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FLAG (fludarabine, cytosine arabinoside, G-CSF) for refractory and relapsed acute myeloid leukemia

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Abstract Twenty-two patients with refractory or relapsed AML were treated with FLAG [25 mg/m^2 fludarabine daily (days 1–5), 2 g/m^2 daily Ara-C (days 1–5) and 400 μg/m^2 daily G-CSF (day -1 till the absolute neutrophil count was >500/μl)]. Median age was 46 years (range 24–63). Eight patients had leukemia which was primarily refractory to conventional regimens, six were in first, seven were in second, and one was in third relapse.

Overall, 11 of 22 (50%) patients achieved complete remission (CR), three had a partial response (PR), and seven did not respond (NR). One patient died of an early cerebral hemorrhage. The median remission duration from achievement of CR after FLAG was 9.9 months and median survival was 13.0 months. One patient is alive in CR at 31.9 months. Hematological toxicity of the regimen was severe. The median time to neutrophil recovery (ANC >500/μl) was 21 days (range 18–33). A median of seven red cell units (range 0–22) and of six platelet concentrate units (range 3–28) had to be given. Median duration of febrile neutropenia was 2 days (range 0–20 days) and patients were on i.v. antibiotics for a median of 16 days (range 0–51). There was no death from infection. Nonhematological toxicity was remarkably low, with almost no neurotoxicity and no major hepatotoxicity. In conclusion, FLAG seems to be an efficient and well tolerated regimen. It may be particularly useful for patients who have a sibling or unrelated donor for subsequent allogeneic bone marrow transplantation.

Key words Acute myeloid leukemia · FLAG · Salvage therapy

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Introduction

High-dose cytosine arabinoside (HidaC) is one of the most effective treatment regimens in AML, alone or in combination with other drugs, it has been successfully used for induction, consolidation or salvage treatment [1–3, 10, 12, 15, 21]. The efficacy of HidaC has been related to the higher intracellular concentration of the active metabolite ara-C 5′triphosphate (ara-CTP). Gandhi et al. [8] have shown in vitro and in vivo that a further increase of intracellular ara-CTP can be achieved upon pretreatment with fludarabine and suggested that administration of fludarabine prior to cytosine arabinoside (ara-C) may enhance the cytotoxicity and clinical efficacy of ara-C. Estey et al. tested the clinical efficacy of this combination in refractory and relapsed AML [5] and later [6] in induction therapy of newly diagnosed AML. In the latter study they added G-CSF to the regimen (FLAG) with the aim of increasing the efficacy by recruitment of leukemic cells into S-phase and to reduce the incidence of infectious complications by shortening the duration of neutropenia. They found that FLAG was highly effective and well tolerated. Based on their findings, we decided to use the FLAG regimen for treatment of refractory and relapsed AML.

Patients and methods

Patients

Twenty-two patients were treated with FLAG. Eligible were patients with refractory and relapsed AML with ECOG-status 0–2.

Table 1 Patient characteristics

Disease status before FLAG	Pat. no.	Age	Sex	FAB	Karyotype (at diagnosis)	Pretreatment blast cell count (before FLAG)
Primary refractory	1	48	f	M1	7q−	85
	2	54	f	M1	inv 3 (q26;q27)	50
	3	25	m	M1	t (3;3), −7	33
	4	59	f	M5a	Normal	25
	5	54	m	M1	Normal	22
	6	57	f	M4 Eo	Normal	83
	7	25	f	M6	t (3;3), −7	10
	8	51	m	M4	Normal	40
Early first relapse	9	32	f	M4	Normal	87
	10	46	f	M5	Unknown	>50
	11	47	m	M2	t (8;21), 45 X0, inv (9)	10
	12	41	f	M5a	Normal	31
Late first relapse	13	29	m	M0	Complex abnormalities	35
	14	24	f	M1	Normal	22
2nd/subsequent relapse	15	43	m	M1	Normal	45
	16	54	m	M1	Normal	18
	17	57	f	M4 Eo	inv (16)	11
	18	39	m	M5	Normal	31
	19	62	m	M2	t (8;21), 45 X0	40
	20	28	f	M4	inv (16)	15
	21	40	m	M2	+8	46
	22	63	m	M4	t (8;21), 45 X0	12

There were no strict rules with regard to previous treatment. Therefore, the patient group was heterogeneous as to the extent of pretreatment. The clinical and laboratory characteristics of these patients at diagnosis are shown in Table 1. Eight patients were refractory to one to three induction regimes, four had an early first relapse (<12 months remission duration), two had a late first relapse (both after bone marrow transplantation), and eight patients had a second or third relapse.

