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ORIGINAL ARTICLE

**Jorge Cortes · Apostolia M. Tsimberidou
Ricardo Alvarez · Deborah Thomas · Miloslav Beran
Hagop Kantarjian · Elihu Estey · Francis J. Giles**

Mylotarg combined with topotecan and cytarabine in patients with refractory acute myelogenous leukemia

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Abstract *Purpose*: Mylotarg, a humanized anti-CD33 antibody linked to an antitumor antibiotic, is approved for the treatment of patients with relapsed acute myeloid leukemia (AML). Topotecan and cytarabine (ara-C) is an effective anti-AML regimen. A pilot study of Mylotarg combined with topotecan and ara-C (MTA) was conducted in patients with refractory AML. *Methods*: MTA consisted of Mylotarg 9 mg/m^2 intravenously (i.v.) over 2 h on day 1, ara-C 1 g/m^2 over 2 h i.v. on days 1 through 5, and topotecan 1.25 mg/m^2 by continuous infusion i.v. on days 1 through 5. *Results*: A group of 17 patients (9 primary resistant, 8 relapsed) with AML or advanced myelodysplastic syndrome (MDS) received 20 courses of MTA. The median age of the patients was 55 years (20–70 years). Two patients (12%) achieved complete remission. The median overall survival was 8.2 weeks. Five patients (29%) developed grade 3/4 hepatic transaminitis, including one patient (6%) who died with hepatic venoocclusive disease. *Conclusions*: MTA was moderately effective and associated with significant toxicity in patients with refractory AML.

Keywords Mylotarg · Topotecan · Cytarabine · Acute myeloid leukemia · Refractory

Introduction

Mylotarg (gemtuzumab ozogamicin; CMA-676; Wyeth Laboratories, Philadelphia, Pa.) has been recently approved by the US Food and Drug Administration (FDA) as single-agent therapy for CD33-positive acute myeloid leukemia (AML) in first relapse in patients ≥60 years of age, who are not considered candidates for standard cytotoxic therapy [4]. Its approval was conditional on the performance of randomized studies comparing conventional cytotoxic anti-AML regimens with or without Mylotarg [4]. As a single agent, Mylotarg is more likely than cytarabine (ara-C) to induce a second complete remission (CR) in patients in first relapse if the initial CR duration was < 6 months, whereas ara-C is more likely to do so if the patient's initial CR was > 6 months [14]. Most Mylotarg-based combinations studied in de novo AML patients have involved Mylotarg, ara-C, and a third drug, including daunorubicin, idarubicin or fludarabine [1, 5,10, 12]. Topotecan is a semisynthetic derivative of camptothecin, with significant single-agent activity in patients with refractory AML [11, 16, 17]. The combination of topotecan and cytarabine is active in patients with either de novo or relapsed AML [3, 6]. We thus conducted a pilot study of Mylotarg combined with topotecan and ara-C (MTA) in patients with refractory AML.

J. Cortes · A.M. Tsimberidou · R. Alvarez · D. Thomas
M. Beran · H. Kantarjian · E. Estey · F.J. Giles (✉)
Department of Leukemia, The University of Texas,
M.D. Anderson Cancer Center,
1400 Holcombe Boulevard,
Houston, Texas 77030, USA
E-mail: frankgiles@aol.com
Tel.: +1-713-7928217
Fax: +1-713-7944297

Patients and methods

Eligibility and evaluation

Eligibility criteria included CD33-positive primary resistant or relapsed AML including refractory anemia with excess blasts (RAEB) or RAEB in transformation (RAEBT) (except acute promyelocytic leukemia), serum bilirubin < 1.6 mg/ml, and serum creatinine ≤ 1.5 mg/ml (if an abnormally elevated creatinine was attributable to leukemia, the patient was considered to be protocol-eligible). The protocol was approved by the institutional review board, and all patients gave signed informed consent indicating that they were aware of the investigational nature of this study. Pretreatment evaluation included a history and physical examination, complete blood count (CBC), differential, platelet count, serum chemistries, bone marrow aspirate, chemical and enzymatic stains, and cytogenetic and molecular studies as indicated. Follow-up studies included CBC, differential, and platelet count three times weekly until CR, weekly thereafter, serum chemistries at least once weekly, and bone marrow aspiration on days 14 and 21 from start of therapy and as clinically indicated. Patients with t(8;21) or

inv(16) were considered "better prognosis", normal karyotype, +8 or <3 numerical abnormalities (not including those involving chromosomes 5 or 7) "intermediate prognosis", and other anomalies as "worse prognosis" cytogenetics.

Therapy

Treatment consisted of Mylotarg 9 mg/m^2 intravenously (i.v.) over 2 h on day 1, ara-C 1 g/m^2 over 2 h i.v. on days 1 through 5, and topotecan 1.25 mg/m^2 by continuous infusion i.v. on days 1 through 5. Patients received saline eye drops, two to each eye three times daily on days 2 through 6, and diphenhydramine 50 mg orally 1 h prior to, and 3 and 7 h after administration of Mylotarg.

