

Use of gemtuzumab ozogamicin in the treatment of pediatric relapsed/refractory Acute Myeloid Leukemia

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Received: 03.06.2007 • Accepted: 19.11.2007

ABSTRACT

Gemtuzumab ozogamicin (GO, Mylotarg™) is an antibody-targeted chemotherapy agent that has been studied in acute myeloid leukemia (AML) at first relapse in adults. There is limited experience in pediatric patients. We report six patients with refractory/relapsed CD33+AML who were treated with GO on compassionate-use basis. One patient attained remission. One patient is still alive following hematopoietic stem cell transplantation (HSCT), and one patient died in remission. Two patients were refractory and three patients had a response with <5% blasts in the bone marrow. Fever and chills, hypotension and hypoxia were observed as side effects. Three patients developed veno-occlusive disease (VOD) of the liver. Two of these three patients had persistence of VOD at the time of their deaths. One patient treated postSCT had bone marrow response without VOD. GO should be used cautiously in chemotherapy-refractory AML pediatric patients due to the high incidence of VOD.

Key words: Gemtuzumab ozogamicin, Mylotarg, pediatric acute myeloid leukemia, sinusoidal obstruction syndrome, veno-occlusive disease

ÖZET

Pediyatrik relaps/refraktör akut myeloid lösemi tedavisinde gemtuzumab ozogamisinin kullanımı

Gemtuzumab ozogamisinin (GO, Mylotarg™) erişkin relaps akut myeloid lösemi (AML) vakalarında kemoterapötik olarak çalışılmış monoklonal bir antikordur. Çocuk hastalarda deneyim sınırlıdır. Biz, tedavisinde GO kullanılan altı pediyatrik relaps/refraktör CD33+AML hastasını sunmak istedik. GO tedavisi sonrası bir hastada remisyon sağlandı, üç hastada kemik iliğinde <5% blast ile yanıt elde edildi, iki hasta ise refrakterdi. İlaç yan etk-

isi olarak ateş ve titreme, hipotansiyon ve hipoksi gözlemlendi. Üç hastada karaciğerde veno-oklusif hastalık gelişti. Bunlardan ikisinde VOD ölüme katkıda bulundu. Bir hasta GO tedavisini hematopoetik kök hücre transplantasyonu sonrasında aldı ve VOD gelişmedi. Gemtuzumab ozogamicin pediatrik relaps/refrakter AML hastalarında VOD riski nedeniyle dikkatli kullanılmalıdır.

Anahtar kelimeler: Gemtuzumab ozogamicin, Mylotarg, pediatrik akut myeloid lösemi, sinüzoidal obstrüksiyon sendromu, veno-oklusif hastalık

INTRODUCTION

Acute myeloid leukemia (AML) represents a heterogeneous group of hematological malignancies that arise within bone marrow precursors of the myeloid, monocyte, erythroid, and megakaryocytic cell lineages, and it accounts for 15-25% of childhood leukemia. The rate of remission is between 75 and 85% at the time of initial diagnosis. The five-year event-free survival (EFS) is approximately 50% [1-3], although selected groups may fare better.

Patients with relapsed/refractory AML respond less well and long-term survival in such patients is less than 20% [4]. Drug resistance and drug-related mortality contribute to the high rate of failure. Many chemotherapeutic agents including high-dose cytarabine (ARA-C), idarubicin (IDA), mitoxantrone, etoposide (VP-16), fludarabine, or 2-chlorodeoxyadenosine (2-CDA) have been used in different combinations with some success [5], but because of the dismal prognosis and high toxicity with existing regimens and nonspecific chemotherapy agents, new approaches including targeted agents are under investigation.

The myeloid cell surface antigen CD33 is expressed on the blood cells in 90% of patients with AML but is not expressed on pluripotent hematopoietic stem cells, lymphoid cells or nonhematopoietic cells [6]. Gemtuzumab ozogamicin (GO; Mylotarg™) is an antibody-targeted chemotherapy agent consisting of the humanized murine CD33 antibody (clone P67.6) to which the calicheamicin is attached via a hydrolyzable bifunctional linker [7]. On binding to the CD33 antigen, the calicheamicin-antibody complex is internalized into the target cells, and calicheamicin is released intracellularly. Calicheamicin is a member of the enediyne family of molecules and binds to the minor groove of DNA, causing double-strand breaks and apoptosis [8,9].