Table 2 lists the treatment regimens which the patients had received prior to FLAG. Almost all patients were heavily pretreated with a variety of regimens. Two thirds ($n=4$) had received intermediate- or high-dose ara-C at some time during the course of their disease. Three patients (2, 11 and 22) who had achieved a CR after FLAG were retreated with FLAG when they relapsed (designated in Tables 2 and 3 as 2a, 11a, and 22a). All patients give written informed consent.

Treatment regimen

The treatment with FLAG was performed as described by Estey et al. [6] with the exception that the dose of fludarabine was 25 mg/m^2 instead of 30 mg/m^2. In this study the addition of G-CSF significantly shortened the recovery of ANC. We therefore chose to include G-CSF into our treatment regimen. In one patient with a high leukocyte count G-CSF was delayed by 1 day. Twenty-one patients received only a single course of FLAG and one patient received two courses. Three patients who relapsed after FLAG were retreated with FLAG.

Statistical analysis

Overall survival was calculated from the start of FLAG, disease-free survival and continuous complete remission from CR after FLAG using the Kaplan-Meier method [13]. Patients undergoing bone marrow transplantation were censored at the time of transplantation.

Results

Patient characteristics

All patients who were treated with FLAG were refractory to standard regimens. Eight patients were primarily refractory to one of three induction regimens. Four patients had an early first relapse (<12 months remission duration). Two of them received FLAG as the primary treatment of relapse, two received FLAG after failure of HAM. Two patients had a late relapse after BMT in first CR and eight patients had a second ($n=7$) or third ($n=1$) relapse (Table 2). The karyotype of the leukemic cells was available for 21 patients. Five had a favorable, ten a normal, and five an unfavorable karyotype (Table 1).

Overall outcome

Of the 22 patients 11 achieved a complete remission; one patient died during treatment because of intracerebral bleeding (she was refractory to platelet concentrates). CR was achieved in 2/8 with primary refractory AML, in one of four with early relapse, in both patients with late relapses after BMT and in 6/8 with second or third relapse (Table 3). Three patients who did not achieve a CR had a good partial response. The median remission duration after FLAG was 9.9 months, and median survival was 13.0 months. The probability of CCR at 12 months is 34.6% and the probability of survival at 12 months is 58% (Figs. 1 and 2). One patient is

Table 2 Treatment prior to FLAG (*DA (3+7)* daunorubicin and ara-C, *DAV* daunorubicin, ara-C and etoposide [9], *HAM* HidaC and mitoxantrone [10], *HidaC* high-dose ARA-C, *IdaC* intermediate dose ARA-C, *BMT* bone marrow transplantation, *allo BMT* allogeneic BMT, *auto BMT* autologous BMT)

Patient	Induction treatment (no. cycles)	Response duration (months)	Salvage treatment 1st relapse	CR (months)	Salvage treatment 2nd relapse	CR (months)
1	DAV (1×)	NR	–	–	–	–
2	DAV (2×), HAM (1×)	NR	–	–	–	–
3	DAV (1×)	NR	–	–	–	–
4	DAV (2×), HAM (1×)	NR	–	–	–	–
5	DAV (3×)	NR	–	–	–	–
6	DAV (2×), DA (1×)	NR	–	–	–	–
7	DAV (1×), HAM (1×)	NR	–	–	–	–
8	DAV (2×), HAM (1×)	NR	–	–	–	–
2a	DAV (2×), HAM (1×)+FLAG	CR (10)	HidaC (1×)	NR	–	–
9	DAV (1×)	CR (2)	HAM (1×)	NR	–	–
10	DAV (1×)	CR (1.8)	–	–	–	–
11	DAV (2×), HAM (1×)	CR (7.1)	–	–	–	–
12	DAV (2×)	CR (8.3)	HAM (1×)	NR	–	–
13	DA (1×), HAM (1×) (allo BMT CR1)	CR (28.9)	–	–	–	–
14	allo MBT (sibling)	CR (41)	Donor leukocyte infusion	NR	–	–
11a	DAV (2×), HAM (1×)	CR (7.1)	FLAG (1×)	CR (1.7)	–	–
15	DA (1×)	CR (8)	DA (1×), HAM (1×)	CR (4.7)	–	–
16	DAV (2×)	CR (3)	HidaC (1×)	CR (0.9)	–	–
17	DA (1×)	CR (9.5)	HAM (1×)	CR (29.7)	–	–
18	DAV (2×)	CR (6)	HAM (1×)	CR (1)	BMT (sibling)	CR (1)
19	DAV (1×)	CR (11)	HAM (1×)	CR (6)	–	–
20	DA (2×)	CR (5.5)	DA (1×), auto BMT (CR2)	CR (8.7)	–	–
21	DAV (2×)	CR (11.1)	DA (1×), auto BMT	CR (14.3)	–	–
22	DAV (1×)	CR (10.2)	HAM (1×)	CR (2)	–	–
22a	DAV (1×)	CR (10.2)	HAM (1×)	CR (2)	IdaC	NR

