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original reports abstract

Augmented Reduced-Intensity Regimen Does N Improve Postallogeneic Transplant Outcomes in Acute Myeloid Leukemia

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PURPOSE Reduced-intensity conditioning (RIC) regimens have extended the curative potential of allogeneic stem-cell transplantation to older adults with high-risk acute myeloid leukemia (AML) and myelodysplasia (MDS) but are associated with a high risk of disease relapse. Strategies to reduce recurrence are urgently required. Registry data have demonstrated improved outcomes using a sequential transplant regimen, fludarabine/amsacrine/cytarabine-busulphan (FLAMSA-Bu), but the impact of this intensified conditioning regimen has not been studied in randomized trials.

PATIENTS AND METHODS Two hundred forty-four patients (median age, 59 years) with high-risk AML (n = 164) or MDS (n = 80) were randomly assigned 1:1 to a fludarabine-based RIC regimen or FLAMSA-Bu. Pretransplant measurable residual disease (MRD) was monitored by flow cytometry (MFC-MRD) and correlated with outcome.

RESULTS There was no difference in 2-year overall survival (hazard ratio 1.05 [85% CI, 0.80 to 1.38] $P = .81$) or cumulative incidence of relapse (CIR) (hazard ratio 0.94 [95%CI, 0.60 to 1.46] $P = .81$) between the control and FLAMSA-Bu arms. Detectable pretransplant MFC-MRD was associated with an increased CIR (2-year CIR 41.0% *v* 20.0%, $P = .01$) in the overall trial cohort with a comparable prognostic impact when measured by an unsupervised analysis approach. There was no evidence of interaction between MRD status and conditioning regimen intensity for relapse or survival. Acquisition of full donor T-cell chimerism at 3 months abrogated the adverse impact of pretransplant MRD on CIR and overall survival.

CONCLUSION The intensified RIC conditioning regimen, FLAMSA-Bu, did not improve outcomes in adults transplanted for high-risk AML or MDS regardless of pretransplant MRD status. Our data instead support the exploration of interventions with the ability to accelerate acquisition of full donor T-cell chimerism as a tractable strategy to improve outcomes in patients allografted for AML.

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INTRODUCTION

Allogeneic stem-cell transplantation (allo-SCT) is an increasingly important treatment modality in adults with acute myeloid leukemia (AML) and myelodysplasia (MDS). The advent of reduced-intensity conditioning (RIC) regimens has permitted the extension of a potentially curative graft-versus-leukemia (GVL) effect to older patients in whom transplantation using myeloablative conditioning (MAC) is precluded by excess toxicity.[1] Indeed, the majority of allografts performed in the United States now use an RIC regimen.

In patients with AML and MDS, the use of an RIC regimen is associated with a higher rate of disease relapse than is observed with myeloablative transplants.[2] Despite the fact that relapse remains the dominant cause of transplant failure, no effective strategies have yet been identified to reduce the risk of disease recurrence after an RIC allograft. Indeed, although a multiplicity of RIC regimens have been developed, most using a fludarabine backbone,[3,4] there have been very few randomized studies to inform choice of regimen, and as a result, clinical practice worldwide is heterogeneous. Single-arm studies using a sequential fludarabine/amasacrine/cytarabine regimen, in which amsacrine-based cytoreductive chemotherapy is delivered 7-14 days prior to a conventional RIC allograft incorporating either low dose total body irradiation or busulphan (Bu), have been reported to reduce the risk of relapse in high-risk AML.[5-7] However, despite the widespread adoption of this regimen in the management of high-risk AML, its benefits have never been examined in a randomized trial.

The presence of measurable residual disease (MRD) measured by flow cytometry, quantitative polymerase chain reaction, or more recently next-generation

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The FIGARO study is the first prospective trial to examine the impact of an intensified conditioning regimen (FLAMSA-Bu) alongside the impact of pretransplant flow cytometric measurable residual disease (MRD) on transplant outcome in patients allografted for acute myeloid leukemia (AML) or myelodysplasia (MDS).

Knowledge Generated

The results of FIGARO demonstrate that pretransplant flow cytometric MRD is correlated with an increased risk of disease relapse after a reduced-intensity allograft by both conventional and unsupervised MRD analyses. Random assignment to an intensified sequential conditioning regimen failed to improve transplant outcome regardless of pretransplant MRD status.

Relevance

Our data do not support the use of an intensified sequential conditioning regimen as a strategy to improve transplant outcome, regardless of pretransplant MRD status. The results further demonstrate the importance of flow cytometry-determined MRD as a pretransplant risk characteristic in patients with AML or high-risk MDS.

sequencing (NGS) is an important determinant of disease relapse in adults with AML treated with intensive chemotherapy.[8-15,16] Although retrospective studies have shown that the presence of pretransplant MRD is associated with an increased risk of relapse post-transplant,[17-30] the reported effect size varies widely and prospective studies addressing the prognostic value of pretransplant flow cytometric MRD, the most commonly used and widely applicable AML MRD technology, are lacking. Hourigan et al[31] recently reported that the presence of pretransplant MRD in the peripheral blood, determined by an innovative but currently research-restricted NGS strategy, was associated with an increase in relapse in recipients of RIC but not MAC regimens, but this study did not examine the impact of flow-determined pretransplant MRD on outcome.

The FIGARO trial compared the outcomes of patients with high-risk AML and MDS transplanted using an intensified FLAMSA-Bu regimen with those receiving a conventional fludarabine-based RIC regimen. The impact of flow cytometric MRD on transplant outcomes was prospectively determined in trial patients.

