Original Article

Reduced-Intensity Conditioning With Fludarabine and Busulfan Versus Fludarabine and Melphalan for Patients With Acute Myeloid Leukemia: A Report From the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

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BACKGROUND: Fludarabine plus busulfan (FB) and fludarabine plus melphalan (FM) are 2 widely used reduced-intensity conditioning (RIC) regimens for allogeneic hematopoietic stem cell transplantation (allo-SCT). **METHODS:** The current survey compared transplantation outcomes for a cohort of 394 acute myeloid leukemia (AML) patients given bone marrow or peripheral blood stem cells from human leukocyte antigen–identical siblings after FB (n = 218) or FM (n = 176). Patients given manipulated grafts and those given T-cell–depleting agents (anti-thymocyte globulins or alemtuzumab) were not included. **RESULTS:** At the time of transplantation, 266 patients (68%) were experiencing their first complete remission (CR), 69 (18%) were experiencing a later CR, and 59 (15%) had advanced disease. The incidences of acute and chronic graft-versus-host disease were similar in the 2 groups of patients. The 2-year relapse incidence (RI), nonrelapse mortality (NRM) rate, leukemia-free survival (LFS) rate, and overall survival (OS) rate were 31% ± 3%, 18% ± 3%, 51% ± 4%, and 54% ± 4%, respectively, for FB patients and 20% ± 3% ($P = .007$), 20% ± 3% ($P = .4$), 60% ± 4% ($P = .08$), and 62% ± 4% ($P = .2$), respectively, for FM patients. Among FB patients given intravenous busulfan (n = 81), the 2-year RI, NRM, LFS, and OS rates were 26% ± 5% ($P = .43$ vs FM patients), 25% ± 6% ($P = .18$), 49% ± 7% ($P = .07$), and 54% ± 7% ($P = .13$), respectively. In multivariate analyses, FM was associated with a lower RI (hazard ratio [HR], 0.5; $P = .01$) and a trend toward higher NRM (HR, 1.6; $P = .1$) with similar LFS (HR, 0.8; $P = .2$) and OS (HR, 0.9; $P = .6$). **CONCLUSIONS:** These results suggest that although FM provides better AML control than FB as an RIC regimen for allo-SCT, the 2 regimens provide similar survival. Multicenter randomized studies are needed to confirm these findings. ***Cancer* 2014;000:000-000.** © *2014 American Cancer Society.*

KEYWORDS: acute myeloid leukemia (AML), busulfan, fludarabine, graft-versus-host disease (GVHD), melphalan, reduced-intensity conditioning (RIC), transplantation.

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The European Group for Blood and Marrow Transplantation registry is a voluntary working group of more than 500 transplant centers; its participants are required once a year to report all consecutive stem cell transplants and follow-up. The list of institutions reporting data included in this study is provided in the supporting information.

Frédéric Baron wrote the article, designed the study, and interpreted the data. Myriam Labopin designed the study, analyzed and interpreted the data, and edited the article. Mohamad Mohty designed the study, interpreted the data, and edited the article. Arnon Nagler participated in the study collection and design, interpreted the data, provided clinical data, and edited the article. Andy Penike, Pavel Jindra, Boris Afanasyev, Miguel A. Sanz, and Eric Deconinck provided clinical data. All authors approved the final version of the article.

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INTRODUCTION

Despite major advances in the field such as the development of demethylating agents,[1] the outcome for older patients with acute myeloid leukemia (AML) fit for intensive chemotherapy has remained dismal.[2] Allogeneic hematopoietic stem cell transplantation (allo-SCT) after reduced-intensity conditioning (RIC) is increasingly recognized as a good treatment option for select patients with intermediate/high-risk AML who are unfit for classical myeloablative conditioning.[3-7] This approach, which relies mainly on immune-mediated graft-versus-tumor effects for leukemic eradication,[8-12] is feasible in patients with a good general status up to 75 years of age.[8,13,14]