Gemtuzumab ozogamicin has been used in adult relapsed/refractory AML, in regimens combined with or without hematopoietic stem cell transplant (HSCT). In adult patients with AML in first relapse, phase I studies demonstrated that 9 mg/m² dose of GO was well tolerated and a post-infusion syndrome of fever and chills was the most common toxic effect [10]. In subsequent phase II studies on patients with AML at first relapse, two doses of 9 mg/m² were used within two weeks with a 30% mean overall response and a 6% complete remission (CR) across three studies [11].

Hepatotoxicity, consistent with veno-occlusive disease (VOD), has been reported in several case reports as well as in phase II studies after the administration of GO, some in association with other chemotherapy agents [12,13].

There is limited experience with GO in the treatment of relapsed/refractory childhood AML. In phase I and phase II studies on pediatric patients, moderate efficacy was observed and no toxic effects were identified that differed from those experienced by adult AML patients. A study of 15 children with relapsed or refractory de novo AML, who were treated with GO, demonstrated similar results with the adult data [14]. In this paper, we report our experience with GO, as a single agent, in six children with relapsed/refractory AML.

MATERIALS AND METHODS

Six children with relapsed/refractory AML were treated with GO on a compassionate-use basis between 2000 and 2003. General treatment consent, after explaining the medication and the possible side effects, was obtained from all patients and/or legal guardians.

One patient with de novo AML refractory to standard chemotherapy, two patients in first relapse of AML, one patient with myelodysplastic

syndrome (MDS) transformed to AML, one patient with AML relapsed post-HSCT and one patient with acute bilineage leukemia were treated with GO, aiming for HSCT.

Patient characteristics are shown in Table 1.

All patients were diagnosed on the basis of morphological findings on the bone marrow aspiration. Immunophenotype and cytogenetic analyses were performed on all patients at the time of diagnosis and relapse, except in Pt 6 for whom analysis was done only at the time of relapse. In Pt 5, APML (AML-M3) diagnosis was made on the basis of the bone marrow aspiration alone without the evidence of t(15;17) translocation. All patients had CD33 expression prior to GO treatment.

Four patients received HSCT post-GO, one patient died before a planned HSCT and one patient received GO post-HSCT. All patients who underwent HSCT received prophylaxis for VOD with continuous heparin infusion at the dose of 100 u/kg/day.

Four of six patients received GO at a dose of 9 mg/m² as a two-hour infusion. One patient was treated with 7.5 mg/m² dose and one patient who was post-HSCT received GO at 6 mg/m² due to concern of increased risk of VOD. Four patients received only one dose and two patients received two infusions with a 14-day interval. All patients received premedication with acetaminophen and diphenhydramine 30 minutes prior to infusion.

Toxicity was graded according to the National Cancer Institute common toxicity criteria (NCI-CTC): 2003 revision.

A diagnosis of VOD was made in the presence of two of the following events: hyperbilirubinemia (>2 mg/dl), hepatomegaly or right upper quadrant

pain of liver origin, and sudden weight gain (>2% of baseline body weight) because of fluid accumulation. Severity of VOD was defined according to the criteria suggested by McDonald *et al.* [15]. To evaluate the reversal of the portal venous circulation, Doppler ultrasound was performed on all patients with clinical symptoms of VOD. None of the patients had a liver biopsy.

Complete remission (CR) was defined as absence of blasts in peripheral blood, percentage of the blasts in the bone marrow of 5% or less by morphology, and recovery of peripheral blood counts with absolute neutrophil count (ANC) of 1500 /μL or higher and platelet count of 100,000/μL or higher. A CRp was defined as CR plus incomplete regeneration of platelets but with platelet independence for at least one week. Patients were considered no remission (NR) if they did not meet all the criteria for CR or CRp [11].