Table 3 Response to FLAG (*URD* unrelated donor, *Amsa-Ara-C* HidaC and amsacrine, *2CdA* 2-chlorodesoxyadenosine)

Patient no.	Cycles (*n*)	Response	Consolidation	Duration of CR (months)	Treatment after FLAG	Survival from start of FLAG (months)
1	1	NR	–	–	Allo BMT (sibling)	7[a]
2	1	CR	4× HidaC	10	FLAG (see 2a)	13.6+
2a	1	CR	–	0.2+	–	
3	2	PR	–	–	AlloBMT (URD)	6.1[a]
4	1	CR	4× HidaC	5.6+	–	6.7+
5	1	PR	–	–	–	5.7+
6	1	NR	–	–	–	4.3
7	1	PR	–	–	AlloBMT (URD)	4.4+[a]
8	1	NR	–	–	–	1.2+
9	1	NR	–	–	–	3.1
10	1	NR	–		–	1.7
11	1	CR	–	1.7	FLAG (see 11a)	7.9+
11a	1	NR	–	–	Amsa-ARAC (NR)	
12	1	NR	–	–	–	2
13	1	CR	HidaC	4.9+	–	6.0+
14	1	CR	HidaC	3.0+	–	4.3+
15	1	CR	–	4.6	–	13.4
16	1	CR	–	0.4	–	2.7
17	1	CR	–	29.7+	–	31.1+
18	1	NR	–	–	–	1.6
19	1	CR	–	4.8	IdaC (CR), 2CdA after 3rd relapse (NR)	21.9
20	1	ED	–	–	–	0.5
21	1	CR	–	2.5	–	5
22	1	CR	IdaC (2×)	12.8	FLAG (see 22a)	14.9+
22a	1	CR	–	0.1	–	