Fludarabine with intermediate doses of busulfan (fludarabine plus busulfan [FB])[10] and fludarabine with intermediate doses of melphalan (fludarabine plus melphalan [FM])[9] are 2 widely used RIC regimens.[15-18] A prior single-center study reported by Shimoni et al[19] compared transplantation outcomes in a cohort of 151 patients with various hematological malignancies given grafts after FB (n = 72) or FM (n = 79). Although a higher proportion of patients with B-cell malignancies were given FM and a higher proportion of patients with myeloid malignancies were conditioned with FB, the study demonstrated more hematological and nonhematological toxicities, a higher incidence of nonrelapse mortality (NRM), and a lower relapse incidence (RI) in FM patients. Furthermore, among patients undergoing transplantation in complete remission (CR), overall survival (OS) was better for FB patients versus FM patients because of lower NRM.[19] The current survey compared FB and FM in a homogeneous cohort of 394 AML patients given grafts from human leukocyte antigen (HLA)–identical siblings. In an attempt at minimizing possible confounding factors, patients given manipulated grafts and those administered in vivo T-cell depletion (with anti-thymocyte globulin [ATG] or alemtuzumab) were not included. The main observations were that the FM regimen was associated with lower RI than FB and also with a trend for higher NRM. A similar suggestion of higher RI was also observed when only patients given intravenous busulfan were considered in the FB group (n = 81), although the difference no longer reached statistical significance, perhaps because of the lower statistical power due to the lower number of patients or because of the higher anti-AML activity of the intravenous formulation. Importantly, OS and leukemia-free survival (LFS) did not significantly differ between FB and FM patients.

MATERIALS AND METHODS

Data Collection

This survey was a retrospective study performed by the Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT). The EBMT registry is a voluntary working group of more than 500 transplant centers; its participants are required once a year to report all consecutive stem cell transplants and follow-up. The scientific board of the ALWP approved this study. The population selection criteria included primary or secondary AML, first allo-SCT from an HLA-identical sibling between 2000 and 2012, bone marrow or granulocyte colony-stimulating factor–mobilized peripheral blood stem cells as a stem cell source, and FB (with a total busulfan dose ranging from 7.1 to 8.9 mg/kg [oral] or from 6.0 to 6.9 mg/kg [intravenous]) or FM (with a total melphalan dose ranging from 130 to 150 mg/m^2). The population exclusion criteria included another chemotherapy drug or total body irradiation in the conditioning regimen and in vivo (ATG or alemtuzumab) or in vitro T-cell depletion. We elected to exclude matched unrelated donor allo-SCT recipients to avoid confounding factors for analyses comparing RI, NRM, and graft-versus-host disease (GVHD) between the 2 groups and because the vast majority of unrelated recipients received in vivo T-cell depletion with ATG or alemtuzumab. The grading of acute and chronic GVHD was performed with established criteria.[20] For the purpose of this study, all necessary data were prospectively collected according to EBMT guidelines and with EBMT minimum essential data forms.

Statistical Analyses

Data from all patients meeting the inclusion/exclusion criteria were included in the analyses. The start time was the date of transplantation for all endpoints. To evaluate RI, patients dying either from direct toxicity of the procedure or from any other cause not related to leukemia were censored. NRM was defined as death in CR. Patients were censored at the time of relapse or last follow-up. Cumulative incidence functions were used for RI and NRM in a competing risk setting because death and relapse were competing together.

For estimating the cumulative incidence of chronic GVHD, death was considered a competing event. OS and LFS rates were calculated with Kaplan-Meier estimates. Univariate analyses were performed with Gray's test for cumulative incidence functions and with the log-rank test for OS and LFS. Associations of patient and graft characteristics with transplantation outcomes (chronic GVHD, RI, NRM, LFS, and OS) were evaluated in multivariate analyses with Cox proportional hazards. The factors included in the Cox models were FM versus FB, CR versus no CR at transplantation, female donor to male

TABLE 1. Patient and Transplant Characteristics

	Flu-Bu (n = 218)[a]	Flu-Mel (n = 176)	P[b]
Patient age, median (range), y	58 (23-76)	54 (21-71)	<.001
Year of SCT, median (range)	2009 (2000-2012)	2007 (2000-2012)	.001
Recipient sex: male, n (%)	124 (57)	83 (47)	.06
Donor sex: male, n (%)	111 (51)	95 (54)	.6
Female donor/male recipient, n (%)	59 (27)	36 (20)	.05
Time from diagnosis to SCT, median, d	178	157	.12
Secondary AML, n (%)	23 (11)	8 (5)	.03
Status at transplantation, n (%)			
CR1	155 (71)	111 (63)	.05
CR2+	39 (18)	30 (17)	
Advanced	24 (11)	35 (20)	
Cytogenetics, n (%)			
Good risk[c]	9 (7)	9 (8)	.87
Intermediate risk[d]	99 (76)	82 (76)	
High risk[e]	23 (18)	17 (16)	
Not reported/failed	87	68	
CMV D−/R−, n (%)	19 (9)	32 (18)	.009
Stem cell source, n (%)			
G-CSF–mobilized peripheral blood stem cells	194 (89)	158 (90)	.8
Bone marrow	24 (11)	18 (10)	
Postgrafting immunosuppression, n (%)			
CSA alone	18 (8)	37 (21)	.001
CSA + MTX	134 (61)	83 (47)	
Other	66 (30)	56 (32)	
CSA+ MMF	42	53	
Tacrolimus + MMF	12	2	
Other	12	1	

