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ORIGINAL ARTICLE

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Mylotarg, fludarabine, cytarabine (ara-C), and cyclosporine (MFAC) regimen as post-remission therapy in 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). Its role as a component of post-remission therapy in AML has not been established. The Mylotarg, fludarabine, cytarabine, and cyclosporine (MFAC) regimen was evaluated in patients in complete remission following Mylotarg-containing regimens. *Methods*: The MFAC regimen comprised: Mylotarg 4.5 mg/m^2 intravenously (i.v.) over 2 h after a loading dose of cyclosporine A (CSA) on day 1; fludarabine 15 mg/m^2 i.v. over 30 min every 12 h for six doses on days 2 through 4; ara-C 0.5 g/m^2 over 2 h every 12 h for six doses on days 2 through 4, 4 h after fludarabine started; CSA 6 mg/kg over 2 h, followed by 16 mg/kg continuous i.v. infusion on days 1 and 2. Patients in complete remission (CR) commenced idarubicin and ara-C (IA) alternating with MFAC or vice versa for 9 months from the date of CR. Idarubicin was administered at 8 mg/m^2 on days 1 and 2 and ara-C at 1.5 g/m^2 on days 1 and 2. *Results*: A total of 22 patients received 76 courses of MFAC (35 courses) alternating with IA (41 courses) or vice versa. The interval between courses, and degrees of myelosuppression, were equivalent in the alternating regimens. Failure-free and 12-month survival rates of were 32% and 55%, respectively. Grade 3/4 toxicities, including sepsis, neutropenic fever, and nausea/vomiting, were equivalent with MFAC and IA. *Conclusions*: Post-remission therapy with MFAC is feasible and well tolerated in patients with AML.

Keywords Mylotarg · Post-remission therapy · Idarubicin · Cytarabine

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Introduction

Mylotarg (gemtuzumab ozogamicin) is an immunoconjugate consisting of a humanized anti-CD33 monoclonal antibody linked to a potent cytotoxic, calicheamicin [1]. In phase II studies, Mylotarg induced complete remission (CR) in 16% of 142 patients with acute myelogenous leukemia (AML) in first relapse [2]. Resistance to Mylotarg is correlated with the expression and function of leukemia blast multidrug resistance (MDR) protein and may be reversed by cyclosporine A (CSA) [1]. Mylotarg-based regimens are being investigated in patients with relapsed or previously untreated AML [3, 4, 5, 6, 7, 8, 9, 10]. The combination of fludarabine and cytarabine (ara-C) is effective in patients with AML. In phase II studies of Mylotarg combined with the fludarabine and ara-C regimen, with the addition of CSA as a potential MDR modifier (MFAC) in patients with either previously untreated or refractory AML, significant activity was observed [8, 10]. No studies have yet been reported on the use of Mylotarg-based regimens as post-remission therapy in AML. We thus conducted a feasibility and safety study of the MFAC regimen in patients in CR following first induction therapy with a Mylotarg-containing regimen for AML.

Patients and methods

Patients in first CR after a Mylotarg-containing regimen, i.e. MFAC or Mylotarg plus interleukin-11 (IL-11), were eligible [10, 11]. 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 or equal to 1.5×10^9/l, no leukemic blasts in the peripheral blood and a platelet count above 100×10^9/l. Remission status was assessed on day 21 of induction therapy and weekly thereafter as required until final response was determined. All patients gave signed informed consent confirming their awareness of the investigational nature of this study. The MFAC regimen comprised Mylotarg 4.5 mg/m^2 intravenously (i.v.) over 2 h after a loading dose of CSA on day 1; fludarabine 15 mg/m^2 i.v. over 30 min every 12 h for six doses on days 2 through 4; ara-C 0.5 g/m^2 over 2 h, every 12 h for six doses on days 2 through 4, 4 h after fludarabine started; CSA 6 mg/kg over 2 h, followed by 16 mg/kg continuous i.v. infusion on days 1 and 2. Patients in CR commenced idarubicin and ara-C (IA) alternating with MFAC or vice versa (in order to investigate if the sequence of consolidation regimens had any impact on efficacy or toxicity) for 9 months from the date of CR. Idarubicin was administered at 8 mg/m^2 on days 1 and 2 and ara-C at 1.5 g/m^2 on days 1 and 2. Toxicity was graded on a scale of 0 to 5 using the National Cancer Institute Common Toxicity Criteria version 2.0. (http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf).

