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SHORT COMMUNICATION

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Pilot study of Mylotarg, idarubicin and cytarabine combination regimen in patients with primary resistant or relapsed acute myeloid leukemia

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Abstract *Purpose*: Mylotarg has moderate activity as a single agent in patients with CD33-positive refractory or relapsed acute myelogenous leukemia (AML). A combination of an anthracycline and cytarabine (ara-C) is the core of most AML induction regimens. We conducted a pilot study of Mylotarg combined with idarubicin and ara-C in patients with refractory or relapsed AML. *Methods*: Mylotarg was administered at 6 mg/m^2 intravenously on days 1 and 15, idarubicin 12 mg/m^2 daily on days 2 through 4, and ara-C at 1.5 g/m^2 daily on days 2 through 5 (MIA). *Results*: Of 14 patients were treated, 4 (29%) had primary resistant AML, and 10 (71%) relapsed AML. The median age of the patients was 61 years (range 34–74 years). MIA induced complete remission (CR) in three patients (21%) and CR with incomplete platelet recovery (CRp) in three patients (21%). The median survival was 8 weeks (range 2–64 weeks), and the median failure-free survival of CR patients was 27 weeks (range 11–64 weeks). All patients developed grade 3/4 myelosuppression – severe sepsis occurred in ten patients (71%). Other grade 3/4 nonhematologic toxicities included hepatic transaminitis, oral mucositis, and diarrhea. Two patients (14%) developed hepatic venoocclusive disease (VOD). *Conclusions*: The addition of Mylotarg to idarubicin and ara-C is feasible. MIA has significant activity in patients with refractory AML. Hepatotoxicity and VOD are significant toxicities of Mylotarg-based combinations.

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Introduction

Mylotarg (gemtuzumab ozogamicin, CMA-676; Wyeth Laboratories, Philadelphia, Pa.) is a humanized anti-CD33 monoclonal antibody linked to a highly potent cytotoxic antibiotic, calicheamicin, which induces cell death by cleaving double-stranded DNA at specific sequences [13]. CD33, a 67-kDa glycosylated transmembrane protein, is expressed on the surface of most mature and immature human myeloid cells and on the blasts from the majority of patients with acute myeloid leukemia (AML). Following binding to CD33, Mylotarg enters the target cells by endocytosis, and calicheamicin release and metabolism follow leading to DNA damage. In phase I/II studies, Mylotarg was associated with a complete remission (CR) rate of 16% in selected patients with first relapse of AML [13]. The combination of Mylotarg with cytotoxic anti-AML agents is being investigated [1, 4, 7, 9]. A combination of an anthracycline and cytarabine (ara-C) is widely used as induction therapy in AML. In a recent comparison of three induction regimens given to 1279 patients with AML at the MD Anderson Cancer Center (MDACC), while an idarubicin and ara-C (IA) combination was equivalent or superior to other induction regimens, a significant number of patients either failed to achieve CR or did so transiently [6].

As a prelude to randomized studies, we conducted a pilot study of Mylotarg combined with IA in patients with refractory AML. A particular concern was whether hepatotoxicity would allow reasonable doses of all three agents to be administered. In phase I/II studies, Mylotarg was associated with an incidence of approximately 20% grade 3/4 hyperbilirubinemia and/or hepatic transaminitis [13]. Hepatic venoocclusive disease (VOD) is also associated with Mylotarg therapy, in patients

both with and without a prior stem cell transplant (SCT) [1, 2, 8, 9, 10, 12, 14].

Materials and methods

Study group

Eligibility criteria included primary resistant or relapsed AML (except acute promyelocytic leukemia) and baseline serum bilirubin and creatinine ≤ 1.5 mg/ml. Patients were not eligible if they had prior SCT. Patients with t(8;21) or inv(16) were considered as "better prognosis", patients with normal karyotype, +8 or <3 numerical abnormalities (not including those involving chromosomes 5 or 7) as "intermediate prognosis", and patients with other anomalies as "worse prognosis". The protocol was approved by the institutional review board. Patients gave signed informed consent indicating that they were aware of the investigational nature of this study.