Abbreviations: AML, acute myeloid leukemia; CMV, cytomegalovirus; CR1, first complete remission; CR2+, second or later complete remission; CSA, cyclosporine A; D−/R−, donor-seronegative/recipient-seronegative; Flu-Bu, fludarabine and busulfan reduced-intensity conditioning; Flu-Mel, fludarabine and melphalan conditioning; G-CSF, granulocyte colony-stimulating factor; MMF, mycophenolate mofetil; MTX, methotrexate; SCT, stem cell transplantation.

[a] This group included 137 patients given oral busulfan (with the total busulfan dose ranging from 7.1 to 8.9 mg/kg) and 81 patients given intravenous busulfan (with the total busulfan dose ranging from 6.0 to 6.9 mg/kg). The 81 patients included 59 patients in CR1, 15 patients in CR2+, and 7 patients with advanced disease at the time of transplantation.

[b] *P* values were calculated with χ^2 statistics for categorical variables and with the Mann-Whitney test for continuous variables.

[c] *Good risk* was defined as t(8;21), t(15;17), inv or del(16), or acute promyelocytic leukemia (these abnormalities only or combined with others).

[d] *Intermediate risk* was defined as all cytogenetics not belonging to the good- or high-risk categories (including trisomies).

[e] *High risk* was defined as 11q23 abnormalities, a complex karyotype, and abnormalities of chromosomes 5 and 7.

recipient versus other sex combinations, donor and recipient seronegativity for cytomegalovirus (CMV) versus other combinations, secondary AML versus primary AML, postgrafting immunosuppression with cyclosporine alone versus other, a year of transplantation more recent than the median (2008), and an age at transplantation greater than the median (56 years). All tests were 2-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with the SPSS 19 (SPSS, Inc, Chicago, IL) and R 2.13.2 software packages (R Development Core Team, Vienna, Austria).

RESULTS

Patients

Data from 394 patients were included. Their characteristics are given in Table 1. Briefly, the median patient age at transplantation was 56 years (range, 21-76 years). The median time from diagnosis to transplantation was 165 days. Among patients with cytogenetic data available at diagnosis (n = 239 or 61%), 8% had good-risk cytogenetics, 76% had intermediate-risk cytogenetics, and 17% had high-risk cytogenetics. Among FB patients (n = 218), 137 patients were given oral busulfan, and 81 were given intravenous busulfan (including 59 patients in their first CR, 15 patients in their second CR or a later CR, and 7 patients with advanced disease at the time of transplantation). In comparison with FB patients (n = 218), those treated with FM (n = 176) were younger (median age at transplantation, 54 vs 58 years; $P < .001$), underwent transplantation earlier and thus had longer follow-up (median follow-up, 42 vs 18 months; $P < .001$), were less likely to be male patients given grafts from female donors (20% vs 27%, $P = .05$), were less likely to have secondary AML (5% vs 11%, $P = .03$), had advanced disease more frequently (20% vs 11%, $P = .05$), were more frequently CMV-seronegative and given grafts from CMV-seronegative donors (18% vs 9%, $P = .009$), and were more likely to have received cyclosporine alone as GVHD prophylaxis (21% vs 8%, $P = .001$). Other characteristics such as the cytogenetic risk, source of stem cells, and interval from diagnosis to transplantation were similar between the 2 groups.

