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Treatment of a Child with Refractory Acute Myeloid Leukemia with Humanized Anti-CD33 Monoclonal Antibody: A Case Report and Review of Drug Development

Alavi S[1]*, Arzanian MT[1]

1. Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University Of Medical Sciences, Tehran, Iran.

***Corresponding Author:** Alavi S, Email: s.alavi@sbmu.ac.ir*

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Abstract

Background: The induction chemotherapy regimen for acute myeloid leukemia has evolved as once induction is completed; patients progress through the consolidation phase and achieve remission in 76% of cases. For patients with relapsed or refractory disease, alternative chemotherapy agents are available. Monoclonal antibody therapy with biological agents, such as the immunotoxin gemtuzumab ozogamicin has been recently used to induce remission in relapsed patients.

Report of the case: Here, we report the first Iranian child, an 8-year-old boy, with refractory acute myeloid leukemia who was treated with gemtuzumab ozogamicin. Unfortunately, remission was not achieved and the patient died of neutropenia and septic shock.

Conclusion: Gemtuzumab ozogamicin therapy in our case was not successful in achieving remission. It could be due to longstanding chemotherapy and its detrimental effects on bone marrow of the patient. Further controlled studies are necessary to learn more about efficacy and safety of this new treatment.

Keywords: Childhood acute myeloid leukemia, refractory, treatment, gemtuzumab ozogamicin

Introduction

Acute myeloid leukemia (AML) is more frequent in adults. In children, AML has an incidence rate of approximately 7.6 per million children per year [1]. In adolescents, AML comprises 30– 40% of leukemias, whereas in younger children this is only 10-20% under 15 years of age [1]. AML is more frequent in the first 2 years of life [1]. Relapsed AML still has a very poor outcome with survival rates of only 20–30%, the main prognostic factor being the interval between initial diagnosis and relapse [2].The main prognostic factors for newly diagnosed AML are cytogenetics and early response to therapy, usually measured as bone marrow blasts at day 15 or after the first course of chemotherapy [3,4].

A variety of study groups through different trials have proposed and tried a combination of protocols to treat pediatric AML patients. Recent results of these trials are addressed in Table-1.

As childhood AML is a heterogeneous disease, the risk factors may differ among the various pediatric AML subgroups. Hence, improvements in outcome may be achieved with the introduction of tailored and/or targeted therapy. Targeted therapy indicates the use of drugs directed against specific genetic or other abnormalities related to the leukemic cell clone, and is supposed to reduce toxicity to healthy tissues. Gemtuzumab ozogamicin (GO) (Mylotarg®; Wyeth Pharmaceuticals, Philadelphia, PA) is a new antibody-targeted chemotherapy agent that targets the CD33 surface antigen of leukemic cells by means of a humanized anti-CD33 monoclonal antibody (hP67.6) conjugated to a derivative of the antitumor antibiotic calicheamicin [5].

Herein, we present the treatment experience of a child with refractory AML, who received GO. To our knowledge he is the first patient reported from Iran.

Report of the case

An 8-year-old boy was referred to our oncology

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Table 1: Results of some recent clinical trials for treating pediatric AML.

Study group	Protocol	Number	Time period	Follow-up time	Event Free Survival %	Overal Survival %	Reference
NOPHO	NOPHO-AML 2004	151	2004-2009	3 years	57	69	Abrahamsson et al. (28)
St Jude Research Hospital	St Jude AML02	216	2002-2008	3 years	63	71	Rubnitz et al. (6)
COG	COG AAML03P1	350	2003-2005	3 years	53	66	Cooper et al. (29)
BFM	AML-BFM 98	473	1998-2003	5 years	49	62	Creutzig et al. (30)
MRC	MRC AML	529	1995-2002	10 years	54	64	Gibson et al. (31)
EORTC	EORTC 58921	177	1992-2002	7 years	49	62	Entz-Werle et al.(32)
NOPHO	AML 93	219	1993-2000	7 years	49	64	Lie et al.(33)
BFM	ALL- BFM 93	471	1993-1998	5 years	51	60	Creutzig et al. (34)
Tokyo CCSG	AML13/14	216	1991-1998	5 years	56	62	Tomizawa et al(35)
LAME	LAME 89/91	268	1988-1996	6 years	48	60	Perel. et al. (36)

NOPHO: Nordic Society of Pediatric Hematology and Oncology; COG: Children's Oncology Group; BFM: Berlin-Frankfurt-Münster; MRC: Medical Research Council; EORTC: European Organization of Research and Treatment of Cancer; NOPHO: Nordic Society of Pediatric Hematology and Oncology; Tokyo CCSG: Tokyo Children's Cancer Study Group; LAME: French Leucemie Aique Myeloide Enfant.

