Salvage therapy for acute myeloid leukemia with fludarabine, cytarabine, and idarubicin with or without gemtuzumab ozogamicin and with concurrent or sequential G-CSF

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The current salvage therapies for relapsed/refractory acute myeloid leukemia (AML) are unsatisfactory. Over the past 7 years, we have used two salvage regimens: fludarabine, cytarabine, and idarubicin with (FLAG-IM) or without gemtuzumab ozogamicin (GO) (9 mg/m^2 on Day 8) (FLAG-I) in relapsed/refractory AML. Three-quarters of patients also received concurrent G-CSF. Seventy-one patients were treated, 23 with FLAG-I and 48 with FLAG-IM. The median duration of follow-up was 30.6 months. The treatment groups were well balanced with median ages of 48 years (range 18–70) and 47 years (range 20–68), unfavorable cytogenetics in 57% and 35%, prior allogeneic stem cell transplant in 43% and 42%, and CR1 duration <1 year in 60% and 67%, respectively, for FLAG-I and FLAG-IM. The complete remission (CR) rate in the FLAG-I group was 39% with an additional 13% achieving a CRp [overall response rate (ORR) 52%]; the CR rate in the FLAG-IM group was 29% with an additional 27% achieving a CRp (ORR 56%). The median duration of response (DOR; 16.8 vs. 8.3 months), event-free survival (EFS; 7.4 vs. 4.1 months), and overall survival (OS; 8.8 vs. 5.0 months) trended to favor FLAG-I over FLAG-IM. The patients who received G-CSF concurrent with chemotherapy had superior overall response rate (ORR; 62% vs. 29%, $P = 0.026$), median EFS (6.2 vs. 3.4 months, $P = 0.010$), and OS (8.8 vs. 3.9 months, $P = 0.004$) when compared with those who sequentially received G-CSF and chemotherapy, regardless of chemotherapy regimen. The addition of GO, at this dose and schedule, to FLAG-I failed to improve the outcomes in patients with relapsed/refractory AML. The patients who received G-CSF concurrently with chemotherapy had improved outcomes. Am. J. Hematol. 84:733–737, 2009. © 2009 Wiley-Liss, Inc.

Introduction

Twenty to 50% of patients diagnosed with acute myeloid leukemia (AML) had primary refractory disease and 20–70% of patients who achieved a complete remission (CR) with initial therapy relapsed [1–3]. Salvage therapy successfully achieves a remission in less than 50% of these patients, and in the absence of consolidative allogeneic stem cell transplantation, remissions and survival are typically brief [3–9]. Important prognostic factors in relapsed disease include the duration of CR1 (<1 year vs. >1 year), the age at relapse, the cytogenetics at diagnosis, and whether the patient has received a prior stem cell transplant [3,4,10,11].

Intermediate- or high-dose cytarabine remains the most active agent in relapsed/refractory AML and it constitutes the backbone of most salvage regimens [11]. A variety of novel agents are currently being tested in combination with cytarabine, including hypomethylating agents (azacitidine, decitabine), novel cytotoxics (clofarabine, voreloxin), chemosensitizers/priming agents (AMD3100, G-CSF), and monoclonal antibodies [gemtuzumab ozogamicin (GO), bevacizumab, lintuzumab] [3,12–20].

GO is a humanized monoclonal antibody that binds CD33 and delivers its payload, the antitumor antibiotic calichaemicin, after internalization. CD33 is not only expressed on the majority of AML blasts (~80%) but also on normal progenitors (CFU-GEMM, BFU-E, and CFU-GM) [17,21,22]. GO is FDA approved for the treatment of elderly patients with relapsed CD33-positive AML and is being investigated both in the front-line and relapsed/refractory settings [23]. For the past 7 years, at the Washington University in Saint Louis, we have primarily used two salvage regimens: fludarabine, G-CSF, idarubicin, and cytarabine with (FLAG-IM) or without GO (FLAG-I) in relapsed/refractory AML. The current retrospective report provides our comparative experiences with these regimens in detail.