Engraftment and GVHD

Three FB patients but no FM patients failed to experience engraftment. The median time for reaching 500 neutrophils was 17 days (1-50 days) for FB patients and 14 days (9-43 days) for FM patients ($P < .001$), probably because of the more frequent use of methotrexate in FB patients. The proportions of patients with grade I, II, III, and IV acute GVHD among FB and FM patients were 12% and 14%, 14% and 16%, 5% and 7%, and 4% and 3%, respectively ($P = .7$). At 2 years, the cumulative incidence of chronic GVHD was 54% ± 4% for FB patients and 48% ± 4% for FM patients ($P = .15$). After adjustments for variables with different distributions for FB and FM, the incidence of chronic GVHD remained similar for FM

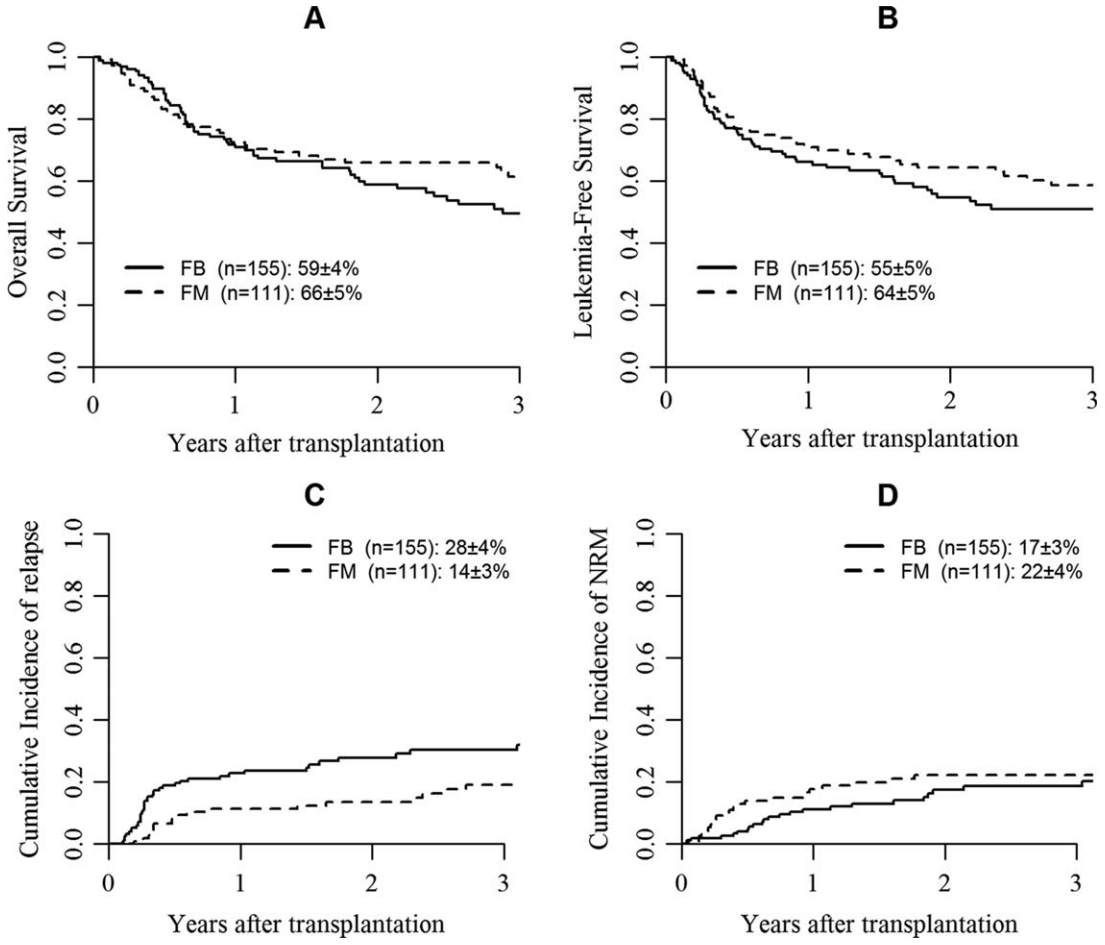

Figure 1. Outcomes of acute myeloid leukemia patients in their first complete remission who were given grafts after FB or FM: (A) overall survival ($P = .53$), (B) leukemia-free survival ($P = .19$), (C) relapse incidence ($P = .005$), and (D) NRM ($P = .21$). Percentages in the figures indicate 2-year results. FB indicates fludarabine plus busulfan; FM, fludarabine plus melphalan; NRM, nonrelapse mortality.

and FB patients (hazard ratio [HR], 0.8; 95% CI, 0.6-1.1; $P = .13$).