PATIENTS AND METHODS

Study Design

FIGARO, an open label phase II randomized trial, was performed in 20 UK transplant centers and recruited patients from October 2013 to February 2017. The trial Protocol (online only; EudraCT 2012-005538-12) was approved by the UK research ethics service, National Research Ethics Service (NRES). An independent data monitoring committee oversaw the trial. Patients were randomly assigned in a one-to-one ratio via a minimization algorithm stratified by underlying disease, cytogenetic risk group, disease status at transplant, intended control transplant regimen, age, and donor type.

Patients

Patients were eligible for trial entry if they had a WHO-defined diagnosis of AML or high-risk MDS, were undergoing their first allo-SCT from a matched sibling or unrelated donor, and had been deemed ineligible for a MAC regimen on the grounds of age or comorbidity. Patients were of age 22 to 75, had a Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI) score of 0-6, and were transplanted using peripheral blood– or bone marrow (BM)–derived stem cells from an HLA identical (HLA-A/-B/-C/-DRbeta1) matched sibling or ≥ 7/8 HLA-A/-B/-C/-DRbeta1 adult-unrelated donor. All patients with AML were in complete remissions (CR1 and CR2) or had primary refractory AML (defined by failure to achieve a morphological CR after two courses of induction chemotherapy). High-risk MDS was defined as patients with an International Prognostic Scoring System score of intermediate-1 with > 5% blasts or intermediate-2 or high risk who had < 5% blasts at the time of random assignment. Cytogenetic risk group was classified as described previously.[32]

Conditioning Regimens and GVHD Prophylaxis

Patients were randomly assigned 1:1 to a control arm determined by the investigator's choice of Flu/B_2/anti-thymocyte globulin (ATG), Flu/Mel/alemtuzumab (A), or Flu/Bu_2/A (details given in the Data Supplement, online only) versus an experimental arm of FLAMSA-Bu (Flu, cytarabine [araC] 2 g/m^2 once a day × 4 days, amsacrine [AMSA] 100 mg/m^2 once a day × 4 days, intravenous Bu total dose 11.2 mg/kg) and ATG 5 mg/kg over 3 days. Patients of age > 60 years received an adjusted FLAMSA-Bu regimen using a reduced dose of araC (1 g/m^2 once a day × 4 days) and Bu (8 mg/kg total). However, after the first 31 patients had received treatment on the experimental arm, additional safety information was published with regard to the FLAMSA-Bu regimen in patients of age ≥

60 years. The experimental regimen in the subsequent 77 patients was modified to Flu, araC 1 g/m^2 once a day $\times$ 4 days, AMSA 100 mg/m^2 once a day $\times$ 4 days, and Bu 6.4 mg/kg for those patients who were $>$ 60 years.

All patients received ciclosporin graft-versus-host-disease (GVHD) prophylaxis. Supportive care was according to institutional guidelines. All patients were formally reviewed at day + 100, 6, and 12 months post-transplant. BMs to determine remission status were reviewed at day + 42, and months 3, 6, 9, and 12 post-transplant. T-cell lineage chimerism was assessed at months 3, 6, 9, and 12 post-transplant.

MRD Quantitation

BMs for multiparameter flow cytometric (MFC) detection of MRD were obtained pretransplant (within 4 weeks of transplant) and at day + 42 post-transplant. Sample logistics, processing, and analysis strategy are provided in the Data Supplement. MFC-MRD analysis was performed centrally, using a standardized manual gating strategy that screened blasts for different-from-normal leukemia-associated immunophenotypes (LAIPs) and any previously identified baseline LAIPs when available. Samples were reported as MRD-negative if no baseline and/or different-from-normal LAIP cells could be quantitated above the limit of detection (approximately 0.02%-0.05%). The results were not reported to treating clinicians.

Recognizing the potential for variation in manual MFC-MRD analysis, an unsupervised approach was applied as an independent measurement of LAIPs. This incorporated (1) a multidimensional clustering algorithm to maximize information from the LAIP marker combinations and (2) statistical criteria to discriminate blast subpopulations that were immunophenotypically most aberrant (compared with reference ranges established from 40 control BMs) and above the limit of quantitation (Data Supplement). The analytic method, similar to standard different-from-normal MFC-MRD, did not require diagnostic samples. Unsupervised MFC-MRD percentages were higher than conventional MFC-MRD as the former summated all quantifiable nonoverlapping abnormal blast subpopulations from an antibody combination, whereas conventional MFC-MRD values are from a single LAIP. Concordance between methods was strongest at higher MRD levels (Data Supplement). The unsupervised MFC-MRD combined test criteria included results from a third antibody combination (stem and progenitor) in addition to standard LAIP markers; positivity required detection of aberrant blasts in at least two of the three antibody combinations (Data Supplement).

Outcomes

The primary outcome was overall survival (OS) defined on an intention-to-treat basis. A sensitivity analysis was conducted to assess OS in a per-protocol population. Secondary outcome measures included event-free survival (EFS), cumulative incidence of relapse (CIR), incidence of GVHD, and transplant-related mortality (TRM). Acute and chronic GVHD were scored according to published criteria.[33,34] Nonhematological grade 3-4 adverse events were classified according to Common Terminology Criteria for Adverse Events Version 4.0.

Statistical Analysis

The sample size was calculated on the basis of previously published data and clinical judgment. Assuming a 2-year OS in the control arm of 25%, to detect a 15% improvement in the experimental arm, a total of at least 214 patients (two-sided $\alpha = 0.15$ and $\beta = 0.16$) were required. To account for the likelihood that 10% of randomly assigned patients would not proceed to transplant, the trial aimed to recruit a minimum of 240 patients. Analysis was conducted in line with the predefined statistical analysis plan on the intention-to-treat population unless otherwise stated. Per-protocol population analysis was restricted to patients who had commenced the conditioning regimen. Standard analysis methods were employed as further outlined in the Data Supplement.