clinic with a history of pallor, fever and malaise for about 2 weeks. On physical examination; pallor in conjunctiva mucosa, very scattered petechiae over the trunk, and a spleen which was palpated 3 cm below costal margin, were significant clinical findings. The complete blood count (CBC) showed white cell count of $8.5\times10^3/\mu L$, with 15% neutrophils, 25% lymphocytes, 2% band, 6% metamyelocytes, 5% myelocytes, 5% promyelocytes, 42% immature cells, 4% NRBC, a hemoglobin of 10 g/dL and platelet count of $145 \times 10^3/\mu L$. He was admitted on oncology department. Bone marrow aspiration was performed for the patient, which revealed increased M/E ratio, with moderate to severely decreased erythroid series and increased myeloid precursors with about 15-20% myeloblasts. Megakaryocytes were also decreased. Flow cytometry showed an increased percentage of CD13 and CD 33, and HLA-DR positive blasts. Due to borderline levels of the blasts in bone marrow smear of the patient a definite diagnosis of acute myeloid leukemia (AML) could not be made at that time. He was determined to undergo a repeated bone marrow aspiration and bone marrow biopsy (BMB) the following week. On the second bone marrow aspiration there were an increasing number of myeloblasts to more than 40%, and severe decrease in erythroid series. There were no Auer rods observed in the blasts. A diagnosis of AML-M2 was made. Flowcytometric study was in concordance with AML. BMB confirmed an acute leukemia which its precise cytology could not be specified by the pathologist. Cytogenetic study was not conclusive. He was scheduled to receive an induction course of DAT including intravenous (IV) cytarabine (Ara-C) 200 mg/m2 for 7 days, daunorubicin 45 mg/m2 for 3 days and 6-thioguanine 100 mg/m2 by mouth for 7 days. He developed an expected prolonged course of pancytopenia following induction course of DAT. After gradually recovering from pancytopenia with support of G-CSF, a bone marrow aspiration for evaluation of the response to the first course of induction was performed which demonstrated moderate to severe decreased cellularity with certain amounts of myeloblasts. According to the percentage of the blasts (5- 20%), he was prepared to receive the second course of DAT induction. Because of unsatisfactory recovery in peripheral blood after about 8 weeks, he underwent another bone marrow aspiration. It again demonstrated myeloblasts with no change in their percentage, however, the cellularity of the bone marrow was

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severely decreased and there was not any evidence of recovery of other hematopoietic precursors.

The condition of the patient was interpreted as "induction failure" as he could not achieve remission in response to two courses of DAT. He was determined to receive mitoxantrone and etoposide as refractory AML. The regimen consisted of mitoxantrone, 10 mg/m2/d (IV) for 3 days, and etoposide, 100 mg/m2/d as short infusion, on days 1 to 5. The patient suffered a long period of neutropenia, and sepsis following this regimen due to cumulative dose of chemotherapeutics and their toxicity. Since he was still refractory and according to the persistence of blasts in the bone marrow (> 5%) after a thorough search in the literature we suggested treatment with GO for the patient. He received 2 courses of GO, 4mg/m2, each course without concomitant cytotoxic chemotherapy. Unfortunately, remission was not achieved and the patient died of neutropenia and septic shock.

Discussion

With improvements in risk-directed therapy and supportive care, event-free survival (EFS) for children with acute lymphoblastic leukaemia (ALL) now approaches 90% [6].By contrast, EFS for children with AML ranges from 49% to 62%. Improving clinical results in AML requires not only the development of new drugs and better supportive care, but also a more precise application of risk-directed therapy [6]. Patients with relapsed or refractory AML have less chance of obtaining remission than patients with newly diagnosed AML [7]. The goals of re-induction chemotherapy vary from achieving a long-term complete remission (CR) to providing a bridge to hematopoietic stem cell transplantation (HSCT), or to temporary prolongation of life and palliation of symptoms. Most regimens currently in use cause substantial toxicity [8]. Rates of second CR (CR2) range from less than 10% to greater than 80% depending on the age, duration of CR1, and cytogenetic characteristics of the patients treated [8,9]. Without HSCT, the median duration of CR2 is generally not more than 6 to 8 months, with a long-term disease-free survival rate of approximately 5% to10% [10].