RI, NRM, LFS, and OS

Two-year RI, NRM, LFS, and OS rates for FB and FM patients were 31% ± 3% and 20% ± 3% ($P = .007$), 18% ± 3% and 20% ± 3% ($P = .4$), 51% ± 4% and 60% ± 4% ($P = .08$), and 54% ± 4% and 62% ± 4% ($P = .2$), respectively. Among FB patients given intravenous busulfan (n = 81), the 2-year RI, NRM, LFS, and OS rates were 26% ± 5% ($P = .4$ in comparison to FM patients), 25% ± 6% ($P = .18$), 49% ± 7% ($P = .07$), and 54% ± 7% ($P = .13$), respectively. When we restricted the analyses to patients undergoing transplantation in their first CR (n = 266; Fig. 1), the 2-year RI, NRM, LFS, and OS rates for FB and FM patients were 28% ± 4% and 14% ± 3% ($P = .005$), 17% ± 3% and 22% ± 4% ($P = .2$), 55% ± 5% and 64% ± 5% ($P = .2$), and 59% ± 4% and 66% ± 5% ($P = .5$), respectively. Among FB patients given intravenous busulfan (n = 59), the 2-year RI, NRM, LFS, and OS rates were 22% ± 6% ($P = .4$ versus FM patients), 23% ± 7% ($P = .5$), 55% ± 8% ($P = .2$), and 60% ± 7% ($P = .4$), respectively.

In univariate analyses using data from all included patients (Table 2), secondary AML versus primary AML was associated with higher NRM ($P = .02$), whereas advanced disease at transplantation was associated with higher RI ($P < .001$), which translated into lower LFS ($P = .003$) and OS ($P = .01$). Furthermore, CMV-seronegative patients given grafts from CMV-seronegative donors had lower NRM ($P = .01$). Finally, patients given cyclosporine A only as GVHD prophylaxis had better LFS ($P = .05$) and OS ($P = .04$).

TABLE 2. Univariate Analyses

			2-Year Results[a]			
		n	RI, %	NRM, %	LFS, %	OS, %
Age	<Median	197	26 ± 3	16 ± 2	57 ± 4	61 ± 4
	>Median	197	26 ± 3	21 ± 3	53 ± 4	55 ± 4
	P		.86	.39	.68	.6
Year of Tx	<Median	205	24 ± 3	20 ± 3	55 ± 3	58 ± 3
	>Median	189	29 ± 4	15 ± 3	56 ± 4	60 ± 4
	P		.32	.41	.73	.93
Patient sex	Male	207	29 ± 3	19 ± 3	52 ± 4	55 ± 4
	Female	187	23 ± 3	18 ± 3	59 ± 4	61 ± 4
	P		.22	.86	.24	.37
Female donor to male recipient	No	297	25 ± 3	16 ± 2	58 ± 3	61 ± 3
	Yes	95	28 ± 5	28 ± 5	44 ± 6	48 ± 6
	P		.58	.15	.18	.17
Secondary AML	No	363	27 ± 2	17 ± 2	56 ± 3	59 ± 3
	Yes	31	20 ± 7	33 ± 9	47 ± 10	47 ± 10
	P		.71	.02	.1	.06
Status at Tx	CR1	266	22 ± 3	19 ± 3	59 ± 3	62 ± 3
	CR2+	69	26 ± 6	19 ± 5	54 ± 7	53 ± 7
	Active disease	59	46 ± 7	14 ± 5	40 ± 7	46 ± 7
	P		.0004	.72	.003	.01
SC source	BM	42	36 ± 8	18 ± 6	46 ± 8	51 ± 8
	PBSCs	352	25 ± 2	18 ± 2	56 ± 3	59 ± 3
	P		.29	.93	.34	.42
CMV D−/R−	No	330	25 ± 2	20 ± 2	55 ± 3	57 ± 3
	Yes	51	26 ± 7	4 ± 3	70 ± 7	73 ± 7
	P		.81	.01	.12	.07
GVHD prevention	CSA	55	18 ± 6	10 ± 4	72 ± 6	76 ± 6
	CSA + MTX	217	28 ± 3	19 ± 3	53 ± 4	57 ± 4
	Other	122	27 ± 4	22 ± 4	51 ± 5	53 ± 5
	P		.31	.23	.05	.04

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; CR1, first complete remission; CR2+, second or later complete remission; CSA, cyclosporine A; D−/R−, donor-seronegative/recipient-seronegative; GVHD, graft-versus-host disease; LFS, leukemia-free survival; MTX, methotrexate; NRM, nonrelapse mortality; OS, overall survival; PBSC, peripheral blood stem cell; RI, relapse incidence; SC, stem cell; Tx, allogeneic hematopoietic cell transplantation. Data on female donor to male recipient were missing in 2 cases while data on CMV D−/R− were missing in 13 cases.