Results

Of 59 patients who received induction therapy with MFAC [10], 28 (47%) showed a CR, and of 33 who received induction therapy with Mylotarg plus IL-11 [11], 9 (27%) showed a CR. Among the 28 patients who responded to MFAC, 17 (61%) received MFAC/IA post-remission therapy, and 11 patients did not (3 received allogeneic stem cell transplant, and 8 declined because the protocol required local follow-up). Among the 9 responders to Mylotarg plus IL-11, 5 received MFAC/IA as post-remission therapy; 4 patients declined study participation. Thus a total of 22 patients received post-remission therapy with MFAC/IA. Patient pretreatment characteristics are summarized in Table 1.

Table 1 Pretreatment characteristics of patients ($n=22$) who received post-remission therapy with MFAC alternating with IA or vice-versa

	Median (range)	No. (%)
Age (years)	57 (27–71)	
WBC ($\times10^9$/l)	3.3 (0.9–183.6)	
Hemoglobin (g/dl)	7.9 (6.2–12.5)	
Platelets ($\times10^9$/l)	51 (13–148)	
Peripheral blood blasts (%)	9 (0–97)	
Bone marrow cellularity (%)	73 (10–95)	
Bone marrow blasts (%)	49 (10–98)	
CD33$^+$ blasts (%)	98 (38–100)	
LDH (IU/L)	747 (402–4433)	
Creatinine (mg/dl)	0.9 (0.4–2.1)	
Bilirubin (mg/dl)	0.6 (0.2–1.1)	
SGPT (IU/L)	28 (11–99)	
Albumin (g/dl)	3.4 (2.3–4.0)	
Male/female		13/9 (59/41)
Performance status		
0–1		18 (82)
2/3		3/1 (14/4)
Cytogenetic group		
"Intermediate" risk		17 (77)
"Worse" risk		5 (23)

The median age was 57 years (range 27–71 years). Seven patients (32%) were >60 years of age. Of the 22 patients who received post-remission therapy with MFAC/IA, 12 began with MFAC and 10 with IA—cycles were alternated in each patient.

A total of 76 courses of post-remission therapy were administered (35 MFAC, 41 IA). The median number of courses was three (range one to eight). Two patients received one course, eight patients received two courses, three patients received three courses, two patients received four courses, three patients received five courses, three patients received six courses, and one patient received eight courses of post-remission therapy.

The median time from documentation of CR to start of post-remission therapy was 7 days (range 0–22 days). As summarized in Table 2, the intervals between post-remission courses in patients who received MFAC alternating with IA, or vice versa, were equivalent as were times to peripheral blood count recovery following first and subsequent courses of therapy. Prolonged myelosuppression (ANC $<1\times10^9$/l or platelets $<50\times10^9$/l on day 43) occurred in eight courses each of MFAC (23%) and IA (20%). Non-hematologic toxicities are shown in Table 3. The majority of the infections were bacterial, and one patient developed cytomegalovirus antigenemia following IA therapy. Grade 3/4 hemorrhagic episodes on MFAC were retinal, nose and vaginal bleeding (one patient each), and on IA, gastrointestinal bleeding in three

Table 2 Interval in days between courses of alternating MFAC and IA post-remission therapies

Post-remission course	Median	Range
1–2	35	26–84
2–3	45	29–77
3–4	44	35–79
4–5	35	22–94
5–6	57	43–72

Table 3 Non-hematologic toxicity in 76 courses of post-remission therapy (MFAC—35 courses; IA—41 courses)