Therapy

Therapy was administered as follows: Mylotarg 6 mg/m^2 intravenously (i.v.) over 2 h on days 1 and 15, idarubicin 9 mg/m^2 i.v. over 30 min daily on days 2 through 4, and ara-C 1.5 g/m^2 by continuous infusion on days 2 through 5. Patients received antiemetic prophylaxis with ondansetron or other nonsteroidal agents as required. Bone marrow aspirate and biopsy were performed on days 14 and 21; thereafter, weekly aspirates were performed until CR status was established.

Endpoints and statistical methods

CR was defined as normalization of bone marrow and peripheral blood with $\leq 5\%$ blasts in a normocellular or hypercellular bone marrow, a granulocyte count $\geq 1\times10^9$/l and a platelet count of $\geq 100\times10^9$/l. CR with incomplete platelet recovery (CRp), was defined as CR with platelet count $<100\times10^9$/l and platelet transfusion-independence for at least 1 week. Overall survival (OS) was measured from the date of administration of the first dose of Mylotarg until the date of death or last follow-up. Adverse events were evaluated using version 2.0 of the National Cancer Institute common toxicity criteria (NCI-CTC).

Results

Between September 2000 and September 2001, 14 patients received protocol therapy. Four patients (29%) had primary refractory AML, ten (71%) had relapsed disease. The pretreatment characteristics of this patient cohort are included in Table 1. The median age of the patients was 61 years (range 34–74 years). Seven patients were ≥60 years of age. One patient had previously received chemotherapy for a prior malignancy. The median duration of first CR (CR1) was 18 weeks (range 0–131 weeks). All patients had received prior ara-C including four who had received IA, three cyclophosphamide, ara-C, and topotecan (CAT), three fludarabine and ara-C, and four topotecan and ara-C.

A total of six patients responded (overall response rate 43%), including three patients (21%) with CR and three (21%) with CRp. Six patients (43%) had early death (within 2 weeks) or death while still aplastic, while two patients were refractory to therapy, including one who fulfilled all the criteria for CR but had a persistently hypoplastic bone marrow. This patient survived for 5 months without further therapy. The median OS was 8 weeks (range 2–64 weeks). The median failure-free survival of patients who achieved CR or CRp was 27 (range 11–64 weeks).

Five of six responders had a diploid karyotype and all six received MIA as first relapse therapy (Table 2). Three of six responders had a CR1 duration of <12 months – this represents a 30% response rate in ten such patients treated on study. A total of 19 courses of MIA were administered as responding patients were allowed a second course of therapy. All courses were associated with grade 3/4 myelosuppression. Grade 3/4 sepsis occurred in ten patients (71%). Eight patients (57%) developed some degree of hepatic transaminitis, which was grade 3/4 in four (29%). This was a transient phenomenon except in two patients (14%) who developed VOD with first MIA therapy. VOD was confirmed by liver biopsy in one patient; the other had supportive ultrasonic and radiographic studies. Other grade 3/4 toxicities included mucositis in two patients (14%) and diarrhea in two patients (14%) – a rate equivalent to that seen with IA alone.

Discussion

The MIA regimen was feasible to administer but was associated with a 14% incidence of VOD – an incidence

Table 1 Clinical and laboratory characteristics of 14 patients treated on study. The data are presented as median (range) or number (percent) as appropriate

