Relato de Caso / Case Report

A rare case of fatal hepatic veno-occlusive disease and rupture of the spleen vein and artery after Gemtuzumab Ozogamicin (Mylotarg®) infusion

Doença veno-oclusiva fatal por Gentuzumab Ozogamicin

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*Gemtuzumab Ozogamicin (Mylotarg®) targets leukemia cells expressing the CD 33 receptor by means of a monoclonal antibody conjugated to a cytotoxic agent, calicheamicin. It was approved for use in elderly patients with relapsed or refractory acute myeloid leukemia and reversible hepatotoxicity is common after administration. The first case of hepatic veno-occlusive disease was reported after Gemtuzumab Ozogamicin infusion in a patient who had been submitted to hematopoietic stem cell transplantation 8 months earlier. Three phase 2 studies with 188 patients with acute myeloid leukemia in first relapse that used Gemtuzumab Ozogamicin were analysed and the incidence of fatal hepatic veno-occlusive disease in these studies was < 1%, and prior hematopoietic stem cell transplantation was the most significant risk factor. The aim of this paper is to report a rare fatal case of hepatic veno-occlusive disease with rupture of the spleen vein and artery in a 68-year-old patient that had received Gemtuzumab Ozogamicin. To the best of our knowledge, it is the first case report of hepatic veno-occlusive disease with rupture of the spleen vein and artery related to Gemtuzumab Ozogamicin. Rev. bras. hematol. hemoter. 2004;**26**(3):218-220.*

Key words: *Gemtuzumab Ozogamicin; Hepatic veno-occlusive disease; spleen vases.*

Introduction

Gemtuzumab Ozogamicin (GO) (Mylotarg®) targets leukemia cells expressing the CD 33 receptor by means of a monoclonal antibody conjugated to a cytotoxic agent, calicheamicin.[1] The drug was approved for use in elderly patients with relapsed or refractory acute myeloid leukemia (AML) and reversible hepatotoxicity is common after administration.[1] GO is associated with an incidence of approximately 20% grade 3 or 4 hyperbilirubinemia and liver transaminitis in elderly patients who had relapsed acute myeloid leukemia (AML).[2]

Hepatic veno-occlusive disease (HVOD) is a life threatening complication of stem cell transplantation that has been described in approximately 6-54% of patients receiving standard myeloablative conditioning regimens.[3] In 2001, Tack et al[4] reported the first case of HVOD after GO infusion in a patient who had been submitted to hematopoietic stem cell transplantation (HSCT) 8 months previously. Since then, this syndrome has been described in patients receiving GO with or without HSCT as a risk factor.[1,2,5]

The aim of this paper is to report a rare fatal case of HVOD with rupture of the spleen vein and artery in a 68-

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year-old patient who received GO during consolidation for AML without HSCT as a risk factor. We reviewed about this potentially fatal side effect with respect to its incidence, management and prognosis.

Case report

A 68-year-old man with a history of AML (FAB-M1) with a normal karyotype received an induction regimen consisting of idarrubicin+ cytarabine (3+7). A bone marrow aspiration on day 21 after chemotherapy revealed a morphologically complete remission. In the consolidation therapy, we added GO to these induction drugs (9 mg/m^2-day 0 and day 14).[1] Six days after the initiation of consolidation therapy, the patient developed fever, increases in bilirubin levels and ascites. Imaging studies confirmed ascites without any mass or intra-abdominal purulent collections. Empirical antibiotic therapy was started with meropenem and teicoplanin. On day 7, the patient presented with increased ascites and renal insufficiency, at that time the activated prothrombin time was 20 seconds (normal range 11-16 seconds). Relief paracentesis was performed but the peritoneal fluid did not show any abnormality. On day 9, the patient continued febrile and amphotericin was added to the therapy regimen. A granulocyte transfusion was performed due to persistency of granulocytopenia (100 cells/μL) despite filgastrim stimulation. On day 15, the patient presented with hypotension with hemorrhagic peritoneal fluid. A technetium-labeled erythrocyte scan revealed left upper quadrant bleeding and an exploratory laparotomy showed rupture of the spleen vein and artery. At that time, multiple hepatic biopsies were performed. The hepatic biopsy showed HVOD. The patient developed multiple organ failure and expired on day 33.