RESULTS

Outcome

With GO, CR was achieved in one patient (Pt 5) while five patients had NR (Table 2).

Patient with CR: One patient (Pt 5) attained remission after one dose of GO at 9 mg/m². He received GO as a first-line treatment for reinduction. No other conventional chemotherapy was administered to induce second remission because of his poor cardiac function secondary to prior chemotherapy. He was diagnosed with VOD nine days post-GO infusion. Nonmyeloablative transplant was performed secondary to the increased risk of VOD of the liver post-HSCT. He died in remission 2 1/2 years post-HSCT with chronic graft versus host disease (GVHD).

Table 1. Patient Characteristics

Pt#	Age (yrs)	Sex	Diagnosis	Cytogenetics	CD33 expression (%)	
					Diagnosis	Relapse
1	2	M	AML-M7	t(11;19) Trisomy 8	99	99
2	14	M	ABL	t(4;11)	11	70
3	8	F	AML/MDS	t(3;15) Monosomy 7	97	–
4	9	M	AML-M4	t(6;9)	85	–
5	20	M	AML-M3	Normal	99	99
6	6	F	AML	N/A	–	99

GO: Gemtuzumab Ozogamicin, ARA-C: Cytosine Arabinoside, IDA: Idarubicin, 2CDC-2-chlorodeoxy adenosine, 6TG: 6- thioguanine, VP-16/Etoposide, ABL: Acute Biphentotypic Leukemia, AML: Acute Myeloid Leukemia, MDS: Myelodysplastic Syndrome

Patients with NR: Three patients (Pt 1, Pt 4 and Pt 6) had less than 5% blasts in the bone marrow post-GO. Two of three patients had hypocellular marrow without blasts and one had recovery of the bone marrow without blasts but remained platelet transfusion-dependent. Pt 1 with AML-M7 had VOD 11 days post-GO. He died 30 days post-GO with VOD. He remained pancytopenic until his death. His bone marrow was hypocellular with no blasts. Pt 4 with AML-M4 underwent HSCT before the total recovery of his peripheral blood counts. His HSCT course was uneventful. He remains in remission five years post-HSCT.

Pt 6 received GO post-HSCT for relapsed AML. There was no liver toxicity during HSCT. She received two doses of GO with a 14-day interval at a dose of 6 mg/m² and had normal bone marrow recovery. She had recovery of peripheral blood counts except platelets and remained transfusion-dependent until her death seven months post-GO in relapse.

There was persistence of disease in two patients post-GO (Pt 2 and Pt 3). Pt 2 had acute bilineage leukemia and was transplanted after one dose of GO at 7.5 mg/m². The bone marrow aspiration 11 days post-GO revealed 70% blasts. HSCT course was complicated with VOD and severe gastrointestinal hemorrhage. He died with VOD and persistent disease, 35 days post-HSCT. Pt 3 with AMLs/pMDS did not respond to two doses of GO

at 9 mg/m². Her transplant course from an HLA-mismatch unrelated donor was benign without VOD. She died due to persistence of disease three months post-HSCT.

Stem cell transplantation in relation to GO

Four patients received HSCT post-GO and Pt 6 had GO post-HSCT. The interval between the GO administration and HSCT was more than three weeks in all patients, ranging from 28-114 days. In one patient, peripheral blood count did not recover before the HSCT. Four patients received myeloablative transplant with total body irradiation and cyclophosphamide. One patient (Pt 5) had a nonmyeloablative transplant.

Toxicity and VOD

Fever and chills (grade 3 or 4) were observed in all patients. All patients had hematological toxicity (grade 3 or 4) post-GO, with two patients being pancytopenic prior to GO administration. One patient had an infusion-related drop in blood pressure requiring fluid replacement (grade 3). Two patients had hypoxia (grade 3) and one patient had pulmonary physical findings without any pulmonary infiltrates. Three patients were diagnosed with VOD on days 9, 11 and 45 post-GO. Doppler ultrasound revealed reversal of the portal venous circulation in one patient. None of the patients had an underlying liver pathology or abnormal liver function tests prior to GO treatment.