Results

Patients

Seventy-one patients were identified for this treatment, 23 who received FLAG-I and 48 who received FLAG-IM. The median age of FLAG-I patients was 48 years (range 18–70) with 13% of patients ≥60 years old; the median age of FLAG-IM patients was 47 years (range 20–68) with 14% of patients ≥60 years old. Of these patients, 43% of the FLAG-I patients had previously received an allogeneic

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TABLE I. Demographics of Patients Treated with FLAG-I and FLAG-IM[a]

	FLAG-I	FLAG-IM
Patients	23	48
Median age (range)	48 (18–70)	47 (20–68)
$N < 60$	20 (87%)	41 (85%)
$N \geq 60$	3 (13%)	7 (14%)
Male	14 (61%)	23 (48%)
Prior MDS	3 (13%)	9 (19%)
Therapy related	1 (4%)	7 (14%)
Cytogenetics		
Favorable	1 (4%)	5 (10%)
Intermediate	8 (35%)	24 (50%)
Unfavorable	13 (57%)	17 (35%)
Unknown	1 (4%)	2 (4%)
Indication		
Primary refractory	2 (9%)	8 (16%)
1st relapse, 1st salvage	9 (39%)	19 (40%)
1st relapse, 2nd salvage	7 (30%)	11 (22%)
2nd or 3rd relapse	5 (22%)	10 (20%)
Duration CR1		
CR1 <12 months	14 (60%)	32 (67%)
CR1 ≥12 months	4 (17%)	6 (13%)
Unavailable	5 (22%)	10 (21%)
Prior allogeneic stem cell transplant	10 (43%)	20 (42%)
% CD33 positive[b]	69	71

N, number of patients; MDS, myelodysplastic syndrome; CR, complete remission.

[a]There was no statistically significant differences between demographic characteristics in the two groups.

[b]≥20% of blasts express CD33.

TABLE II. Outcomes with and Consolidation Strategies Following FLAG-I and FLAG-IM

	FLAG-I	FLAG-IM	*P*-value
CR rate (%)	9 (39%)	14 (29%)	0.428 (Fisher's)
CRp rate (%)	3 (13%)	13 (27%)	0.235 (Fisher's)
Overall response rate (%) (CR + CRp)	12 (52%)	27 (56%)	0.803 (Fisher's)
Treatment-related mortality	8 (35%)	11 (23%)	
Progressive disease	3 (13%)	10 (21%)	
Consolidation			
DLI	2 (17%)	8 (30%)	
Allogeneic stem cell transplant	5 (42%)	15 (56%)	
Investigational agent on clinical trial	1 (8%)	0	
Chemotherapy	1 (8%)	1 (4%)	
Other	3 (25%)	3 (11%)	
Median duration of response (months)	16.8 months	8.3 months	0.126 (log rank)
Median EFS (months)	7.4 months	4.1 months	0.1784 (log rank)
Median OS (months)	8.8 months	5.0 months	0.569 (log rank)

CR, complete remission; CRp, complete remission with incomplete platelet recovery; ANC, absolute neutrophil count; DLI, donor lymphocyte infusion; EFS, event-free survival; OS, overall survival.

stem cell transplant; 42% of the FLAG-IM patients had previously received an allogeneic stem cell transplant. FLAG-I was delivered as 2nd or higher order salvage to 52% of patients; FLAG-IM was delivered as 2nd or higher order salvage to 42% of patients. The myeloblasts in 69% of patients receiving FLAG-I expressed CD33, and the myeloblasts in 71% of patients receiving FLAG-IM expressed CD33. The remainder of patient characteristics are summarized in Table I. The median duration of follow-up in surviving patients was 30.6 months (30.5 months for patients receiving FLAG-I and 30.7 months for patients receiving FLAG-IM).

Responses

The CR rate was 39% with FLAG-I and 29% with FLAG-IM; the CRp rate was 13% with FLAG-I and 27% with FLAG-IM (Table II). The differences in CR versus CRp rates were not statistically significant. The ORR was 52% for FLAG-I and 56% for FLAG-IM.