Additional analysis in the per-protocol populations was conducted to assess the effect on OS, CIR, and TRM of pretransplant MRD by the different MFC-MRD analysis methods and for various MRD thresholds. No adjustment for multiple testing was made within the MRD threshold analysis; however, the results are interpreted with caution and focused on identifying the highest level of discrimination from a range of significant results.

RESULTS

Enrollment

Of 255 patients screened for trial entry, 244 fulfilled eligibility criteria and were randomly assigned to receive trial therapy (Fig 1). Twenty-eight randomly assigned patients did not receive their allocated treatment (two deaths, 14 withdrawn because of clinical deterioration or patient or physician choice, and 12 relapses prior to transplant). Of the 108 patients who were transplanted on the control arm, 63 received Flu/B_2/ATG, 31 Flu/Mel/A, and 14 Flu/B_2/A. The median follow-up was 35 months. Patient and transplant characteristics of randomly assigned patients are summarized in Table 1. One hundred sixty-four patients had an initial diagnosis of AML of whom 154 were in CR1 or CR2 and nine had primary refractory AML at the time of random assignment. Eighty patients had high-risk MDS. The median age of the study population was 59 years (range, 22-75 years).

Survival

The 2-year OS was 58.8% in patients treated on the control arm and 60.9% in patients assigned to FLAMSA-Bu (hazard ratio [HR] 1.05 [85% CI, 0.80 to 1.38] log-rank *P* value = .81; Fig 2A). The EFS at 2 years was 48.7% in the

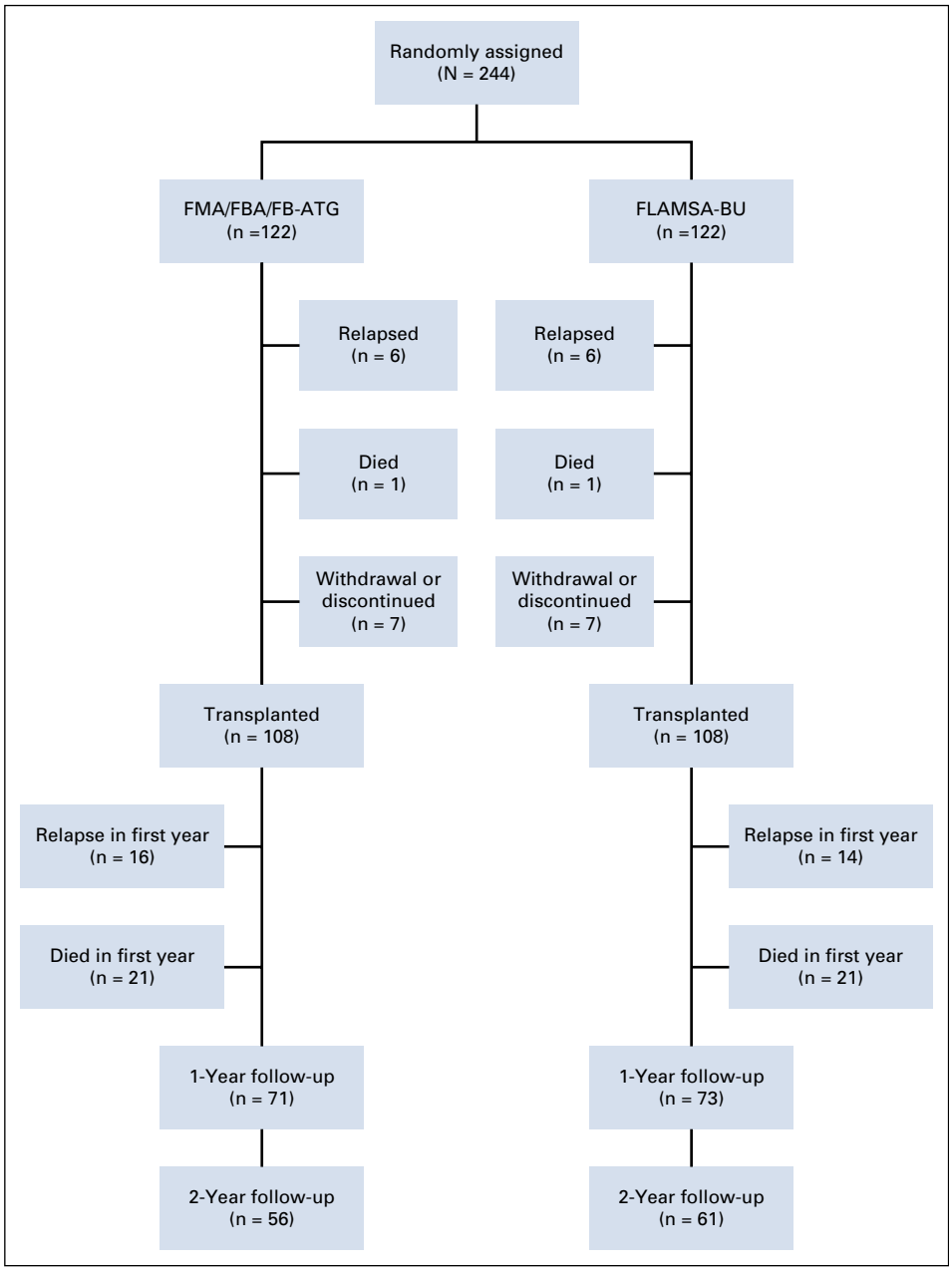

FIG 1. Trial CONSORT diagram. FBA, fludarabine/busulphan/alemtuzumab; FB-ATG, fludarabine/busulphan/antithymocyte globulin; FMA, fludarabine/melphalan/alemtuzumab; FLAMSA-Bu, fludarabine/amsacrine/cytarabine-busulphan.