A second course of therapy was administered on day 42 if the patient had a partial remission (PR) or better, and recovery from extramedullary toxicity to grade 2 or less had occurred. The daily dose of topotecan was reduced by 25% if the serum creatinine had increased up to 2.0 mg/ml and by 50% if creatinine had increased to >2.0 mg/ml in a prior course of study therapy. Second course doses were reduced by 25% if extramedullary toxicity of grade 2 or more occurred. Empiric antibiotic prophylaxis was given to all patients while on study as follows: fluconazole 200 mg orally daily, valacyclovir 500 mg orally daily, and trimethoprim/sulfomethoxazole double-strength one tablet orally daily.

Endpoints and statistical methods

CR was defined as normalization of the blood and bone marrow with 5% or less blasts, normocellular or hypercellular bone marrow, a granulocyte count above 10^9/l and a platelet count above 100×10^9/l. Patients who met these criteria but still had 6% to 25% marrow blasts were considered to have a PR. CR with incomplete platelet recovery (CRp) was defined as for CR, but with platelet counts remaining below 100×10^9/l. Other responses were considered as failures and categorized as: (1) early death if death occurred within 3 weeks from the start of therapy; (2) aplastic death if death occurred during therapy without evidence of hematological recovery and with less than 20% marrow leukemia infiltrate (MLI, percentage of blasts×marrow cellularity); (3) secondary resistance if MLI was reduced below 20% but increased later; and (4) primary resistance if MLI did not decrease below 20%. Toxicity was graded on a scale of 0 to 5 using the National Cancer Institute version 2.0 criteria. All patients who received any cytotoxic therapy on study were considered evaluable for toxicity.

Venoocclusive disease (VOD) was diagnosed, using the Seattle and Baltimore standard criteria, as the occurrence of hyperbilirubinemia (bilirubin >2 mg/dl) with one or more of the following: painful hepatomegaly, fluid retention, e.g. ascites, or sudden weight gain (>5% of pretreatment weight) in the absence of other causative factors. Event-free survival (EFS) was measured from the time of CR or CRp until relapse, death or last contact. Overall survival was measured from the date of administration of the first dose of Mylotarg until the date of death or last follow-up.

Results

Patient characteristics

Clinical and laboratory characteristics of the 17 patients treated on study are summarized in Table 1. Their median age was 55 years (range 23–75 years). Eight patients were ≥60 years of age. The median duration of the first CR for relapsed patients was 30 weeks (range 6–119 weeks). Nine patients had primary resistant AML and had never achieved CR. All eight patients who had achieved a prior first CR had received post-remission ara-C-containing consolidation (high-dose ara-C) and maintenance therapy. No patient had received prior stem cell transplantation or received prior topotecan/ara-C therapy.

Table 1 Clinical and laboratory characteristics of patients ($n=17$) with refractory/relapsed AML

	Median (range)	No. (%)
Age	55 (20–70)	
WBC ($\times10^9$/l)	22.7 (1–129)	
Hemoglobin (g/dl)	8.8 (7.4–12.1)	
Platelets ($\times10^9$/L)	25 (3–159)	
Peripheral blood blasts (%)	28 (0–99)	
Bone marrow blasts (%)	46 (17–87)	
CD33-positive blasts (%)	97 (19–100)	
LDH (IU/l)[a]	1252 (190–7233)	
Creatinine (mg/dl)	0.8 (0.4–1.7)	
Bilirubin (mg/dl)	0.4 (0.2–0.8)	
SGPT (IU/l)	24 (12–161)	
Male/female		12/5 (71/29)
Performance status		
0/1		1/9 (6/53)
2		7 (41)
Cytogenetic groups		
"Intermediate" risk		6 (35)
"Worse" risk		11 (65)
Primary refractory		9 (53)
Relapsed		
CR duration <1 year		6 (35)
CR duration ≥1 year		2 (12)
First CR duration (weeks)	30 (6–119)	
Prior salvage regimens		
None		8 (47)
One		5 (29)
Two or three		4 (24)

[a]LDH normal range 316–618 IU/l

Responses

Two patients (12%) achieved CR. One responder was a 20-year-old female with normal karyotype first-relapse AML and a first CR duration of 25 weeks. She had received both induction and post-remission therapy with high-dose ara-C and liposomal daunorubicin. The second patient who responded was a 65-year-old male with –5 karyotype primary resistant AML who received the study regimen as first salvage therapy. Both responding patients received subsequent allogeneic stem cell transplantation. One patient died in ongoing CR from graft versus host disease (GVHD) 32 weeks after peripheral blood stem cell transplantation, and the second was alive at the time of this report in CR at 50 plus weeks after bone marrow transplantation. Overall median survival was 8 weeks (range 1–58); the 12-month survival rate was 6%.

