor lysis syndrome, veno-occlusive disease (VOD), pulmonary events, and liver and renal impairment.

Infusion-related reactions: Infusion reactions have been noted to produce a symptom complex of fever and chills and, less commonly, dyspnea and hypotension. The reaction tends to occur during the first 24 hours after administration. Prophylactic premedication with diphenhydramine 50 mg and acetaminophen 650–1,000 mg orally (PO) prior to administering the agent, with two additional doses of acetaminophen 650–1,000 mg PO at hours four and eight, have been useful in ameliorating infusion-related symptoms. These symptoms generally occur after the end of the two-hour IV infusion and resolve within two to four hours, with supportive therapy of acetaminophen, diphenhydramine, and IV fluids. Fewer infusion-related events were observed after the second dose.

Infection and sepsis: Myelosuppression occurred in 100% of patients treated. Infection and sepsis were reported to occur in 28% of patients participating in clinical trials of the drug.

Tumor lysis syndrome: Tumor lysis syndrome has been reported and can be a consequence of any leukemia-related therapy. Signs of tumor lysis include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Appropriate interventions include administration of allopurinol and hydration. Prior to treatment with gemtuzumab ozogamicin, patients may be candidates for hydroxyurea to reduce the total white blood cell (WBC) count to less than 30,000 cells/mm^3 to reduce the risk of tumor lysis and subsequent renal failure secondary to hyperuricemia.

Veno-occlusive disease: VOD, a potentially fatal complication, has been reported. Symptoms of VOD include rapid weight gain (more than 5% of pretreatment weight), right upper quadrant pain, hepatomegaly, ascites, and elevation in bilirubin or liver enzymes. Patient's bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels should be evaluated prior to initiation of therapy. Patients should not be treated with gemtuzumab ozogamicin if their bilirubin level is greater than 2 mg/dL.

Pulmonary events: Severe pulmonary events have occurred infrequently with this agent. Signs and symptoms have included dyspnea, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency, and hypoxia, along with acute respiratory distress syndrome. These events may occur as sequelae of infusion reactions, and patients with WBC counts of more than 30,000 cells/mm^3 are at increased risk.

Liver and renal impairment: In the initial clinical trial, 23% (33/141) of patients experienced reversible grade 3 or 4 hyperbilirubinemia. AST and ALT abnormalities and renal failure also have been reported with this agent.

Interactions: Unknown

Contraindications: Gemtuzumab ozogamicin is contraindicated in patients with a known hypersensitivity to gemtuzumab ozogamicin or any of its components: anti-CD33, antibody, calicheaminic derivatives, or inactive ingredients.

Route and dosage: Gemtuzumab ozogamicin is administered as a two-hour IV infusion. Patients should receive prophylactic medications one hour prior to administration. This agent must not be pushed or bolused. It may be administered through a peripheral or central line. The dose of gemtuzumab ozogamicin is 9 mg/m^2 on days 1 and 14. Full hematologic recovery between doses is not required.

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