control arm versus 54.2% for FLAMSA-Bu (HR 0.96 [95% CI, 0.68 to 1.35] log-rank *P* value = .82; Fig 2B). Two-year OS and EFS were similar between both arms in a per-protocol sensitivity analysis (Data Supplement). In the preplanned subgroup analysis, no survival benefit of the FLAMSA-Bu regimen was evident in patients diagnosed with either AML or MDS, in patients with AML according to cytogenetic risk category, or in patients under or over 60 years of age. No difference in outcome was evident when analysis was restricted to patients over 60 in the experimental arm after adoption of the protocol amendment.

Transplant-Related Mortality, GVHD, and Disease Relapse

The 1-year TRM was 16.8% in the control arm and 20.5% in the experimental arm (HR 1.20 [95% CI, 0.68 to 2.13], Gray's test *P* value = .53). There were no statistically significant differences in the cumulative incidences of acute GVHD at day + 100 (with death and relapse as competing events) between the control and FLAMSA-Bu arms (grades 2-4, 10.1% *v* 8.3%, Gray's test *P* value = .93; grade 3-4, 1.7% *v* 5.8%, Gray's test *P* value = .23). The cumulative incidence of chronic GVHD at 1 year was

TABLE 1. Patient Characteristics by Random Assignment

Characteristic		Control (FMA/FBA/FB-ATG) n (%)	FLAMSA-BU n (%)	Overall n (%)
Age	≤ 60 years	71 (58)	69 (57)	140 (57)
	> 60 years	51 (42)	53 (43)	104 (43)
Sex	Female	51 (42)	48 (39)	99 (41)
	Male	71 (58)	74 (61)	145 (59)
HCT-comorbidity index	≤ 2	66 (57)	79(68)	145 (62)
	≥ 3	33 (28)	18 (15)	51 (22)
	Unknown	23(19)	25(20)	48 (20)
Diagnosis	AML	82 (67)	82 (67)	164 (67)
	MDS	40 (33)	40 (33)	80 (33)
AML cytogenetic risk	Adverse	24 (29)	26 (32)	50 (30)
	Intermediate	53 (65)	52 (63)	105 (64)
	Favourable	4 (5)	3 (4)	7 (4)
	Unknown	1 (1)	1 (1)	2 (1)
AML disease status	CR1 or CR2	77 (94)	77 (94)	154 (94)
	Primary refractory	5 (6)	4 (5)	9 (5)
	Unknown	0	1 (1)	1 (1)
AML *FLT3*-ITD	Yes	20 (24)	23 (28)	43 (26)
	No	49 (60)	52 (63)	101(62)
	Unknown	13 (16)	7 (9)	20 (12)
AML-mutated *NPM1*	Yes	17 (21)	23 (28)	40 (24)
	No	50 (61)	53 (65)	103 (63)
	Unknown	15 (18)	6 (7)	21 (13)
MDS IPSS	≤ 2	33 (83)	33 (83)	66 (83)
	> 2	0 (0)	2 (5)	2 (3)
	Unknown	7 (18)	5 (13)	12 (15)
Transplant				
Donor type	Sibling	25 (20)	24 (20)	49 (20)
	Unrelated	97 (80)	98 (80)	195 (80)
Graft type	PBSCs	101 (94)	107 (99)	208 (96)
	BM	7 (6)	1 (1)	8 (4)
Pretransplant MFC-MRD status	Positive	43 (35)	52 (43)	95(39)
	Negative	46 (38)	35 (29)	81 (33)
	Inadequate	14 (11)	13 (11)	27 (11)
	No sample	19 (16)	22 (18)	41 (17)

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; FBA, fludarabine/busulphan/alemtuzumab; FB-ATG, fludarabine/busulphan/antithymocyte globulin; FLAMSA-Bu, fludarabine/amsacrine/cytarabine-busulphan; FMA, fludarabine/melphalan/alemtuzumab; HCT-CI, hematopoietic cell transplant-comorbidity index; IPSS, International Prognostic Scoring System; ITD, internal tandem duplication; PBSC, peripheral blood stem cells; MDS, myelodysplasia; MFC, multiparameter flow cytometric; MRD, minimal residual disease.

25.2% and 19.2% in the control and FLAMSA-Bu arms, respectively (Gray's test P value = .53). Twenty-eight patients received DLI in the control arm (19 for mixed chimerism from day + 115, nine for relapse) and 14 in the experimental arm (10 for mixed chimerism from day + 104, four for relapse) (Data Supplement). There was no evidence of DLI impact on the incidence of GVHD with eight and five episodes of chronic GVHD post-DLI in the control and FLAMSA-Bu arms, respectively.