Age (years)	61 (34–74)
White blood cells ($\times10^9$/l)	2.8 (0.8–102)
Absolute neutrophil count ($\times10^9$/l)	0.5 (0–7.5)
Hemoglobin (g/dl)	8.7 (7.3–11.3)
Platelets ($\times10^9$/l)	34 (6–176)
Peripheral blood blasts (%)	5 (0–99)
Bone marrow cellularity (%)	30 (10–90)
Bone marrow blasts (%)	46 (9–78)
CD33+blasts (%)	87 (42–100)
LDH (IU/l)	726 (223–2902)
Creatinine (mg/dl)	0.9 (0.7–1.2)
Bilirubin (mg/dl)	0.7 (0.1–1.0)
SGPT (IU/l)	24 (17–90)
Albumin (g/dl)	3.0 (2.3–4.2)
Male/female	13/1 (93/7%)
Performance status	
0–1	11 (79%)
2/3	2/1 (14/7%)
Cytogenetic groups	
"Intermediate" risk	10 (71%)
"Worse" risk	4 (29%)
Primary refractory	4 (28%)
Relapsed with CR duration <1 year	6 (44%)
Relapsed with CR duration ≥1 year	4 (28%)
CR1 duration (weeks)	31 (4–131)
No. of prior salvage regimens	
None	11 (79%)
1	1 (7%)
≥2	2 (14%)

Table 2 Characteristics of patients achieving CR or CRp (*I* idarubicin, *A* ara-C, *C* cyclophosphamide, *T* topotecan)

Age (years)	Gender	Karyotype	CD33 (%)	Performance status	CR1 duration (weeks)	Induction regimen	Number of prior salvage regimens	Response	Survival (weeks)	Event-free survival (weeks)
48	M	Diploid	49	1	36	IA	0	CR	30	19
39	F	Diploid		1	84	CAT	0	CR	17	12
59	M	Diploid	42	0	53	CAT	0	CRp	64	60
53	M	-3-5-12-15-16 -17-18 add (7)	96	1	63	CAT	0	CRp	27	17
67	M	Diploid	87	2	Primary refractory	IA	0	CRp	11	4
71	M	Diploid	83	1	4	IA	0	CR	34	29

equivalent to that seen in patients receiving Mylotarg combined with regimens other than IA [8]. In a recent pilot study by the Medical Research Council (MRC) for the AML 15 protocol the incidence of VOD was greatly reduced by including only one dose of Mylotarg (6 mg/m^2) in a combination with daunorubicin and ara-C, while sequential administration of two courses of this regimen was not feasible as 5 of 18 patients (28%) developed VOD on the latter regimen [9]. In a recent pilot study of Mylotarg plus ara-C, VOD was dose-limiting and a schedule of Mylotarg 6 mg/m^2 on day 1, 4 mg/m^2 on day 8, combined with ara-C 100 mg/m^2 was chosen for further study [3]. The mechanisms underlying Mylotarg-associated VOD are unclear and may include direct damage to hepatic sinusoids by free calicheamicin (which is detectable in some patients after Mylotarg administration), direct binding of Mylotarg to CD33-positive Kupffer cells, release of calicheamicin from leukemia blasts within the hepatic sinusoids or processing of Mylotarg-soluble CD33 complexes within the liver [4, 11, 12]. While Mylotarg-associated VOD can occur even in previously untreated patients who receive single-agent therapy, most cases have been reported in patients who have received higher doses (>6 mg/m^2) given at shorter intervals (<14 days) with other cytotoxic agents [1, 8, 9]. Confirmation of the MRC data suggesting a dose-toxicity relationship for Mylotarg-related VOD will allow more rapid development of Mylotarg-based regimens.

Although the small cohort of patients treated on this protocol had very refractory AML (all intermediate or adverse karyotype, 10 of 14 (71%) with CR1 durations <12 months), a CR/CRp rate of 43% (95% CI 18%–71%) was associated with MIA therapy. Three patients each achieved CR or CRp (21% each, 95% CI 5%–51%). The use of standard high-dose ara-C regimens as relapse therapy in patients whose CR1 is <12 months is associated with a second CR rate of 14% [5]. There is a marked heterogeneity in patients with refractory AML [5]. A randomized study to establish whether MIA represents a true advance over IA alone appears warranted. Based on this study's findings, and those emerging from the MRC, a single day of Mylotarg should be included in future investigational MIA regimens.

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