[a] Including time after BMT

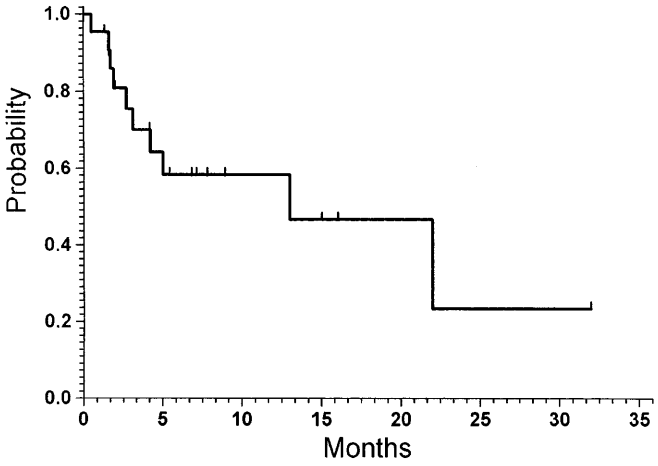

Fig. 1 Overall survival after FLAG

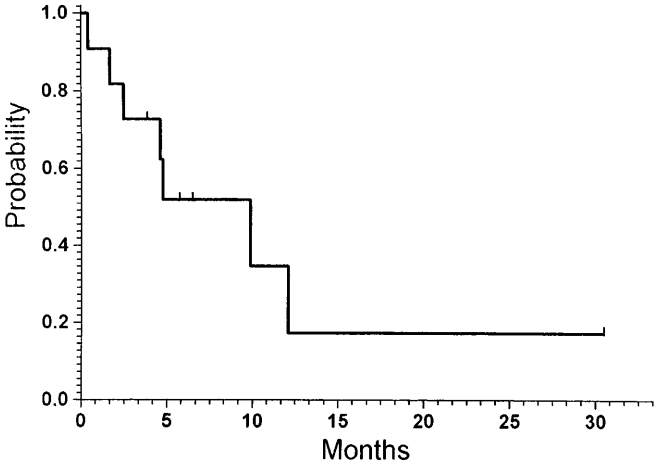

Fig. 2 Remission duration in patients who achieved CR after FLAG

alive in third CR at 31.9 months. Three patients (1, 3, 7) who had achieved a partial remission after FLAG underwent allogeneic BMT (two unrelated, one sibling donor). One of these (no. 1) died of transplant-related complications, another (no. 3) recovered with blasts immediately after BMT and died of leukemia, and the third (no. 7) achieved CR after BMT and is in CCR 70 days after BMT.

Patient 2, who had achieved a CR with FLAG, had a first relapse after 10 months. She was refractory to HAM but achieved a second CR after FLAG. Patient 22 relapsed 12.8 months after FLAG. He was refractory to intermediate-dose ARA-C and achieved a third remission after FLAG.

Hematological toxicity

All patients had severe myelosuppression and required intensive support with red cells and platelets. Blast cells were cleared from the peripheral blood in all cases. The median time for recovery to an ANC of $>500/\mu l$ was 21 days (calculated from day 1) with a range of 18–33 days (Table 4). The median number of days with febrile neutropenia was only 2; four patients had no fever at all and seven only 1 day of febrile neutropenia. There was no death from infection. Sites of infection were the lungs ($n=6$), paranasal sinus ($n=1$), and the gut ($n=2$). In 11 febrile patients no site of infection was identified.

Nonhematological toxicity

The nonhematological toxicity was mild (Table 5). There was no grade 4 or more toxicity. The most common side effects were drug fever, nausea, and vomiting. There was no serious CNS toxicity.

Discussion

The prognosis of patients with refractory or relapsed AML is poor. Patients refractory to standard induction therapy or with early relapse have only a small chance of achieving a CR with salvage treatment [11]. Patients with late relapses have a relatively good chance of a second remission, but the remission duration is usually short and there is only a small chance of cure by chemotherapy [14, 19]. In the absence of randomized trials, it is uncertain which of the various salvage regimens [12, 21] has the highest efficacy. Recently, Estey et al. [6] showed that the combination of fludarabine, high-dose ara-C, and G-CSF (FLAG) is highly effective; it produced a high remission rate in newly diagnosed acute myelogenous leukemia. The basis for this combination is the finding of Gandhi et al. [8] that infusion of fludarabine immediately before high-dose ara-C markedly enhances the concentration of intracellular ara-CTP, and thereby the antileukemic activity of ara-C. In addition, fludarabine itself may have antileukemic activity, particularly on resting cells. The inclusion of G-CSF in the protocol is based on the assumption that its administration before and during HidaC renders the leukemic cells more susceptible to the action of ara-C, and the administration post chemotherapy shortens the duration of neutropenia and reduces infectious complications.

Our data indicate that FLAG is an effective regimen for treatment of refractory or relapsed AML. Since this was not a randomized study, it is impossible to know whether FLAG is more effective than other salvage regimens. However, it should be noted that two patients who were refractory to two standard induction regimens and one salvage regimen (HAM) attained a complete remission after FLAG, lasting 10 and 5.6 months, respectively. Moreover, six of eight patients with a second or third relapse achieved a CR, with two remissions lasting 31.9+ months and 13+ months, respec-