The 2-year CIR was 29.5% in patients in the control arm and 26.7% in patients assigned FLAMSA-Bu (Fig 2C) (Gray's test P value = .81). There was no statistically significant effect of disease (AML *v* MDS), patient age, and

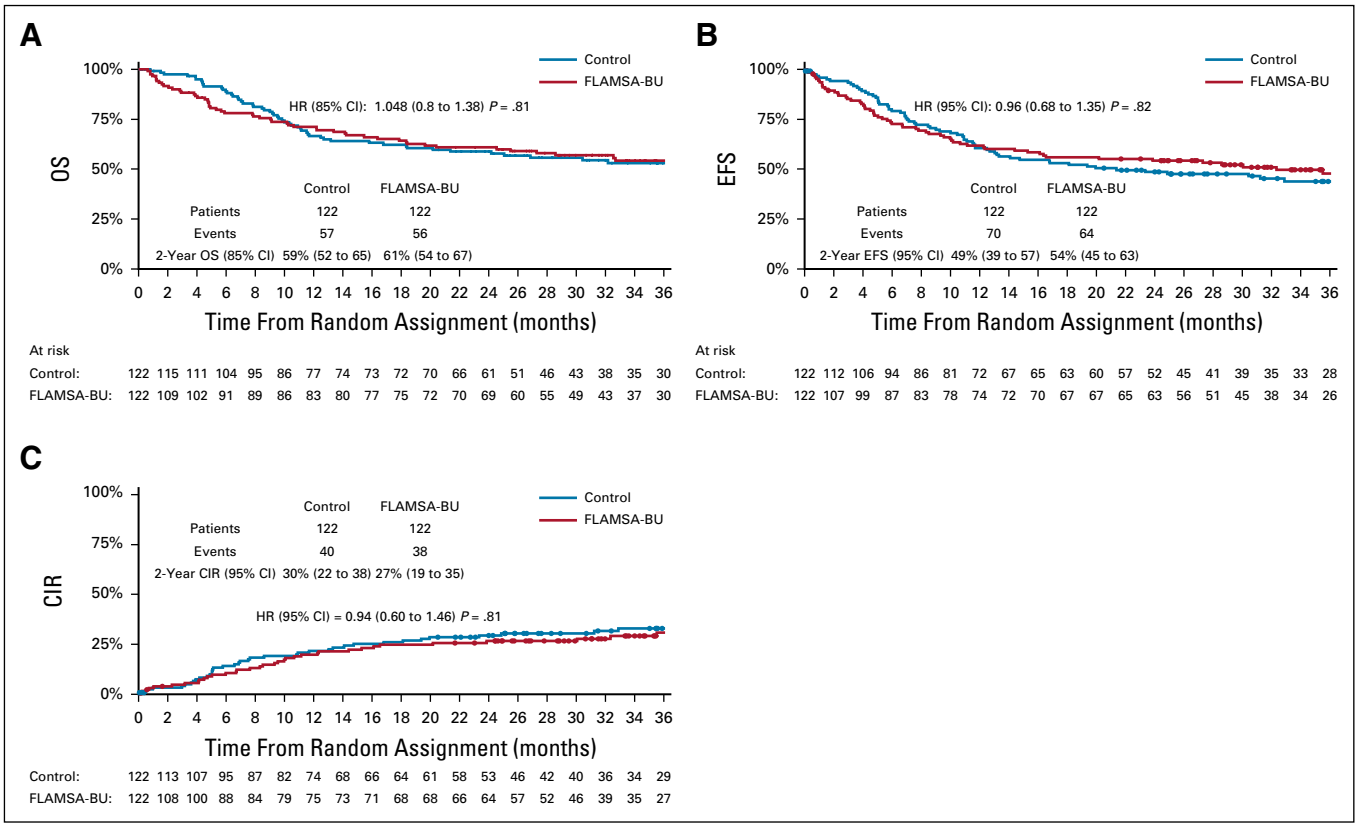

FIG 2. (A) OS, (B) EFS, and (C) CIR by conditioning regimen in the intention-to-treat population. 85% CIs are reported for overall survival to align with the type I error rate applied in the sample size calculation (described in the Data Supplement). CIR, cumulative incidence of relapse; EFS, event-free survival; FLAMSA-Bu, fludarabine/amsacrine/cytarabine-busulphan; HR, hazard ratio; OS, overall survival.

treatment arm (including by different control regimens) on relapse risk (Data Supplement).

Pretransplant MRD Status and Post-Transplant Outcome

Pretransplant MRD data, excluding inadequate BMs, were available in 176 randomly assigned patients of whom 156 proceeded to transplant (Data Supplement, distribution of clinical characteristics by MRD status in Data Supplement). MRD at any level was detected by flow cytometry in 43% of the 156 patients (38 of 79 receiving control regimens and 29 of 77 receiving FLAMSA-Bu) (median MRD level of 0.2%, range 0.02%-12.3%). In randomly assigned patients, pretransplant MRD positivity was associated with an increased relapse risk (2-year CIR 41.0% *v* 20.0% (HR 1.97 [95% CI, 1.18 to 3.28], Gray's test *P* value = .01) and a borderline significant reduction in 2-year OS (70.1%-51.4% log-rank *P* value = .05) (Data Supplement). No statistically significant difference was observed in TRM (2-year TRM 12.1% MRD-positive *v* 21.6% MRD-negative (HR 0.60 (95% CI, 0.29 to 1.27), Gray's test *P* value = .18). There was no interaction between MRD status and conditioning intensity in the preplanned subgroup survival analysis (heterogeneity test *P* = .56) or on relapse risk (treatment MRD interaction term *P* = .92). No difference in post-transplant MRD clearance was apparent between treatment arms from MRD results at day + 42 (Data Supplement). Although flow cytometric methodology represents the most widely applicable MRD assay in AML, its reliance on operator analysis expertise is a recognized limitation that may potentially contribute to variation in its prognostic value.[27] We therefore used an unsupervised computational approach to analyze flow cytometric sample files to obtain independent evaluation of the impact of conventionally determined MFC-MRD (Data Supplement) on outcome in the transplanted cohort. Twenty patients with pretransplant conventional MFC-MRD results were excluded since their samples had fewer than the minimum requirement of 1,000 blast events. Outcomes (Table 2, Fig 3) and test accuracy for relapse prediction (Data Supplement) were comparable between both methods in transplanted patients, supporting reproducibility of the prognostic effect from immunophenotypic MRD. The prognostic significance of pretransplant MRD above the thresholds that provided the most discrimination in this RIC allo-SCT setting (0.2% by conventional analysis, 1% by unsupervised) (Fig 3B-C, Table 2) was retained for relapse in an analysis adjusted for additional factors with the potential to determine transplant outcome (Table 2). To further test the robustness of these MFC-MRD–predicted outcomes, we applied stringent criteria (quantifiable, unsupervised MFC-MRD in at least 2 different antibody combinations) to select