[a] Censored at 2 years.

After adjustments for variables having different distributions between FB and FM and associated with $P < .05$ in univariate analyses, RI remained significantly lower for FM patients versus FB patients (HR, 0.5; 95% CI, 0.3-0.8; $P = .01$), whereas there was a suggestion of higher NRM for FM patients versus FB patients (HR, 1.6; 95% CI, 0.9-2.7; $P = .1$). This translated into similar progression-free survival (HR, 0.8; 95% CI, 0.6-1.2; $P = .2$) and OS (HR, 0.9; 95% CI, 0.6-1.3; $P = .6$) for FM and FB patients. Other factors influencing transplantation outcomes in multivariate analyses included the following: transplantation for advanced leukemia was associated with higher RI (HR, 0.3; 95% CI, 0.2-0.5; $P < .001$) and lower LFS (HR, 0.5; 95% CI, 0.3-0.8; $P = .001$) and OS (HR, 0.5; 95% CI, 0.4-0.8; $P = .006$); CMV-seronegative patients given grafts from CMV-seronegative donors were associated with lower NRM (HR, 0.2; 95% CI, 0.5-0.9; $P = .03$), which translated into better OS (HR, 0.5; 95% CI, 0.3-1.0; $P = .04$); cyclosporine A only as GVHD prophylaxis was associated with better LFS (HR, 0.5; 95% CI, 0.3-0.9; $P = .03$) and OS (HR, 0.5; 95% CI, 0.3-1.0; $P = .04$); and secondary AML was associated with higher NRM (HR, 2.5; 95% CI, 1.2-5.3; $P = .01$; Table 3).

RI, NRM, LFS, and OS for FB patients and FM patients according to their disease status at transplantation are shown in Figures 1 and 2.

DISCUSSION

This study compared 2 widely used RIC regimens in a relatively large cohort of AML patients given grafts from HLA-identical siblings and no in vivo T-cell depletion (to avoid confounding factors for analyses comparing relapse and GVHD between the 2 groups[21]). The main observation was that the FM regimen was associated with a lower RI, and this was in agreement with prior observations by Shimoni et al[19] in a cohort of patients undergoing transplantation for various hematological malignancies. This is

TABLE 3. Cox Models Including Variables Having Different Distributions and Associated With $P < .05$ According to Univariate Analyses

