Successful treatment with gemtuzumab ozogamicin monotherapy in a pediatric patient with resistant relapse of acute myeloid leukemia

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There are few therapeutic options in relapsed or refractory acute myeloid leukemia patients. CD33 antigen is expressed on approximately 90% of myeloblasts, and gemtuzumab ozogamicin, as a monoclonal antibody directed against the CD33 surface antigen, may be a good target for these patients. Herein, we present a 15-year-old acute myeloid leukemia patient who was resistant at relapse and could achieve remission with gemtuzumab ozogamicin at a total dose of 9 mg/m^2, divided into three doses and delivered to hematopoietic stem-cell transplantation; however, the patient relapsed in a short time without application of transplantation.

Key words: pediatric hematology/oncology, acute myeloid leukemia, gemtuzumab ozogamicin, resistant, relapse.

The estimated incidence of acute myeloid leukemia (AML) in children up to four years of age is 0.9 per 100,000, and for individuals between 15 to 19 years of age, it is 0.8 per 100,000[1]. Despite gradual improvements over the years, only 50 to 60% of all children with newly diagnosed AML will be cured with currently available treatment[2,3]. Since 10% of newly diagnosed AML cases can not achieve complete remission and remission rates after relapse are even much lower, allogeneic hematopoietic stem cell transplantation (HSCT) from a matched-related donor can improve survival in children with AML in first remission compared with chemotherapy alone or autologous HSCT[4]. Thus, the primary goal in AML cases is to perform HSCT after achievement of remission by intensive chemotherapy. Unfortunately, patients who relapse or can not achieve remission have very few therapeutic options.

CD33 antigen is expressed on approximately 90% of AML myeloblasts[5]. Gemtuzumab ozogamicin (Mylotarg CMA-676; Wyeth Pharmaceuticals, Philadelphia, PA) is a humanized monoclonal antibody directed against the CD33 surface antigen that is conjugated to a derivative of the cytotoxic antibiotic calicheamicin[6,7]. Response rates of approximately 25% have been observed in adult patients with refractory AML treated with gemtuzumab ozogamicin[8-10]. The data on the use of gemtuzumab ozogamicin in resistant or refractory AML cases in the pediatric age group is limited. Brethon et al.[11] reported a complete remission rate of 25% among 12 children treated with gemtuzumab on a compassionate basis. Arceci et al.[12] reported comparable remission rates in patients with refractory (30%) and relapsed (26%) disease. The data on the pediatric dose of gemtuzumab ozogamicin is also variable. Herein, we report a 15-year-old AML patient who was resistant at relapse and could achieve remission with gemtuzumab ozogamicin at a total dose of 9 mg/m^2, divided into three doses.

Case Report

Acute myeloid leukemia, M7 according to French-American-British (FAB) classification, was diagnosed in a 15-year-old male patient, and cytarabine (100 mg/m^2/day, x7) and daunorubicin (45 mg/m^2, x3) were initiated; however, remission could not be achieved. The

initial immunophenotyping by flow cytometry revealed CD33: 79%, CD13: 73%, CD34: 62%, CD117: 72%, CD45: 95%, CD42a: 25%, and CD41a: 37%. FLAG-Ida protocol including fludarabine (30 mg/m^2, 1-4 days), cytarabine (2 g/m^2, 1-4 days) and idarubicin (12 mg/m^2, 2-4 days) chemotherapeutics was initiated in order to induce remission, and by the completion of the second FLAG-Ida, hematological remission was achieved. However, because cardiomyopathy with ejection fraction of 59% and increased end-diastolic diameter developed, HSCT could not be urgently performed. AML-MDS 2003 maintenance protocol was started and remission could be maintained for six months. The patient was resistant to sequential administration of FLAG without idarubicin, Berlin-Frankfurt-Munster AML induction and cytarabine (500 mg/m^2, x2) plus mitoxantrone (12 mg/m^2, x3). The bone marrow exhibited 100% myeloblasts with decreased megakaryocytes, and gemtuzumab ozogamicin was given at a total dose of 9 mg/m^2, divided into three doses given on days 1, 4 and 7. White blood cell count (WBC) on day 1 was 44x10^9/L, hemoglobin: 9.7 g/dl and platelet 9x109/L. By the 24th hour of completion of the last dose of gemtuzumab, WBC was 1x10^9/L. Peripheral blood CD33 on day 1 was 99%. The peripheral CD33 measured 24 hours after the last dose of gemtuzumab ozogamicin was 72%, in a gating of 2% blasts. Figure 1 summarizes the WBC and CD33 alterations after onset of gemtuzumab ozogamicin. Bone marrow sampling revealed disappearance of blasts with still decreased megakaryocytes, and flow cytometric analysis of bone marrow showed remission in a gating of 2% blasts with 73% CD33, 7% CD41 and 6% CD42a. Although remission was achieved, platelet recovery was incomplete. The patient was closely monitored for adverse reactions, and hepatic and renal functions were normal during the follow-up and no sinusoidal obstruction syndrome was observed. The patient was referred for HSCT after induction of remission; however, he unfortunately relapsed in a short time and died without application of HSCT.