TABLE 2. Conventional and Unsupervised MRD Comparison: Outcomes by Pretransplant MRD Status

Pretransplant MRD status	2-Year CIR (95% CI)	Unadjusted *P*	Adjusted HR (95% CI) *P*	2-Year TRM (95% CI)	*P*	2-Year OS (95% CI)	Unadjusted *P*	Adjusted HR (95% CI) *P*
MRD-negative n = 73	20.7% (12.2 to 30.7)	.034	1.8 (0.94 to 3.42) .075	16.6% (9.1 to 26.1)	.63	72.1% (60.2 to 81)	.08	1.54 (0.88 to 2.7) .13
MRD-positive n = 63	38.3% (26.3 to 50.2)			12.9% (6 to 22.6)		53% (39.9 to 64.6)		
UnSup MRD-negative n = 86	22.1% (14 to 31.4)	.022	1.82 (1.00 to 3.34) .051	16.5% (9.5 to 25.2)	.82	66.9% (55.7 to 75.8)	.12	1.22 (0.69 to 2.15) .49
UnSup MRD-positive n = 50	40.5% (26.6 to 53.9)			12.2% (4.9 to 23)		57% (41.9 to 69.5)		
MRD < 0.2% n = 104	22.2% (14.7 to 30.7)	.001	2.39 (1.23 to 4.61) .01	16.5% (10.1 to 24.4)	.79	67.8 (57.8 to 75.9)	.037	1.73 (0.95 to 3.15) .075
MRD ≥ 0.2% n = 32	50% (31.5 to 66.4)			9.6% (2.4 to 23)		48.2 (30 to 64.3)		
UnSup MRD < 1% n = 103	21.4% (14 to 29.8)	< .001	2.52 (1.3 to 4.9) .006	17.8% (11 to 25.9)	.35	66.2% (56.1 to 74.6)	.11	1.41 (0.77 to 2.58) .28
UnSup MRD ≥ 1% n = 33	52% (33.3 to 67.8)			6.1% (1 to 17.9)		54% (35.5 to 69.2)		
UnSup-combined MRD-negative or equivocal n = 102	20.6% (13.3 to 28.9)	< .001	2.44 (1.25 to 4.74) .009	15.9% (9.5 to 23.7)	.86	68.2% (58.1 to 76.3)	.007	2.03 (1.13 to 3.63) .018
UnSup-combined MRD-positive n = 34	50.5% (32.2 to 66.2)			12% (3.7 to 25.5)		51.7% (33.7 to 67)		

NOTE. Conventional and unsupervised (computational) MRD comparisons are in transplanted patients. Adjusted results are the results of cox proportional hazard models adjusted for age, cytogenetic risk, *FLT3*-ITD presence, treatment arm, and HCT comorbidity.

Abbreviations: CIR, cumulative incidence of relapse; HR, hazard ratio; MRD, measurable residual disease (flow cytometric); UnSup, unsupervised (computational) MRD analysis; UnSup-combined MRD, unsupervised MRD applying criteria of MRD-positive = aberrant blasts in at least 2 of the 3 antibody combinations (standard and stem cell), MRD-negative or equivocal = aberrant blasts in 0-1 of 3 antibody combinations; TRM, transplant-related mortality.

patients with the most extensive immunophenotypic blast aberrancies. Most patients with test positivity by these criteria had conventional MRD levels ≥ 0.2% (Data Supplement). The 2-year CIR after transplant for patients with a positive test was 50.5% compared with 20.6% for patients with a negative or equivocal test (Gray's test *P* value < .001) (Fig 3D, Table 2), and the overall accuracy for relapse prediction was 73% (Data Supplement).

Chimerism and Transplant Outcome

To explore the contribution of a putative GVL effect to post-transplant outcome, we studied the impact of acquisition of full donor T-cell chimerism (FDTCC) on transplant outcome. Acquisition of FDTCC was similar in control and experimental arms and not affected by pretransplant MRD status (Data Supplement). Acquisition of FDTCC at 3 months post-transplant was associated with lower CIR (Gray's test *P* value < .001) with 2-year CIR in patients with FDTCC of 13.1% (95% CI, 7.3 to 20.5) compared with 44.8% (95% CI, 30.0 to 58.3) (Data Supplement). In patients with pretransplant MRD positivity, acquisition of FDTCC at 3 months post-transplant was associated with a comparable outcome with that achieved by patients without detectable pretransplant MRD (Fig 4).