		P	Hazard Ratio	95% Confidence Interval
Leukemia-free survival	FM vs FB	.23	0.81	0.57-1.15
	CR vs advanced[a]	**.001**	0.50	0.33-0.76
	Female donor to male recipient	.32	1.20	0.83-1.74
	Year of transplantation > median (2008)	.78	1.05	0.75-1.48
	Age at transplantation > median	.84	0.97	0.69-1.36
	CMV D−/R− vs others	.08	0.61	0.35-1.06
	Secondary AML	.56	1.19	0.67-2.11
	CSA alone vs other	**.03**	0.52	0.28-0.95
Overall survival	FM vs FB	.64	0.92	0.63-1.32
	CR vs advanced[a]	**.006**	0.54	0.35-0.84
	Female donor to male recipient	.24	1.26	0.86-1.84
	Year of transplantation > median (2008)	.93	0.98	0.69-1.41
	Age at transplantation > median	.82	0.96	0.67-1.37
	CMV D−/R− vs others	**.04**	0.52	0.28-0.96
	Secondary AML	.30	1.37	0.76-2.49
	CSA alone vs other	**.04**	0.52	0.27-0.97
Cumulative incidence of relapse	FM vs FB	**.01**	0.51	0.32-0.82
	CR vs advanced[a]	**.000005**	0.31	0.19-0.52
	Female donor to male recipient	.73	1.09	0.67-1.77
	Year of transplantation > median (2008)	.33	1.24	0.80-1.93
	Age at transplantation > median	.44	0.84	0.54-1.31
	CMV D−/R− vs others	.82	0.93	0.50-1.73
	Secondary AML	.28	0.59	0.23-1.52
	CSA alone vs other	.27	0.66	0.31-1.39
Cumulative incidence of nonrelapse mortality	FM vs FB	.10	1.57	0.92-2.68
	CR vs advanced[a]	.61	1.23	0.55-2.77
	Female donor to male recipient	.18	1.47	0.84-2.55
	Year of transplantation > median (2008)	.52	0.84	0.49-1.44
	Age at transplantation > median	.56	1.17	0.69-1.99
	CMV D−/R− vs others	**.03**	0.21	0.05-0.89
	Secondary AML	**.01**	2.54	1.22-5.29
	CSA alone vs other	.07	0.38	0.14-1.07
Cumulative incidence of chronic graft-versus-host disease	Flu-Mel vs Flu-Bu	.13	0.77	0.55-1.08
	CR vs advanced[a]	.11	0.69	0.44-1.09
	Female donor to male recipient	.72	1.07	0.74-1.53
	Year of transplantation > median (2008)	.53	0.90	0.65-1.25
	Age at transplantation > median	.56	1.10	0.79-1.53
	CMV D−/R− vs others	**.03**	0.55	0.32-0.95
	Secondary AML	.46	1.26	0.68-2.30
	CSA alone vs other	**.04**	0.59	0.35-0.97

Abbreviations: AML, acute myeloid leukemia; CMV, cytomegalovirus; CR, complete remission; CSA, cyclosporine A; D−/R−, donor-seronegative/recipient-seronegative; FB, fludarabine plus busulfan; Flu-Bu, fludarabine and busulfan reduced-intensity conditioning; Flu-Mel, fludarabine and melphalan conditioning; FM, fludarabine plus melphalan.
Bolded values are significant.
[a] *Advanced* indicates not in CR.

in line with the fact that FM might be more intense than FB. Indeed, prior studies comparing outcomes of AML patients receiving grafts after myeloablative or RIC regimens observed a higher RI in the latter group,[22] and this demonstrates the impact on RI of the dose intensity in the conditioning regimen for allo-SCT in AML patients. However, as observed in analyses comparing myeloablative and RIC regimens, the lower RI observed in our FM patients did not translate into better OS because of a suggestion of higher NRM in FM patients versus FB patients, and this was in agreement with Shimoni et al.[19] Other potential explanations for the higher risk of relapse in FB patients might be a possibly inherent higher anti-AML potential of melphalan in comparison with busulfan and the possibility that some patients (especially those given oral busulfan) might have been underexposed to busulfan because of the well-demonstrated variability of busulfan pharmacokinetics.[23] Interestingly, a similar suggestion for higher RI was also observed when only patients given intravenous busulfan were considered in the FB group (n = 81), although the difference no longer reached statistical significance, perhaps because of the lower statistical power due to lower number of patients or because of the higher anti-AML activity of the intravenous formulation.