Table 4 Hematological toxicity

Patient no.	ANC before therapy	Days until ANC >500/μl	Febrile neutropenia (days)	Days on i.v. antibiotics	Transfusion requirements	
					Red cells (units)	Platelets (units)
1	0	19	4	20	8	14
2	380	20	5	18	6	4
2a	980	21	1	10	6	3
3	0	25	2	5	10	6
4	310	20	0	7	6	4
5	770	20	1	17	6	4
6	4840	24	2	12	12	5
7	6110	28	1	18	14	8
8	1470	17	1	3	0	5
9	7350	[a]	3	21	6	8
10	840	24	17	51	20	23
11	3960	28	5	25	12	6
11a	3960	18	2	9	2	3
12	3140	18	2	9	2	3
13	2680	30	20	33	22	22
14	2400	24	0	10	4	6
15	820	21	1	20	10	12
16	2000	20	0	0	6	4
17	110	32	11	29	14	28
18	3840	25	7	27	10	14
19	2580	21	3	18	4	7
20	150	[b]	0	0	12	16
21	110	33	1	15	10	12
22	1070	21	1	8	0	4
22a	350	23	4	14	10	6
Median	1270	21	2	16	7	6
Range	(0–7350)	(18–33)	(0–20)	(0–51)	(0–22)	(3–28)

[a] Did not recover
[b] Patient died before recovery

Table 5 Nonhematological toxicity (according to WHO)

		Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	Bilirubin	7	1	1	0
	SGOT/SGPT	4	3	1	0
	Alkaline phosphase	7	1	1	0
	Oral	6	6	0	0
	Nausea/vomiting	4	3	7	0
	Diarrhea	4	2	2	0
	Constipation	6	0	0	0
Renal	BUN or blood urea	3	0	0	0
	Creatinine	6	0	0	0
	Proteinuria	0	0	0	0
	Hematuria	5	1	0	0
Neutrotoxicity	State of consciousness[a]	4	0	0	0
	Peripheral	3	1	0	0
Pulmonary		0	0	0	0
Others	Drug fever	6	16	0	0
	Allergic	2	0	0	0
	Cutaneous	9	1	1	0
	Infection	9	6	5	0
	Pain	7	5	3	0

[a] One case of intracerebral bleeding

tively. It is also interesting to note that some patients who were refractory to HidaC or IdaC achieved a CR with FLAG.

Since in 21 of the 22 patients the karyotype at diagnosis is known some statement about the relationship between the karyotype and the response to FLAG is possible. The response rate in patients with t(8;21) and inv(16) was high (CR in three of four); four of ten with normal metaphases had a CR. Particularly interesting are the three patients with abnormalities of chromo-

some 3. The patient with inv 3 was refractory to two DAV cycles and one cycle of HAM but had a complete response after FLAG which lasted 10 months. The relapse was refractory to HidaC, but a second CR was achieved with FLAG. Two patients with t (3;3) and monosomy 7 achieved a good partial remission (5 and 7% blasts in the marrow). It is interesting that Visani et al. [20] also achieved a sustained remission with FLAG in a primary refractory patient with inversion 3, -7. It is known that patients with abnormalities of chromosome 3 have an extremely poor prognosis with conventional chemotherapy [7, 17]. It may be that patients with inversion or t (3;3) are particularly responsive to FLAG, but further observations are needed to support this assumption. Patients with favorable cytogenetics may also respond well to FLAG.

A remarkable result of our study was the fact that none of our patients died of infectious complications. The only death occurred in a patient who was refractory to platelet transfusions and had cerebral bleeding. A similar observation was made by Visani et al. [20]. In their study, which also included refractory and relapsed patients, they observed only one infectious death in 18 patients. The number of days with febrile neutropenia was low in our study (median 2 days). There may be a number of reasons for the low incidence of life-threatening infections. The patients were selected in both studies (median age in our patients was 46 years); they had to be afebrile and free of infections before treatment was started. Almost all patients had ANC >500 at the start of FLAG. It can only be speculated to what extent the administration of G-CSF contributed to the low rate of infections. In recently completed randomized studies G-CSF did not significantly reduce the rate of severe infectious complications and death from infection when given after induction treatment [4, 9]. In the treatment of refractory or relapsed patients the situation may be quite different. Infection occurs in such patients usually not until 2 weeks after the start of treatment, and a shortening of the granulocytopenia by about 5 days may be critical for the prevention of these late infections. Another unresolved question is whether the higher dose of G-CSF as used in the FLAG regimen may be more effective in the prevention and control of infections after chemotherapy. Addition of other drugs such as idarubicin [16, 18] to the FLAG regimen will probably increase the efficacy, but also the toxicity.

In conclusion, our data indicate that FLAG is a well-tolerated regimen for refractory and relapsed AML which should be compared in randomized studies with other salvage regimens. Because of the low rate of serious infections, FLAG might be particularly useful for patients who have a sibling or unrelated donor for subsequent allogeneic transplantation.

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