Groups that received concurrent or sequential therapy were well balanced within FLAG-IM, but the sequential FLAG-I group had higher rates of adverse prognostic features: unfavorable cytogenetics (50% vs. 71%, $P = 0.722$), prior allogeneic stem cell transplantation (38% vs. 57%, $P = 0.701$), and shorter duration of CR1 (<1 year 50% vs. 85%, $P = 0.489$) than the concurrent FLAG-I group. The ORR to FLAG-I was higher in the concurrent group (69%) than in the sequential group (14%) ($P = 0.027$ Fisher's exact test). A similar, nonsignificant trend was seen in the FLAG-IM group (ORR concurrent G-CSF: 59% versus sequential G-CSF: 44%) ($P = 0.477$ Fisher's exact test). The ORR, regardless of chemotherapy regimen, was superior in patients who received concurrent G-CSF versus sequential G-CSF (62% vs. 29%, $P = 0.026$).

OS, EFS, DOR

The median OS in the FLAG-I group was 8.8 months with 17% of patients alive for 36 months, and the median OS in the FLAG-IM group was 5.0 months with 13% of patients alive for 36 months (log rank $P = 0.569$) (Table II and Fig. 1). The median EFS was 7.4 months in the FLAG-I group and 4.1 months (log rank $P = 0.178$) in the FLAG-IM group. The median DOR was 16.8 months in the FLAG-I group and 8.3 months in the FLAG-IM group (log rank $P = 0.126$).

OS was significantly longer in patients achieving CR versus CRp, regardless of regimen (31.0 vs. 8.2 months, log rank $P = 0.001$). Likewise, EFS was longer in patients achieving a CR when compared with a CRp (20.6 vs. 6.1 months, log rank $P = 0.0082$). While comparing regimen and response, the quality of response predicted the following median OS regardless of regimen: CR with FLAG-I 31.0 months versus CRp with FLAG-I 10.2 months (log rank 0.018), and CR with FLAG-IM 29.8 months versus CRp with FLAG-IM 6.3 months (log rank 0.012).

The median EFS (10.5 vs. 2.7 months; $P = 0.030$ log-rank test) and OS (11.9 vs. 2.7 months; $P = 0.022$ log-rank test) were longer in the FLAG-I group that received concurrent G-CSF when compared with patients who received sequential G-CSF. In the FLAG-IM group, there was a modest trend toward improved median EFS (4.3 vs. 3.6 months; log-rank test $P = 0.124$) and OS (5.9 vs. 4.6 months; log-rank test $P = 0.076$) with concurrent G-CSF. The median EFS (6.2 vs. 3.4 months; log-rank test $P = 0.010$) and OS (8.8 vs. 3.9 months; log-rank test $P = 0.004$) were superior, regardless of regimen, in patients who received concurrent G-CSF (Fig. 1C,D).

Postremission therapy

The details of postremission therapy are reported in Table III. There was a trend toward a longer time between salvage therapy and postremission therapy with FLAG-IM (66 days vs. 82 days; $P = 0.093$). About 59% of patients in the FLAG-I group and 86% of patients in the FLAG-IM group continued to receive immunologic therapy: either a donor lymphocyte infusion (DLI) or an allogeneic stem cell transplant (Fisher's exact test $P = 0.102$). A hetegeneous group of conditioning regimen were used for allogeneic transplantation depending on physician's preference. Of the patients subsequently undergoing an allogeneic transplant, five patients in the FLAG-IM cohort underwent a prior autologous transplant. One patient developed veno-occlusive disease (VOD), following allogeneic transplantation. No mortality due to graft versus host disease (GVHD) was