It has been observed that more than 80% of AML patients have myeloid blast cells that express the CD33 surface antigen [11,12].This antigen also is present on the leukemic stem cells from at least some patients [13]. It is present on normal maturing hematopoietic progenitor cells and absent from normal hematopoietic stem cells [13]. The CD33 antigen is not expressed by non hematopoietic cells or tissues [14]. On the basis of these properties, antibodies to the CD33 antigen have been explored as possible specific agents for AML treatment, either in their unmodified form or as carriers for antileukemic agents [15]. When iodinated anti-CD33 monoclonal antibody is used, it rapidly accumulates in the marrow of AML patients and becomes internalized into leukemia cells. This observation suggests that CD33 might be an appropriate target for an antibody chemotherapy-conjugate [14,15,16]. Calicheamicin, a highly potent antitumor antibiotic that cleaves double stranded DNA at specific sequences, has been conjugated to a humanized anti-CD33 monoclonal antibody to produce Mylotarg (GO; CMA-676; Wyeth Laboratories, Philadelphia, PA)[17,18]. Mylotarg was evaluated in a dose-escalation trial with relapsed or refractory CD33-positive AML patients. Leukemic cells were eliminated from the peripheral blood and bone marrow of eight of the 40 patients, and Mylotarg was reasonably well tolerated [19]. The drug has recently been approved for use in the United States for elderly patients with relapsed AML [20]. Phase 1 and 2 studies of GO therapy in adults with relapsed AML have been performed and have shown response in approximately 30% of patients [20,21,22]. Sievers et al. have reported the preliminary data of a phase 1 study with GO in 18 children with relapsed or refractory AML, concluding that the adverse events are similar to those in adults [23,24]. The clinical experience of GO in children with relapsed/refractory AML treated on compassionate-use basis has been reported by Zwaan et al.; 15 children with relapsed/refractory AML were treated with GO monotherapy up to 3 doses on compassionnate use basis [25].Two patients had undergone HSCT before they were treated with GO. It was given at dosages of 4 to 9 mg/m2/course. Seven patients only received one infusion of GO, 5 patients received 2 infusions, and 3 patients received 3 infusions. After GO treatment a response was observed in 8 of 15 patients. Response to GO was defined according to the following criteria: a bone marrow blast percentage of 5% or less, in the absence of leukemia in the peripheral blood or elsewhere. To diagnose a complete remission (CR), sufficient

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recovery of peripheral blood values (> 1000 ×106/L granulocytes and >100 ×109/L platelets) was required. In 5 of these 8 patients a CR, although without full platelet recovery (CRp), was observed, but no CRs were diagnosed, that is, absence of leukemia with full hematologic regeneration [27]. In a preliminary report of the phase 1 study with GO in CD33+ relapsed/refractory AML among 18 children by Sievers et al., 4 patients had less than 5% bone marrow blasts after the second dose of GO [25,26]. Considering GO side effects, hematologic toxicity was difficult to assess due to subsequent HSCT or underlying leukemia. With regard to non hematologic toxicity, GO toxicity was relatively mild with the exception of liver toxicity. No mucositis or severe infection was documented. In this series only one patient developed GO-related venoocclusive disease (VOD) after a prior HSCT, which is a well-known risk factor to develop VOD after subsequent GO treatment [26].Two others developed transient hepatic toxicity, which resolved spontaneously. In one child the hepatic toxicity could be attributed to progressive leukemia and infiltration of the liver. In the phase 1 study by Sievers et al, 4 of 18 patients experienced grade 3 or 4 side effects, including respiratory failure, hyperbilirubinemia, prolonged pancytopenia, gastrointestinal bleeding, congestive heart failure, and transient transaminase elevation [24]. It is noteworthy that one of the patients in Zwaan et al. study had been treated repeatedly with GO and responded each time without showing any signs of additional toxicity [25]. Although our experience is limited to this patient, it suggests that palliative treatment of some patients with AML with repeated dosages of GO at relatively long time intervals is feasible, and needs to be explored further.

Subsequent to the approval of this drug, a large number of spontaneous reports of severe adverse events in patients receiving GO prompted an early review of post marketing safety data. Nine out of 142 cases developed severe hypersensitivity reactions after treatment with GO; four of them were fatal. Eight patients experienced pulmonary events. Most reactions occurred during or within 2 hour after infusion including fever, rigors, chills, diaphoresis, and anaphylactoid type reaction [20]. Calicheamicin as well as GO are both known to cause hepatotoxicity/VOD in preclinical models [20].

A report of the efficacy and safety of GO (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence has been published in which 277 patients (median age, 61 yrs) were treated with GO, and 71 patients (26%) achieved remission. The median recurrence-free survival was 6.4 months for patients who achieved CR and 4.5 months for patients who achieved CRp [27].

Recently most investigations are being performed on combining cytotoxic chemotherapeutics with GO, in order to achieve higher rates of remission. What is obvious from all these studies is that treatment with GO, alone or in combination would not result in a long term and durable remission but might be able to keep the patient in remission, until HSCT would be feasible. Meanwhile it is needed to clearly establish the clinical efficacy and safety of GO in pediatric AML with more stringent eligibility and dose and scheduling criteria.

Conclusion

GO therapy in our case was not successful in achieving remission. It could be due to longstanding chemotherapy and its detrimental effects on bone marrow of the patient. Further controlled studies are necessary to learn more about efficacy and safety of this new treatment.

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