Gemtuzumab ozogamicin plus cytarabine determines complete remission in acute myeloid leukemia refractory to a double conventional treatmeNnt: a case report

Monoclonal antibody chemotherapy is a promising therapy in patients with acute myeloid leukemia (AML). Gemtuzumab Ozogamicin (GO) consists of a anti-cancer antibiotic, calicheamicin, linked to a recombinant humanized murine anti-CD33 monoclonal antibody. A few phase II studies have showed the efficacy and safety of GO, used as single agent or in combination with other drugs, in patients with *de novo* or first relapse AML. We treated successfully an elderly AML patient, previously refractory to two lines of standard chemotherapy, with a combination GO-cytarabine obtaining a complete remission with incomplete platelet recovery (CRp). The novelty of this report consists, in our opinion, in the obtainement of a CRp in a primary refractory adult case. Outcome in refractory leukemia is extremely poor and the only possible curative option to date has been allogeneic stem cell transplantation. However, better results are possible if a complete remission is obtained before trasplantation. Our results, if confirmed on a larger series of patients, could open a new therapeutic role for GO, suggesting its use in refractory patients as a component of intensive regimens in order to induce/reinforce a complete remission before allogeneic stem cell or autologous transplantation in this poor prognostic group of AML patients.

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The treatment options remain limited in acute myeloid leukemia (AML) patients over 60 years, who respond poorly to standard therapy regimens and often experience dose-limiting toxicity from intensive chemotherapy. In addition, factors such as cytogenetics, intrinsic multidrug resistance and morphology are frequently prognostically adverse. Monoclonal antibody based chemotherapy is therefore attractive because it affects mainly the leukemic population, sparing normal cells. Gemtuzumab Ozogamicin (GO) is a novel antitumor agent consisting of a recombinant humanized murine anti-CD33 monoclonal antibody linked to the anti-cancer antibiotic calicheamicin.[1,2] Phase II trials have showed the efficacy and safety of GO, used as a single agent as part of combination therapy, in the treatment of patients with de-novo or relapsed AML.[1-10] GO is able to induce a remission rate of up to 30% in patients with AML in first relapse and a median overall survival of 5.6 months.[2] Few data are present in elderly patients primary refractory to standard induction and salvage therapy.[11] Here, we describe a 69-year-old lady with refractory M2-AML who has been treated successfully with GO in combination with cytarabine.

Case report

On May 2002 a 69-year-old lady was referred to our hospital presenting with thrombocytopenia and intravasal disseminated coagulopathy. A diagnosis of M2-AML was made according to French-American-British (FAB) criteria.[12] Bone marrow examination showed 40% of myeloid blasts and CD33 antigen was positive in 90% of the cells. The cytogenetic examination resulted normal. The patient was treated unsuccessfully with a conventional combination regimen (MICE: cytarabine at 100 mg/m^2 daily on days 1 through 5 and mitoxantrone 5 mg/m^2 on days 1 and 3). The second line therapy was based on a FLAT course (fludarabine 15 mg/m^2, cytarabine 2 g/m^2 and topotecan 1,25 mg/m^2 on days 1 through 4). The peripheral blood picture post therapy was: Hb 7.1 g/L, WBC 10×10^9/L with 50% blast cells, platelets 35×10^9/L. Transfusion support was required. The bone marrow examination showed 50% blast cells; more than 80% of them were CD33 positive. At the same time, fatigue and dispnea increased and diffuse skin hematomas were present.

GO was administered intravenously at 6 mg/m^2 on days 1 and at 4 mg/m^2 on day 8 along with continuous i.v. cytarabine at 100 mg/m^2 daily on days 1 through 7 plus G-CSF 5 micrograms/Kg daily starting on day +11 from the beginning of GO. On day 28 after therapy, the bone marrow examination showed less than 3% blasts. The blood picture was Hb 9.4 g/L, WBC 5.2×10^9/L, platelets 50×10^9/L. Afterwards, the patient received two monthly doses of GO (2 mg) as consolidation therapy. The patient remained well, with normal blood counts and a good quality of life for 4 months after the end of GO plus cytarabine therapy. She was transfusion independent during remission. After 4 months, the bone marrow biopsy showed a relapse, with more than 50% blasts; anaemia and thrombocytopenia were present. The diagnosis of relapse was confirmed by flow cytometry. The patient died from leukemia progression 2 months after the last dose of GO. Infusion-related adverse events included grade I-II transient fever and chills that occurred five hours after the end of the first GO infusion. A grade III oral mucositis occurred and analgesic therapy was administered for 7 days. GO therapy was complicated by a severe skin infection caused by Stenotrophomonas Maltophilia and fever. Antibiotic therapy was rapidly administered with success. No hepatic toxicity or VOD occurred. Considering hematological toxicity, the patient developed a grade III thrombocytopenia and neutropenia. Times to recovery to 0.5×10^9 PMN/L and to 20×10^9 PLT/L were 22 and 26 after the first dose, respectively.

Discussion

Outcome in refractory leukemia is known to be extremely poor. Hereby, we describe that GO was able to induce CRp and improve quality of life in an old AML patient refractory to different induction regimens and with dismal prognosis. In addition, the adverse events during treatment were transient and manageable. GO has been approved for use (in the US and Italy) for the treatment of CD33-positive AML patients aged over 60 years who are in first relapse and who are not considered candidates for other cytotoxic chemotherapy.[2] The published phase II studies[1-8] report above all on adults treated in first relapse. In the pediatric setting, Zwaan *et al.*[10] suggested a clinical efficacy and a moderate safety of GO, as single agent, in the treatment of 15 children with refractory (4 cases) and relapsed AML. Eight out of 15 children (2 refractory and 6 relapsed) obtained a response (3 CR and 5 CRp). In 6 of 8 responding patients autologous or allogeneic transplantation (5 cases) was performed and 2 patients are still alive. The novelty of this report is, in our opinion, the obtainment of a complete remission in a primary refractory adult case. Tsimberidou et al treated 11 adult AML refractory patients with GO plus chemotherapy obtainig a response (one CR and one CRp) in 2 cases. However, it is important to underline that *the two decribed patients*

were defined refractory after only one induction chemotherapy regimen. The only possible curative option to date for refractory AML has been allogeneic stem cell transplantation. However, the reported results on transplant in patients with active leukemia are unsatisfactory, due to the rapid relapse of the disease. On the contrary, better results are possible if a complete remission is obtained before trasplantation. In a previous study[13] on acute phase of chronic myeloid leukemia, we showed that the reduction of the leukemia burden with the obtainment of a second chronic phase, even of short duration, before transplantation is the key step for the improvement of the prognosis after bone marrow transplantation. Consequently, the observation that GO, alone or in combination with other agents, is able to produce CR or CRp in primary refractory AML patients is noteworthy although the remissions obtained are of brief duration and need consolidation. Our results, if confirmed on a larger series of patients, could open a new therapeutic role for GO, suggesting its use in refractory patients as a component of intensive regimens in order to induce/reinforce a complete remission before allogeneic stem cell or autologous transplantation in this poor prognostic group of AML patients.

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