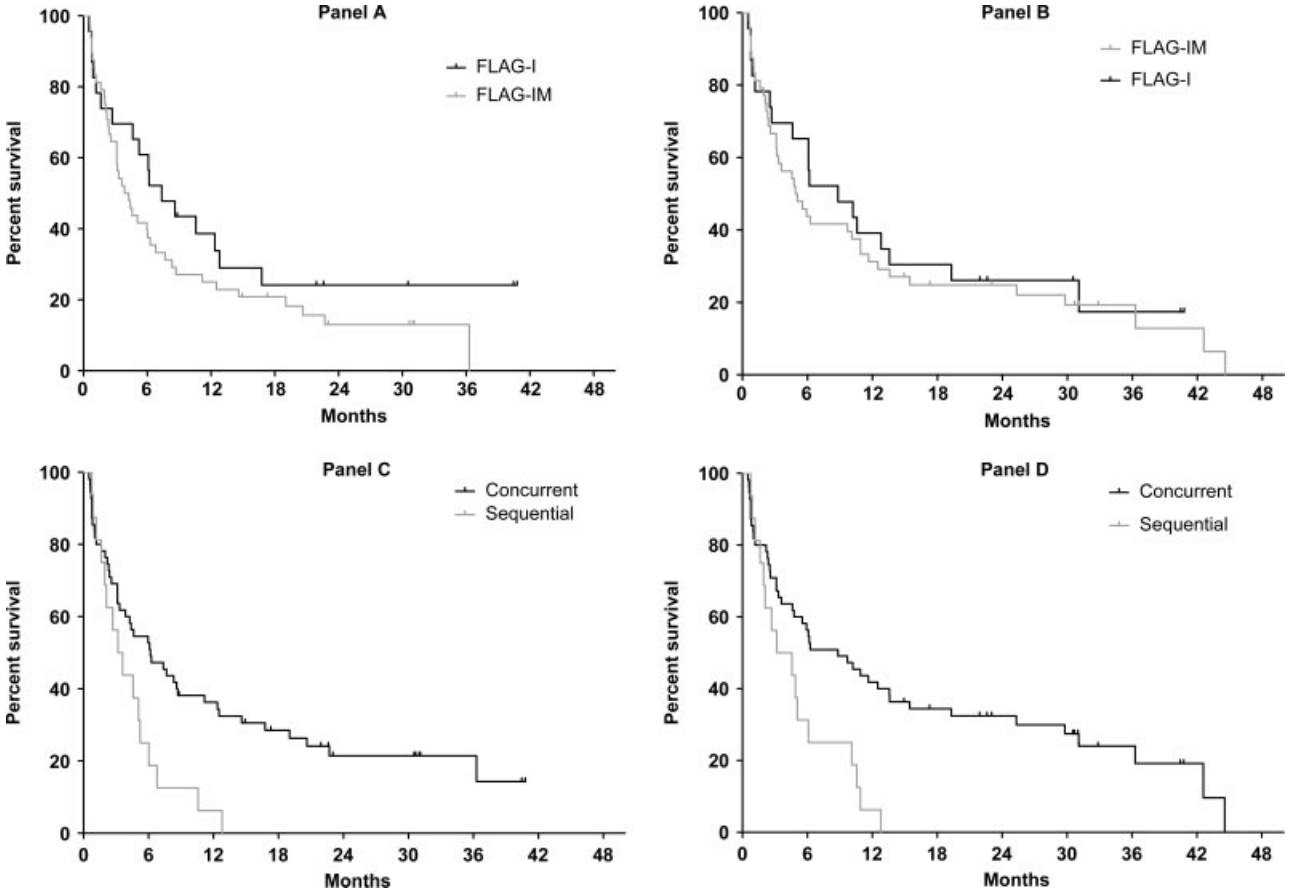

Figure 1. Kaplan-Meier curves of EFS (Panel A) and OS (Panel B) for FLAG-I versus FLAG-IM. Kaplan-Meier curves of EFS (Panel C) and OS (Panel D) for concurrent versus sequential G-CSF, regardless of regimen. CR, complete remission; CRp, complete remission with incomplete platelet recovery.