Toxicity	Grade 1/2		Grade 3/4	
	MFAC (%)	IA (%)	MFAC (%)	IA (%)
Infections	–	–	6 (18)	7 (17)
Neutropenic fever	–	–	8 (23)	8 (19)
Fever of unknown origin	–	1 (2)	–	–
Oral mucositis	7 (20)	5 (12)	–	–
Hemorrhage	2 (6)	1 (2)	3 (9)	3 (7)
Cardiovascular	1 (3)	–	1 (3)	3 (7)
Transaminitis	3 (9)	1 (2)	1 (3)[a]	N/A
Hyperbilirubinemia	4 (16)	–	1 (3)[a]	1 (2)
Neurologic	1 (3)	–	–	–
Renal	1 (3)	2 (5)	–	–
Nausea/vomiting	5 (14)	3 (7)	3 (9)	1 (2)
Rash	5 (14)	3 (7)	–	1 (2)
Other	18 (51)	12 (29)	–	1 (2)[b]

[a]Sepsis-associated hepatotoxicity
[b]Peripheral edema

Table 4 MFAC and other Mylotarg-based combination regimens in AML

Stage of therapy	Reference	No. of patients	CR (%)	Grade 3/4 hepatotoxicity (%)	VOD (%)
De novo					
MFAC	10	61	46	38	7
Relapse					
MIA	7	14	21	29	14
MDAC	20	11	9	54	0
MTA	9	17	12	48	6
MFAC	8	32	28	62	9
Maintenance					
MFAC	Current report	22	N/A	4	0

patients. Cardiovascular toxicities were mainly arrhythmias with IA, and one patient suffered a subendomyocardial infarction on MFAC. MFAC was more frequently associated with grade 1/2 hyperbilirubinemia and transaminitis. Both regimens had comparable grade 3/4 hepatotoxicity. One episode of transient ascites of unknown etiology occurred 24 days after the administration of MFAC. The patient with grade 3/4 transaminitis developed fatal disseminated *Candida albicans* infection on day 20 of the third course of MFAC.

With a median follow-up of 10 months, the median survival from time of CR was 16 months (range 3–18 months) and the 12-month overall survival rate was 55%. At the time of this report, ten patients (45%) had died, eight from relapsed leukemia. Two patients died in CR (one as above from *Candida* sepsis, a second from sepsis 13 days after matched related stem cell transplantation), and 13 patients (59%) had relapsed. The median failure-free survival was 8 months and the 12-month failure-free survival rate was 32%.

Discussion

MFAC as post-remission therapy was safe and had comparable toxicity to IA. Mylotarg-containing induction or relapse regimens are associated with hepatic veno-occlusive disease (VOD) [3, 4, 5, 6, 7, 9, 12, 13, 14, 15, 16]. No VOD occurred in patients on this study. This is in contrast to two other recent studies with the MFAC regimen in previously untreated and relapsed patients with AML respectively [8, 10] (Table 4). In these studies, 4 of 59 (7%) and 3 of 32 (9%) of patients, respectively, developed VOD [8, 10]. Other than stem cell transplantation, no specific risk factors for Mylotarg-associated VOD have been identified [6, 15, 17]. Mylotarg as a single-agent causes grade 3/4 hyperbilirubinemia and/or hepatic transaminitis in approximately 20% of patients with relapsed AML [2]. The incidence of grade 3/4 hyperbilirubinemia in the current study was 1%. Transient grade 1/2 hyperbilirubinemia occurred in 16% of patients in this study, was associated with CSA administration, and was of no clinical consequence.

In large randomized studies, only 50%–69% of patients received all assigned post-remission therapy—the percentage was even lower in patients with adverse cytogenetics [18, 19]. The MFAC regimen is worthy of further investigation as post-remission therapy in patients with AML. The endpoints of a potential randomized study of MFAC versus standard maintenance approaches might include time to treatment failure, safety, and quality of life. The hypothesis that Mylotarg-associated VOD may be a phenomenon confined to patients with high tumor loads is also worthy of further study.

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