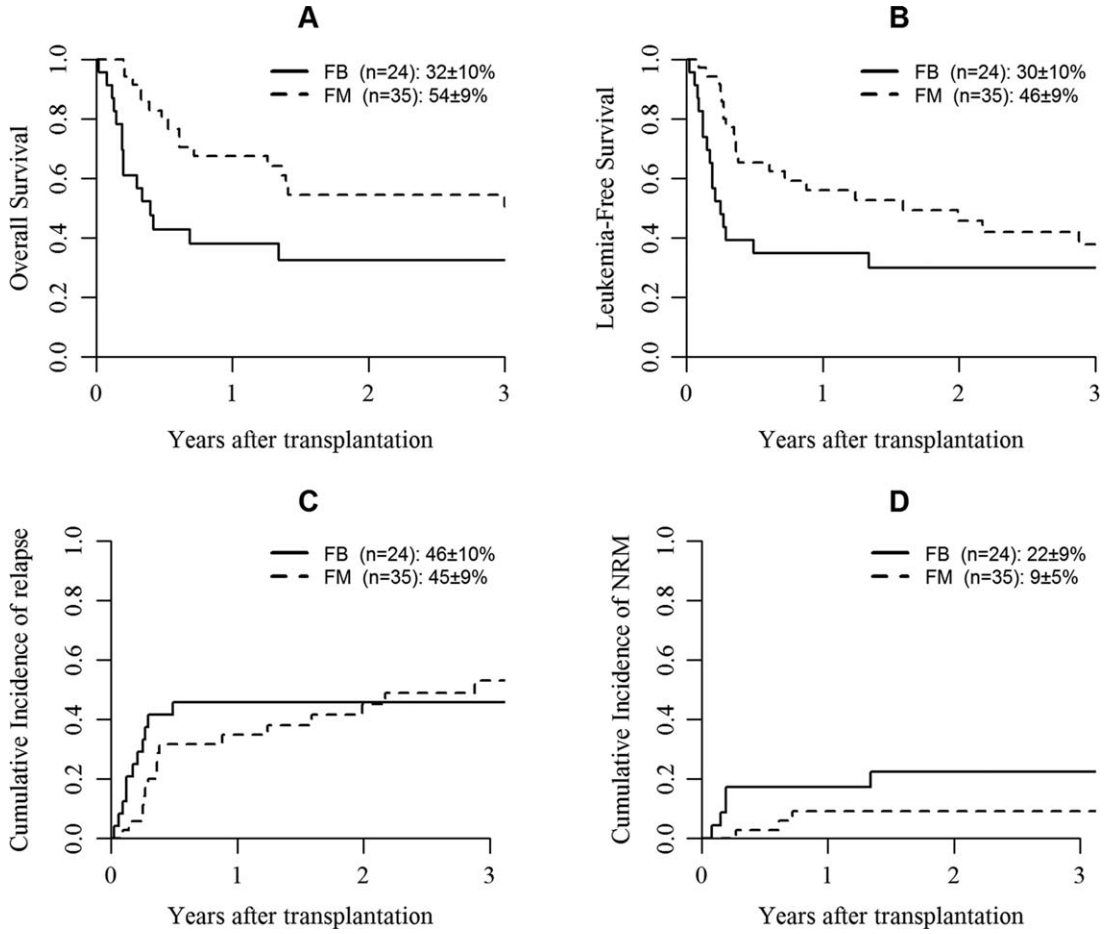

Figure 2. Outcomes of acute myeloid leukemia patients not in complete remission at transplantation who were given grafts after FB or FM: (A) overall survival ($P = .02$), (B) leukemia-free survival ($P = .03$), (C) relapse incidence ($P = .51$), and (D) NRM ($P = .16$). Percentages in the figures indicate 2-year results. FB indicates fludarabine plus busulfan; FM, fludarabine plus melphalan; NRM, nonrelapse mortality.

Although the difference between the 2 groups did not reach statistical significance, 3 FB patients but none of the FM recipients experienced graft rejection in the current study. This observation is consistent with prior observations by Valcarcel et al[24] and Shimoni et al[19]: the FB patients were more likely to have a mixed chimera early after transplantation than those treated with FM because of the previously observed association between low donor chimerism levels and a higher incidence of graft rejection.[25]

In contrast to what was observed by Shimoni et al[19] (a higher incidence of GVHD in FM patients), the incidences of acute and chronic GVHD were similar for the FB and FM patients in the current study. This apparent discrepancy between the 2 studies might be due to the fact that the current survey included only patients given grafts from HLA-identical siblings, whereas Shimoni et al's study also included patients given grafts from HLA-matched or HLA-mismatched unrelated donors.

Another finding of the current study was that the use of cyclosporine alone as GVHD prophylaxis was associated with better LFS and OS. Although this observation should be taken with caution because of the low number of patients (n = 55) given cyclosporine alone as GVHD prophylaxis in the current survey, it is in agreement with recent data from Rubio et al[26] for patients given grafts from HLA-identical siblings after ATG and intravenous busulfan–based RIC. Furthermore, in agreement with other recent observations from our group for a larger cohort of patients undergoing transplantation after myeloablative conditioning or RIC,[27] CMV-seronegative patients given grafts from CMV-seronegative donors had lower NRM and better OS in the current series.

In summary, these data suggest that although FM provides better AML control than FB as an RIC regimen for allo-SCT, the 2 combinations lead to similar survival rates. Even though that the current survey included a relatively large cohort of patients, multicenter randomized studies are needed to confirm these results. Ideally, these studies should use a fixed dose of busulfan area under the curve (AUC) in the FB arm.

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