TABLE III. Details of Consolidation Allogeneic Stem Transplantations

	FLAG-I	FLAG-IM	*P*-value
Patients	5	15	
Matched sibling transplant	3	5	
Unrelated donor transplant	2	10	
Relapse after transplant	2 (40%)	9 (60%)	
Death after transplant	2 (40%)	9 (60%)	
Median time to relapse	8.0 months (range, 7.4–8.6)	7.7 months (range, 4.3–20.6)	
Median EFS after transplant	Not reached	11.2 months	0.315 (log rank)
Median OS after transplant	Not reached	34.0 months	0.746 (log rank)

EFS, event-free survival; OS, overall survival.

observed. All deaths occurring following allogeneic transplantation were related to disease progression. Of the 12 surviving patients (median follow-up of 30.6 months), nine patients received a consolidative allogeneic stem cell transplant, two received a DLI, and one received an experimental therapy.

Toxicity

Among patients achieving a CR/CRp, the median time until neutrophil recovery ($\geq$1000 μl^{-1}) was 27 days (range 21–44 days) for patients receiving FLAG-I and 33 days (range 18–62) for patients receiving FLAG-IM (Mann-Whitney test $P = 0.009$). Among patients who achieved a CR there was a trend toward a longer median time to platelet recovery with FLAG-IM (42 days, range 26–110) than FLAG-I (41 days, range 30–48) ($P = 0.097$), and nearly half of all patients responding (48% of responses were CRps) to FLAG-IM did not recover their platelets (Table IV). Febrile neutropenia was universal in both groups, and there was a trend toward more fungal infections in the FLAG-IM arm (predominately due to candidal species). While grade 3/4 hepatoxicity was comparable, three patients (15%) with prior allogeneic stem cell transplants (two matched sibling and one unrelated donor transplant) died in the FLAG-IM group from VOD. The treatment-related mortality was 35% for FLAG-I and 23% for FLAG-IM cohorts.

Discussion

This large, single-institution retrospective study of AML salvage therapy contrasted outcomes achieved with FLAG-I and FLAG-IM. The patients were well balanced between the treatment groups for prognostically significant variables with few exceptions; there was a trend toward more unfavorable cytogenetics in the FLAG-I group (57% vs. 35%) and more therapy-related disease in the FLAG-IM group (4% vs. 14%). ORR in both groups was greater than 50%, but there was a trend toward more CRps in the FLAG-IM group, where they accounted for nearly 50% of the responses. The patients who received G-CSF concurrent with FLAG-I had a higher ORR, whereas a more modest, nonstatistically significant difference was seen with FLAG-IM.

FLAG-I had numerically superior median DOR, EFS, and OS, but none of these comparisons were statistically significant. Regardless of the regimen, patients achieving a CR, when compared with those attaining a CRp, had improved

survival. Concurrent administration of G-CSF with FLAG-I significantly improved median EFS and median OS; similar modest trends were seen in the FLAG-IM group. When considered regardless of chemotherapy regimen, patients who received concurrent chemotherapy and G-CSF had superior outcomes when compared with those who received chemotherapy followed by G-CSF. These findings may be explained by the imbalance of adverse prognostic factors in the sequential and concurrent G-CSF FLAG-I groups and the small sample size of this study. Alternatively, these findings may suggest a clinically significant priming effect with concurrent G-CSF, as others have reported [14–16].

FLAG-IM was significantly more toxic than FLAG-I. The durations of neutropenia and thrombocytopenia were longer with FLAG-IM, and 15% of the patients (3/20) treated with FLAG-IM who had received a prior allogeneic stem cell transplant developed fatal VOD. Patients who received FLAG-IM also received two additional doses of idarubicin, which may have contributed to the increased toxicity. Our experience suggests a lack of benefit of adding GO (at this dose and schedule) to FLAG-I salvage chemotherapy for AML.