Toxicity

A total of 20 courses of MTA were administered. The median number of courses was one (range one to

three). All courses were associated with grade 4 myelosuppression – patients were not given routine recombinant growth factor support. The median time to platelet recovery to $\geq 100 \times 10^9$/l was 26 days and the median time to absolute neutrophil count (ANC) recovery $\geq 10^9$/l was 21 days. Grade 3/4 nausea/vomiting and/or mucositis both occurred in three patients (18%). Three patients (18%) developed grade 3 hyperbilirubinemia. Five patients (30%) developed grade 3/4 hepatic transaminitis after a median of 13 days (range 7–19 days) from the start of therapy, including one patient who developed hepatic VOD. None of the patients had overt hepatic failure or VOD with prior therapy. The patient who developed VOD had abrupt onset of very significant weight gain, associated with ascites, abdominal distension, and right upper quadrant pain. The patient did not have possible alternate explanations for this clinical picture including acute hepatitis, progressive systemic or abdominal sepsis, pancreatitis, or bowel obstruction at the time of diagnosis of VOD.

Three patients (18%) had documented infections, controlled by antimicrobial therapy, at the start of therapy. All patients developed febrile episodes after initiation of study therapy. In ten patients (59%) febrile episodes were neutropenic fever without isolation of any microorganism or documented site of infection. Seven patients (41%) had pneumonia; three were of fungal origin (two *Aspergillus fumigatus*, one *Candida albicans*). Five patients (29%) had early death, four of whom had grade 3/4 hepatic transaminitis, including one with VOD. One patient died in CR from grade 4 gastrointestinal and skin GVHD after allogeneic peripheral blood stem cell transplant. The remaining ten patients died from progressive disease.

Discussion

Mylotarg is a novel chemotherapeutic agent consisting of a humanized anti-CD33 antibody (hP67.6) linked to *N*-acetyl-gamma calicheamicin, a potent enediyne antitumor antibiotic [7]. The anti-CD33 antibody targets the calicheamicin derivative to CD33-expressing cells by binding the CD33 antigen. Following internalization, acid hydrolysis releases the calicheamicin derivative from the antibody, and a reactive intermediate of the calicheamicin derivative is formed through reduction by glutathione. This reactive intermediate causes double-strand breaks in DNA following binding to the minor groove of the DNA duplex. By targeting CD33-expressing hematopoietic cells, Mylotarg offers a potentially relatively specific antileukemia approach. As a single agent, Mylotarg offers an approximate 10% CR rate in unselected older patients with relapsed AML. In previously untreated elderly patients with AML, Mylotarg is inferior to idarubicin and ara-C [8]. Mylotarg's approval by the FDA was conditional upon the conduct of studies involving its combination with standard anti-AML regimens [4]. Thus a major focus of current developmental therapeutics in AML involves the investigation of Mylotarg-based regimens. The logical agents to add to a Mylotarg/ara-C combination include daunorubicin, idarubicin, and fludarabine – these regimens are being investigated [1, 5, 10, 12]. Another potential agent of interest is topotecan as significant activity in patients with both de novo and refractory myeloid malignancies has been reported either with the single-agent or as a component in combination regimens [2, 3, 16, 17, 18].

The combination of a novel monoclonally targeted toxin, topoisomerase I inhibitor, and a nucleoside analog is conceptually attractive. Thus in this study the MTA regimen was investigated in patients with refractory AML. However, among 17 patients, the CR rate was a disappointing 12% and the regimen was associated with severe hepatotoxicity, including fatal VOD in one patient (6%). Mylotarg as a single-agent causes grade 3/4 hyperbilirubinemia and/or hepatic transaminitis in approximately 20% of patients with relapsed AML [4]. The use of Mylotarg-containing regimens has been associated with the development of VOD [1, 10, 12, 13]. A selective local accumulation of Mylotarg and/or calicheamicin is common to the proposed mechanisms involved in the genesis of Mylotarg-associated VOD. These include selective targeting of CD33-expressing cells in the sinusoids of the liver, activation of stellate cells, damage to sinusoidal endothelial cells, sinusoidal vasoconstriction, or ischemic hepatocyte necrosis [15].

The patient who developed overt VOD died. It is sometimes difficult to precisely assess the relative contribution of VOD to death in patients who have received Mylotarg therapy, as resistant leukemia and its consequences may be contributory factors in some patients. The incidence of VOD in this study (6%) is directly comparable to that reported with other Mylotarg-based regimens [1, 5, 10, 19]. Topotecan has been demonstrated to be directly toxic to rat hepatocytes in a time- and dose-related manner [9]. Thus, although VOD has not been reported with either topotecan alone or topotecan and ara-C in patients with AML, it is possible that Mylotarg and topotecan may be a particularly hepatotoxic combination. It might be argued that even lower doses of Mylotarg be investigated in combination with topotecan/ara-C in the format of a formal phase I study, but in view of the study MTA regimen's modest activity, we would not advocate this approach. No other extramedullary toxicities appear to be significantly increased by the addition of Mylotarg to the topotecan and ara-C regimen. In conclusion, Mylotarg combined with topotecan and ara-C as administered in this study had limited activity and significant toxicity in patients with refractory AML. As recent data indicate that topotecan and ara-C is inferior to idarubicin and ara-C as an induction regimen for patients with AML [6]. we do not intend to further investigate the MTA regimen.

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