Table 2. Gemtuzumab Ozogamicin Treatment, Response and Outcome

Pt#	Diagnosis	Induction	Timing of GO treatment	GO Dose	Response to GO	VOD	Outcome	Cause of Death
1	AML-M7	POG 9822	Reinduction II	9mg/m ² x1	Hypocellular bone marrow	Yes	Exitus	VOD
2	ABL	POG 9906	Reinduction II	7.5mg/m ² x1	Persistent disease	Yes	Exitus and relapse	VOD
3	AML/MDS	GO	Induction	9mg/m ² x2	Persistent disease	No	Exitus	Relapse
4	AML-M4	POG 9822	Reinduction II	9mg/m ² x1	Hypocellular bone marrow	No	Alive in remission	
5	AML-M3	POG 9421	Reinduction I	9mg/m ² x1	Remission	Yes	Exitus	Chronic GVHD
6	AML	ARA-C IDA VP-16 Azacytadine	Reinduction II	6mg/m ² x2	Hypocellular bone marrow	No	Exitus	Persistent disease

GO: Gemtuzumab Ozogamicin

VOD: Venoocclusive disease

GVHD: Graft versus Host Disease

DISCUSSION

Six pediatric patients with relapsed/refractory AML were treated with GO on a compassionate-use basis. All patients had extremely poor prognosis.

There is still little information on GO in pediatric use. The safety and efficacy of GO in pediatric patients were reported by Arceci *et al.* [16] in 2005 and appeared to be similar to that described in adults. In two reports where GO was used on a compassionate-use basis [14,17], GO had no different side effects in pediatric patients as compared to adults. In our patient group, it was reasonably well tolerated and none of our patients had mucositis, cardiotoxicity or neurotoxicity from GO, which is an advantage over conventional chemotherapy. One patient had a hypotensive episode and hypoxia requiring fluid bolus, supplemental oxygen and intensive care unit admission for close monitoring. Pt 3 with hypoxia and Pt 4 with pulmonary exam findings recovered within 12 hours on antibiotic and supplemental oxygen. With the acute side effects of GO during infusion, close monitoring is crucial.

On the other hand, VOD was a significant side effect as a potentially fatal hepatotoxicity in our patient group. Two of our patients (Pt 1 and Pt 2) had VOD at the time of their deaths and it was the leading cause of death in at least one of them (Pt 1). It is not yet clear how GO causes VOD. In several studies, the relation of VOD following the regimens combining GO with HSCT has been reported [12,18] and in our group of patients, one of the three had VOD post-HSCT. However, successful use of defibrotide as prophylaxis for VOD in a small group of pediatric patients who underwent HSCT following treatment with GO has been reported [19].

The response to GO was found to be comparable to that found in two pediatric series reported by Zwaan *et al.* (14) and Brethon *et al.* [17]. Fifteen children treated with GO were reported by Zwaan *et al.* and eight of them had a response, including five CRp; none of the patients achieved remission. Of the 12 patients treated with GO in Brethon *et al.*'s study, only three responded and only one was alive with partial remission. In this report, response was defined as a bone marrow blast percentage of less than 5, in the absence of leukemia in the peripheral blood or elsewhere. In

adult phase I and phase II studies as reported by Sievers *et al.* [10,11], overall response was defined as the total percentage of patients in CR and CRp. All patients who did not meet these criteria were reported as NR. In our group of patients, three fit the criteria of "response" by Zwaan *et al.*, including one survivor following HSCT, but the outcome of patients with "response" as defined by Zwaan *et al.* remains unknown and needs to be further explored.

In conclusion, although GO stands as a reasonable and somewhat effective chemotherapy alternative, especially for patients with existing toxicities from prior cytotoxic regimens, the potentially fatal liver toxicity is a matter of concern. Our observation on these limited number of pediatric patients reemphasizes and supports the literature regarding the effectiveness of GO in refractory AML. This high incidence of VOD seems typical. Current and future studies may help to increase the effectiveness by using GO in combination with other chemotherapeutic agents.

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