DISCUSSION

Strategies with the potential to reduce the risk of relapse in patients with AML or MDS transplanted using RIC include both intensification of the antitumor properties of the conditioning regimen[35] and optimization of the GVL effect.[5] The cytoreductive properties of distinct RIC regimens vary considerably, and relapse rates ranging from 30% to 60% have been reported in patients using commonly adopted transplant protocols.[3,36] In unrandomized phase II trials and retrospective registry data, the FLAMSA-Bu protocol, which incorporates additional cytoreductive chemotherapy prior to a fludarabine-based RIC regimen, has been reported to reduce relapse and improve outcome in high-risk AML or MDS and as a consequence has become widely adopted despite its attendant substantially increased in-patient stay and potential toxicity.[5-7] Our data, however, show no impact on either relapse rate or survival in patients transplanted using this intensified regimen. Differences in control regimens and age-related FLAMSA-Bu dose adjustments constitute potential limitations to this analysis, but we did not detect a differential effect on outcomes from any of these variables. Of particular note, FLAMSA-Bu did not result in improved survival in predefined subgroups including patients with an adverse-risk karyotype.

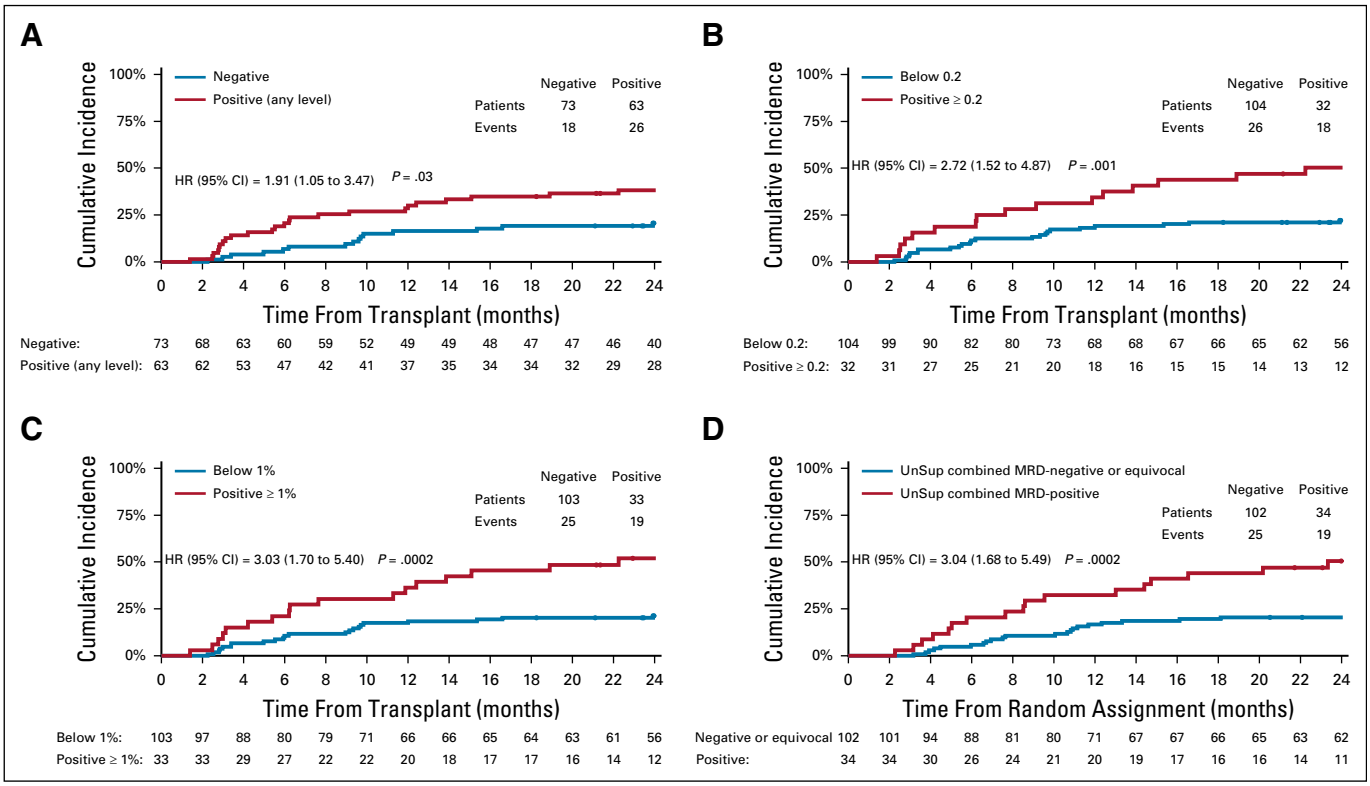

FIG 3. (A) CIR by conventional MFC-MRD status, (B) CIR by conventional MFC-MRD with 0.2% cutoff, (C) CIR by unsupervised (computational) MFC-MRD with 1% cutoff, (D) CIR by unsupervised (computational) combined MFC-MRD test status. Impact of flow cytometric MRD on outcomes of transplanted patients are shown with comparison of results from conventional and unsupervised (computational) analysis approaches. Unsupervised MFC-MRD cutoff is higher than conventional MFC-MRD as the former values summate all quantifiable nonoverlapping abnormal blast subpopulations from an antibody combination, whereas conventional MFC-MRD values are from a single LAIP. UnSup-combined MRD is unsupervised MRD applying criteria of MRD-positive = aberrant blasts in at least two of the three antibody combinations (standard and stem cell) and MRD-negative or equivocal = aberrant blasts in 0-1 of 3 antibody combinations. CIR, Cumulative incidence of relapse; LIAP, leukemia-associated immunophenotype; MFC-MRD, flow cytometric measurable residual disease; UnSup, unsupervised (computational) MRD analysis.