Discussion

The presented case represents a compassionate use of gemtuzumab ozogamicin monotherapy in a barely remission-induced AML patient who was resistant at relapse to any measure. Zwaan et al.[13] reported 15 children (4 with de novo disease, 11 with relapsed/refractory disease) who were administered gemtuzumab ozogamicin between 4 to 9 mg/m^2 per course, with a clinical response of complete remission in three patients. In the series of Arceci et al.[12], of 29 children (19 relapsed and 10 refractory patients) who received gemtuzumab ozogamicin (6 to 9 mg/m^2 per dose for two doses (separated by 2 weeks), six (40%) developed venoocclusive disease (VOD) and eight (28%)

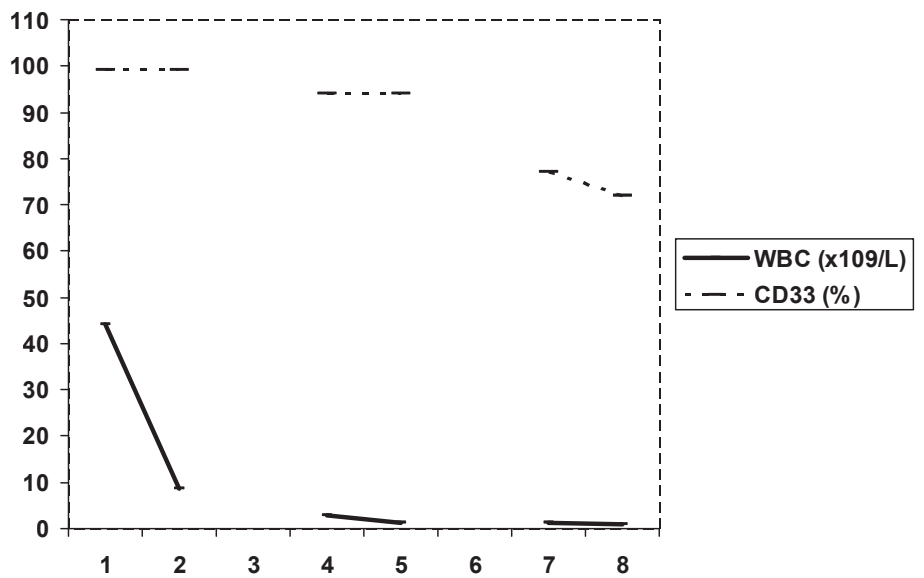

Fig. 1. White blood cell (WBC) and peripheral blood CD33 alterations after onset of gemtuzumab ozogamicin.

patients achieved overall remission. Remissions were comparable in patients with refractory (30%) and relapsed (26%) disease. Arceci et al.[12] also suggested that a clinical dose-escalation trial demonstrated that gemtuzumab ozogamicin can be used with acceptable safety and comparable efficacy at 6 mg/m^2 dose in pediatric patients with relapsed and refractory AML, as a single agent. In the study by Brethon et al.[11], none of the patients was found to achieve remission with a gemtuzumab dose of 1x9 mg/m^2, whereas two out of three of the remitted patients were given gemtuzumab as 3x3 mg/m^2 on days 1, 4 and 7. Our patient also received gemtuzumab ozogamicin at a dose of the latter schedule.

The most clinically important toxicities associated with this drug have been abnormalities in hepatic function[9,10]. Arceci et al.[12] showed an increased risk of sinusoidal obstructive syndrome (40%) in patients who underwent HSCT in less than 3.5 months after the last dose of gemtuzumab ozogamicin.

The post-remission persistent thrombocytopenia after intensive chemotherapy with or without HSCT has been described previously in AML patients[14], but this could not be ascribed to binding of megakaryocytes by gemtuzumab ozogamicin, since CD33 is found on less than 20% of megakaryocytes[15]. However, in our case, FAB subtype was AML-M7, and this may explain the post-remission thrombocytopenia in our patient.

In conclusion, gemtuzumab ozogamicin monotherapy may be effectively used at a total dose of 9 mg/m^2, divided into three doses given on days 1, 4 and 7 in relapsed and refractory children with AML, especially for the induction of remission before HSCT. Special precautions must be obtained during HSCT follow-up of patients who achieved remission with gemtuzumab ozogamicin, in order to prevent the development of sinusoidal obstruction syndrome.

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