Why did the addition of GO, a drug with significant single-agent activity in AML, fail to improve outcomes? [21] OS in this study was associated with the quality of remission in the entire group and within each regimen. The numeric advantage in OS, EFS, and DOR for patients receiving FLAG-I was possibly related to the higher percentage of patients achieving a CR as opposed to a CRp. Similarly, in the randomized study of mitoxantrone, etoposide, and cytarabine (MEC) ± lintuzumab (an unconjugated anti-CD33 monoclonal antibody), the authors reported that patients achieving a CRp had inferior outcomes when compared with those achieving a CR [18]. Taksin et al. [24] also observed a trend toward shorter disease-free survival in patients achieving CRp with fractionated low-dose GO.

CD33 is highly expressed on the majority of AML blasts and normal CFU-GEMMs, BFU-Es, and CFU-GMs [17,25]. Both in vitro and in vivo evidence suggest that G-CSF can sensitize AML blasts to GO and it may also sensitize normal progenitors to GO [14–16,26,27]. In contrast to our report, Chevallier et al. [24] did not administer G-CSF prior to GO (9 mg/m^2), and a much lower fraction of CRps was observed. Although it is plausible that G-CSF sensitized normal progenitors to GO and increased toxicity, alternative hypotheses do exist. Only a prospective, randomized trial can answer whether GO added to FLAG-I will be beneficial or harmful to patients with relapsed/refractory AML.

Our results with FLAG-I compared with concurrent G-CSF were favorable to other regimens for relapsed/refractory AML previously published [4–8,29,30] (Table V). More than 50% of our patients received FLAG-I as 2nd or higher order salvage. Previous studies have reported CR rates of $<$10% with 2nd- and 3rd-line salvage regimens [4,31]. Our results with FLAG-I are similar to those reported by Pastore et al. [29], but the patient populations were markedly different. They used sequential G-CSF, and all patients were in either first relapse (80%) or had primary refractory disease (20%). It is possible that G-CSF priming allowed us to overcome the unfavorable patient characteristics in our cohort to achieve similar results. Our results add to the growing in vitro and in vivo evidence suggesting the efficacy of priming.

Others have reported CR rates from 14 to $>$50% with a wide variety of salvage regimens and patient populations with median OS rarely exceeding 1 year [4–8]. Much of the heterogeneity seen in these reports is likely due to differences in the patient populations and limited numbers of patients studied. Randomized trials are needed to define the optimal salvage regimens for AML.

Our study is limited by its retrospective, nonrandomized design. The comparisons between regimens are hypothesis generating only. It is possible that variables that were not captured in the chart review were imbalanced between the groups, such as performance status and comorbidities.

In conclusion, this large, single-institution retrospective study failed to show a benefit with the addition of GO at 9 mg/m^2 on Day 8 to FLAG-I salvage therapy in refractory/relapsed AML. These results do support the use of FLAG-I, particularly with G-CSF given concurrently, as an extremely effective salvage regimen for patients with relapsed/refractory AML. GO may be beneficial when administered with chemotherapy in alternative settings, doses, and schedules such as front-line therapy, low-dose fractionated schedules, or in combination with novel agents.

TABLE IV. Toxicity Data with FLAG-I and FLAG-IM

	FLAG-I	FLAG-IM	*P*-value
Median days until ANC $>$1,000	27 (21–44 days)	33 (18–62 days)	0.009 (Mann-Whitney)
Median days until Plts $>$100,000	41 (30–48 days)	42 (26–110 days)	0.097 (*T*-test with Welch's correction)
Grade ¾ ALT	3 (13%)	9 (19%)	
Grade ¾ AST	3 (13%)	6 (13%)	
Grade ¾ Bilirubin	5 (22%)	6 (13%)	
Grade 5 VOD	0	3 (6%)	
Documented fungal infection	2 (9%)	9 (19%)	0.484 (Fisher's exact)

ANC, absolute neutrophil count; Plts, platelets; VOD, veno-occlusive disease.