In exploratory studies, pretransplant MRD, measured using a widely used flow cytometric methodology, was prospectively examined as a prognostic determinant of transplant outcome. Pretransplant MRD status was identified as an important prognostic factor for relapse in multivariable analysis, confirming previous retrospective analyses. However, although the US CTN 0901 trial identified the presence of NGS-determined pretransplant MRD as a predictor of outcome in patients transplanted using a reduced intensity but not a MAC regimen,[31] in the FIGARO trial, we observed no benefit accruing in MRD-positive patients from intensification of RI conditioning. Of interest, the risk of relapse after transplant in the RIC arm of US-CTN 0901 (48% at 18 months[2]) was strikingly higher than that observed in the FIGARO trial despite both trials using similar RIC regimens.

One of the major limitations of the widely used flow cytometric MRD assays has been the inevitable subjectivity from manual gating of immunophenotypic raw data. Using a novel unsupervised analysis approach as independent evaluation of conventional flow cytometric MRD, we were able to confirm the reproducibility of the prognostic significance of immunophenotypic pretransplant MRD in this older age group typically considered for RIC regimens. Incorporating comprehensive genetic information for genetic subtype MRD interpretation (such as *FLT3*-ITD[29,31]), consideration of under-representation of MRD from hemodilution or hypoplasia and potentially MRD as a continuous variable will further progress refining and validating flow cytometric MRD thresholds for transplant decision making.

There is much debate concerning the benefit of an RIC allograft in patients with evidence of pretransplant MRD. It is therefore of interest that approximately 50% of FIGARO patients with evidence of pretransplant MRD did not relapse, confirming the validity of transplantation using an RIC regimen as a therapeutic strategy in high-risk AML—even in patients with detectable MRD. There is compelling evidence of a potent GVL effect in patients with AML allografted using an RIC regimen.[37] The observation that the adverse prognostic impact conferred by the presence of

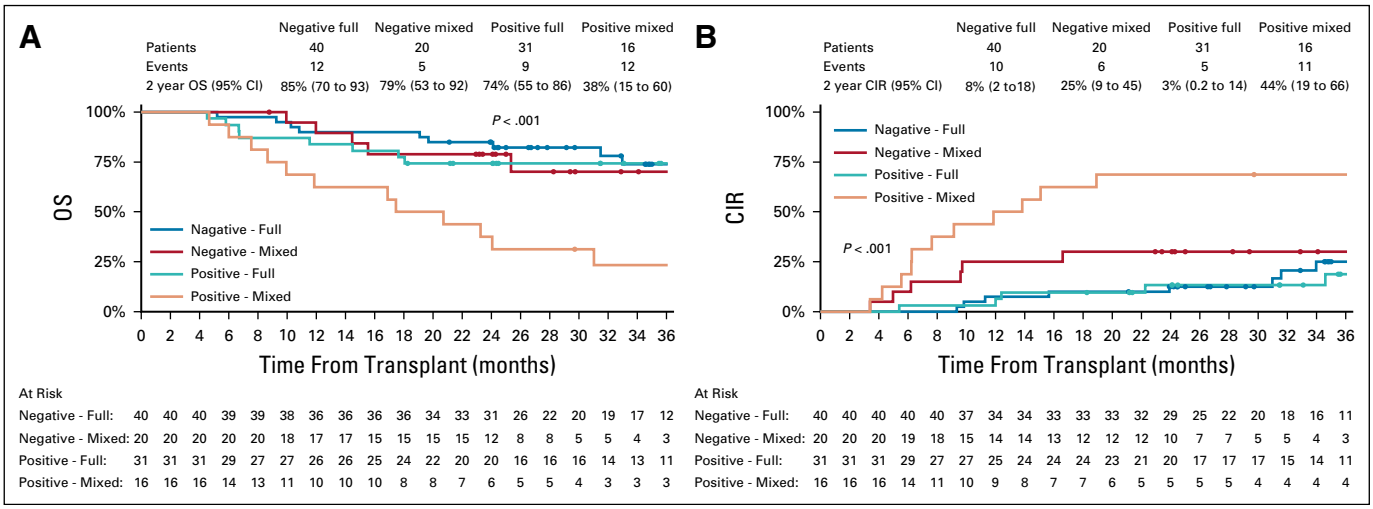

FIG 4. (A) OS by month 3 Chimerism with pretransplant MRD status and (B) CIR by month 3 Chimerism with pretransplant MRD status. Outcomes are for transplanted patients who were alive and relapse-free at day + 100. MRD status is by conventional flow MRD. Negative—full, pretransplant MRD-negative and month 3 full donor T-cell chimerism. Positive—full, pretransplant MRD-positive and month 3 full donor T-cell chimerism. Negative—mixed, pretransplant MRD-negative and month 3 mixed donor T-cell chimerism. Positive—mixed, pretransplant MRD-positive and month 3 mixed donor T-cell chimerism. CIR, Cumulative incidence of relapse; MRD, measurable residual disease; OS, overall survival.

pretransplant MRD was mitigated by the acquisition of FDTCC at 3 months requires further prospective examination and identifies optimization of the GVL effect as an important approach to improve outcome in patients transplanted using an RIC regimen. Such strategies include using a T replete graft, a rapid taper of post-transplant immunosuppression, or early administration of pharmacological agents such as azacitidine, decitabine,[38-40] or DLI.

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CLINICAL TRIAL INFORMATION

FIGARO

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Augmented Reduced-Intensity Regimen Does Not Improve Postallogeneic Transplant Outcomes in Acute Myeloid Leukemia

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