Discussion

HVOD is characterized by tender hepatomegaly and/or or right upper quadrant tenderness, unexplained weight gain or ascites and hyperbilirubinemia.[3] The clinical diagnosis is based on the presence of at least two of these findings within 10 days of HSCT.[3] This syndrome is thought to be secondary to hepatic sinusoid and venule endothelial cell damage from high dose chemotherapy and radiation therapy.[6] The most significant risk factor for the development of HVOD is pre-transplantation elevation of transaminase levels.[3] Currently, the management includes fluid and sodium restriction, albumin replacement and transfusion support.[3] GO, a humanized anti-CD 33 monoclonal antibody conjugated with calicheamicin for the treatment of AML, was reported as a causative agent of HVOD in a patient who underwent HSCT 8 months previously.[4] Since then, a few cases have been reported. [1,2,5] Our group reports the first case of fatal HVOD with rupture of spleen vein and artery in a 68-year-old patient following therapy with GO without HSCT as a risk factor. Probably, this rupture was due to the high pressure of the portal system due to hepatic sinusoid and venule endothelial cell damage.

Martin et al[7] reported the incidence of HVOD in 5 (20%) of 25 patients who received GO during anti-leukemia therapy and subsequently underwent allogeneic transplantation. The mean time from last GO cycle to HSCT was 88 days. Based on this study, they concluded that prior GO therapy increased the risk of HVOD in patients who received high dose myeloablative therapy.

Giles et al[2] assessed the incidence of HVOD in 119 patients who had received GO containing non-HSCT regimens. Fourteen (12%) patients developed HVOD. Five (36%) out of 14 patients had received no prior anti-leukemic cytotoxic therapy, including two patients who received single GO therapy. HVOD occurred when GO was used either as a single agent or when it was given with other cytotoxic agents. Our patient received GO during consolidation in combination with idarrubicin and cytarabin and developed HVOD on day 6 of this regimen. Nine days after this, he developed hypotension due to spleen vein and artery rupture. Langston et al[5] reported on two cases of HVOD soon after the initiation of GO therapy in patients without any history of HSCT (similar to our patient) and both improved spontaneously with supportive care.

Stadtmauer et al[8] reviewed the predisposing factors for HVOD after the treatment with GO. Three phase II studies with 188 patients with AML in first relapse were analysed. The incidence of fatal HVOD in these studies was < 1%, and prior HSCT was an important risk factor (p-value = 0.002). No correlation was found between the occurrence of HVOD and gender, baseline bilirubin levels, prior chemotherapeutic regimens or concomitant administration of medications. Only prior HSCT was considered to be a risk factor for the development of HVOD in patients with AML in first relapse that received GO therapy.

Rajvanshi et al[9] reviewed the clinical outcomes of 23 patients who were given GO for AML who had relapsed after HSCT. Liver injury developed in 11 patients after GO administration. Results of liver histological examinations in five patients showed extensive sinusoidal fibrosis, centrilobular congestion and hepatocyte necrosis similar to the findings evidenced in our patient. Nevertheless, no patient developed spleen vessel rupture. We can suggest that GO targets CD 33 + cells residing in hepatic sinusoids as the mechanism for its hepatic toxicity and HSCT probably contributes to liver injury due to high dose chemotherapy.

The etiology of the liver injury following GO remains unknown. Further studies on this topic are needed but it

is clear that careful patient selection remains the best method to prevent HVOD. We believe that further studies are necessary to improve the knowledge about fatal HVOD related to GO.

Resumo

*Gentuzumab Ozogamicina (GO) (Mylotarg®) tem como alvo células leucêmicas que expressam CD33 através de um anticorpo monoclonal conjugado a um agente citotóxico, a caliqueamicina. Esta droga foi aprovada para uso em pacientes idosos com leucemia mielóide aguda (LMA) recaída ou refratária e hepatotoxicidade é comum após sua administração. Tack e colaboradores apresentaram o primeiro caso de doença hepática veno-oclusiva (DHVO) após infusão de GO em um paciente que tinha realizado transplante de medula(TMO) há 8 meses. Três estudos de fase II com 188 pacientes com LMA foram analisados e a incidência de HVOD fatal foi inferior a 1%, sendo a realização de TMO o fator de risco mais importante. O objetivo deste artigo é relatar um caso raro de DHVO fatal com ruptura de veia e artéria hepática em um paciente de 68 anos que recebeu GO. Acreditamos que este é o primeiro relato de HVOD com ruptura de vasos hepáticos relacionado ao uso de GO. Rev. bras. hematol. hemoter. 2004;**26**(3):218-220.*

Palavras-chave: *Gentuzumab Ozogamicina; doença hepática veno-oclusiva; vasos hepáticos.*

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