

Fatal hypersensitivity reaction to gemtuzumab ozogamicin associated with platelet transfusion

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Gemtuzumab ozogamicin is a humanized monoclonal antibody labeled in the United States for use as monotherapy in patients ages 60 years or older with a first relapse of acute myelogenous leukemia (AML) who are ineligible for other cytotoxic chemotherapy.¹⁻⁵ Gemtuzumab is a conjugate of a monoclonal antibody and the cytotoxic antitumor antibiotic, calicheamicin.¹⁻⁵ Gemtuzumab specifically targets the CD33 antigen, an adhesion protein found on more than 80% of leukemic blasts and immature myelomonocytic normal cells but not on normal hematopoietic stem cells.^{1,2} The specific binding to the CD33 antigen results in a complex that is ultimately internalized. After internalization by the leukemic cell, the calicheamicin derivative is released inside the lysosomes of myeloid cells, causing DNA site-specific double-stranded breaks and cell death.³

The recommended dose of gemtuzumab ozogamicin is 9 mg/m² administered as a two-hour i.v. infusion.¹ Gemtuzumab should not be administered as an i.v. push or bolus dose. Premedications often given

Purpose. A case of a fatal hypersensitivity reaction to gemtuzumab ozogamicin in a patient who received a platelet transfusion on the same day is presented.

Summary. A 75-year-old man went to a hematology clinic in April 2005 because of anemia and thrombocytopenia. He was diagnosed with acute myelogenous leukemia (AML). In May 2005, the patient was started on induction chemotherapy with cytarabine and idarubicin. During the induction phase, the patient received platelet transfusions on multiple occasions without any evidence of transfusion reactions. He went into partial remission and received two cycles of cytarabine and idarubicin followed by one cycle of high-dose cytarabine. In March 2006, the patient relapsed, and he received dose number one of the first cycle of gemtuzumab ozogamicin at a dose of 9 mg/m² on March 28, 2006. He tolerated the infusion. He had received multiple platelet transfusions during the week before gemtuzumab infusion without reaction but received no transfusions

on the same day as the gemtuzumab infusion. On April 4, 2006, the patient received an infusion of gemtuzumab at 11 a.m., and he received 6 units of leukocyte-depleted, irradiated platelets at 6:40 p.m. At 1 a.m. the next morning, the patient developed fever and shortness of breath and went into severe distress. Despite treatment, the patient died shortly after.

Conclusion. A patient with AML developed severe respiratory distress and died after receiving gemtuzumab and 6 units of platelets on the same day. The fact that he had previously received gemtuzumab and platelets safely on separate days suggests that the gemtuzumab-platelet combination contributed to a fatal hypersensitivity reaction.

Index terms: Allergies; Antibodies; Cytarabine; Death; Drugs, adverse reactions; Gemtuzumab ozogamicin; Geriatrics; Idarubicin; Leukemia; Platelets; Transfusions

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before gemtuzumab administration include diphenhydramine and acetaminophen. Vital signs should be monitored for four hours following administration of gemtuzumab.

The recommended treatment course with gemtuzumab is a total of two doses, 14 days apart. The second dose should be administered despite cases of partial hematologic recovery.

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The prescribing information currently includes a boxed warning of severe hypersensitivity reactions associated with gemtuzumab, including infusion reactions, anaphylaxis, and pulmonary events.¹⁻³ While infusion-related reactions are generally transient and reversible, anaphylaxis and pulmonary events can be fatal. The overall frequency of treatment-related mortality with gemtuzumab is 16%.³ Gemtuzumab infusion should be interrupted in patients experiencing dyspnea or severe hypotension.¹ Discontinuation of further gemtuzumab challenge should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome.¹ It is unknown if the risk of hypersensitivity reaction increases with administration of blood products on the same day of gemtuzumab infusion.

We report a case of a fatal hypersensitivity reaction to gemtuzumab in a patient who received a platelet transfusion on the same day.

Case report

A 75-year-old man came in April 2005 to the hematology clinic because of anemia and thrombocytopenia. He had a bone marrow biopsy that showed 44% blasts consistent with acute leukemia with a background of dysplasia, suggesting that the acute leukemia was secondary to myelodysplastic syndrome. Flow cytometry of the bone marrow was diagnostic of AML, M2 subtype. The results of cytogenetic studies were normal.

The patient was started on induction chemotherapy in May 2005 with cytarabine (seven consecutive days) and idarubicin (three consecutive days). During the induction phase, the patient received platelet transfusions on multiple occasions without any evidence of transfusion reac-

tions. The patient went into partial remission and received two cycles of cytarabine (five days) and idarubicin (two days) followed by one cycle of high-dose cytarabine. A repeat bone marrow biopsy in March 2006 showed relapse. The patient was admitted for gemtuzumab ozogamicin infusion, and he received the first dose (9 mg/m²) of the first cycle on March 28, 2006. He tolerated the infusion well without documented reactions. The patient received multiple platelet transfusions during the week before the gemtuzumab infusion without documented reactions but did not receive any platelet transfusion on the day of the gemtuzumab infusion. On April 14, 2006, he was admitted to the hospital for the next dose of gemtuzumab. The infusion was started at 11 a.m. after he received the appropriate premedications (dexamethasone phosphate 20 mg [as the sodium salt] i.v., diphenhydramine hydrochloride 50 mg orally, and acetaminophen 650 mg orally) and finished at 1 p.m. without any signs of distress or reaction. He received 6 units of leukocyte-depleted, irradiated platelets at 6:40 p.m. At 1 a.m. the next morning, he developed fever and shortness of breath and went into severe respiratory distress. The patient was treated with i.v. hydrocortisone 100 mg (as the sodium succinate ester), i.v. diphenhydramine hydrochloride (50 mg), and i.v. meperidine hydrochloride (50 mg) but did not respond and died shortly after.

Discussion

Our patient had a severe reaction when he received a gemtuzumab infusion and a platelet transfusion on the same day. When he received a previous dose of gemtuzumab without concomitant platelet transfusion, he did not have any reaction. Also, the patient had received platelet

transfusions on multiple occasions prior to gemtuzumab infusion without any complications. Furthermore, because of the patient's severe reaction, the reported reaction was fully investigated by the blood bank, and it found no in vitro incompatibility between the donor and the patient. The platelets were leukocyte reduced and irradiated.

The patient's presentation is highly suggestive of a relation between the concomitant use of gemtuzumab and platelet transfusion and the patient's severe hypersensitivity reaction.

We found no similar reports in the literature and have no explanation why this apparent interaction between gemtuzumab and platelets occurred.

Conclusion

A patient with AML developed severe respiratory distress and died after receiving gemtuzumab and 6 units of platelets on the same day. The fact that he had previously received gemtuzumab and platelets safely on separate days suggests that the gemtuzumab-platelet combination contributed to a fatal hypersensitivity reaction.

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