TABLE V. Comparison of Various AML Salvage Regimens

Regimen	*N*	Median age	%CR1 less than 1 year	Prior allo (%)	Poor-risk cytogenetics (%)	CR (%)	CRp (%)	Median DOR/EFS (months)	Median OS (months)
FLAG-I	23	48	60	43	57	39	13	16.8/7.4	8.8
FLAG-IM	48	47	67	42	35	29	27	8.3/4.1	5.0
IDAC [4]	62	NR	66	0	29	40	NR	NR	4.5
HDAC [4]	52					40	NR		
CLAG-M [8]	114	45	92	4	25	58	NR	17.0	9.0
MIDAM [28]	62	56	37	3	18	50	13	NR/4.4	9.5
FLAG-IDA [29]	46	41	100	4	33	52	NR	12.0/NR	11.0
MEC [7]	32	24	NR	19	NR	66	NR	4.0/NR	9.0
MEC [6]	50	37	NR	0	NR	68	NR	12.0/6.0	9.0
MEC [15]	97	55	100	6	NR	23	5	NR	8.0
Clofarabine [20]	31	54	52	3	29	55	13	6.0/NR	6.0
Clo + AraC [19]	25	59	55	NR	NR	24	17	NR	5.5

N, number of patients; IDAC, intermediate-dose cytarabine; HDAC, high-dose cytarabine; CR, complete remission; CRp, complete remission with incomplete platelet recovery; EFS, event-free survival; OS, overall survival; DOR, duration of response; NR, not reported.

Methods

Patients and salvage therapy. This retrospective study was approved by the Institutional Review Board at Washington University. All patients who received inpatient fludarabine and cytarabine between January 1, 2001, and July 31, 2008, at the Washington University were identified through a pharmacy database search. The patients' charts were reviewed and data were extracted by two of the authors, with a third author resolving any discrepancies. The patients who were 18 years of age and older were eligible if they received FLAG-I (fludarabine 25 mg/m^2 IV, Days 1–5; cytarabine 2000 mg/m^2 IV, Days 1–5; idarubicin 12 mg/m^2, Days 1–3) or FLAG-IM (fludarabine 25 mg/m^2 IV, Days 1–5; cytarabine 2000 mg/m^2 IV, Days 1–5; idarubicin 12 mg/m^2, Days 1–5; GO 9 mg/m^2 on Day 8) for relapsed or refractory AML. Two patients in the FLAG-I group received five doses of idarubcin and one patient received two doses of idarubicin. The use of G-CSF was variable, that is, 70% (16/23) of the patients in the FLAG-I group received G-CSF concurrently with chemotherapy and 77% of patients in the FLAG-IM group received concurrent G-CSF. The remainder of the patients received sequential chemotherapy and G-CSF.

The patients who received a stem cell transplant less than 2 weeks after starting either regimen were excluded. The choice of salvage regimen was made at the discretion of the attending physician. Antifungal and antibacterial prophylaxes were administered at the discretion of the treating physician. The patients did not receive prophylaxis against VOD. The choice of postremission therapy was at the discretion of the attending physician. Cytogenetic risk groups were defined as previously described by Byrd et al. [32] with respect to OS. Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/reporting/ctc.html).

Responses. In accordance with the National Cancer Institute Working Group criteria (NCIWG), CR was defined as bone marrow blasts $<5\%$ with neutrophils $>1{,}000\ \mu l^{-1}$ and platelets $>100{,}000 \mu l^{-1}$; complete remission with incomplete platelet recovery (CRp) was defined with the same bone marrow and neutrophil criteria but without platelets $>100{,}000\ \mu l^{-1}$ [33]. The responses were defined based on morphology alone and not on cytogenetic or molecular studies. The ORR was calculated as the sum of the CR and CRp.

Statistical analysis. The primary end point of this study was the ORR of each regimen. Secondary endpoints were OS, EFS, DOR, and a safety analysis; OS, EFS, and DOR were defined according to the NCIWG criteria. The survival times were calculated from the first day of chemotherapy until death or date of last follow-up. Median OS, EFS, and DOR were determined by Kaplan-Meier estimates and compared by the log-rank test. Groups were compared with the Fisher's exact test or *t*-tests, as appropriate. All *P*-values are two-sided, and the *P*-values <0.05 were considered statistically significant.

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