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Original Study

On Behalf of the SFGM-TC: Retrospective Comparison of Reduced and Higher Intensity Conditioning for High-Risk Myelodysplastic Syndrome Treated With Allogeneic Stem-Cell Transplantation

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Abstract

We conducted a retrospective analysis of 427 patients undergoing allogeneic stem cell transplantation for high-risk myelodysplastic syndrome. Seventy-two patients (16.9%) received sequential FLAMSA-RIC, 270 (63.2%) received FluBu2, and 85 (19.9%) received FluBu3/FluBu4. No significant differences in outcomes (overall survival, progression-free survival, nonrelapse mortality, relapse incidence, and graft versus host disease relapse-free survival) were observed between the 3 groups. The only factor influencing survival is cytogenetic risk at transplantation.

Background: Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) remains the best curative option for high-risk myelodysplastic syndrome . We retrospectively compared patient outcomes after allo-HSCT according to the intensity of the conditioning regimen. **Patients and Methods:** Three conditioning regimens were compared in 427 patients allografted for high-risk myelodysplastic syndrome: reduced-intensity conditioning (RIC), fludarabine (150-160 mg/m^2) and busulfan (6.4 mg/kg); sequential FLAMSA-RIC, fludarabine, amsacrine, and aracytine followed by RIC; and myeloablative with reduced toxicity (RTC), fludarabine and busulfan (9.6 mg/kg or 12.8 mg/kg). **Results:** The patients in the 3 conditioning groups were different in regards to the number of treatment lines ($P < .001$), percentage of blasts in bone marrow ($P < .001$), and disease status at transplantation ($P < .001$). No significant differences in outcomes (overall survival, progression-free survival, nonrelapse mortality, relapse incidence, and graft versus host disease relapse-free survival) were observed between the 3 groups. Using propensity score analysis to overcome baseline imbalances, we compared 70 patients receiving FLAMSA-RIC to 260 patients receiving RIC, and compared 83 patients receiving RTC to 252 patients receiving RIC. The only factor influencing overall and progression-free survival was cytogenetic

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risk at transplantation. After the covariate adjustment using propensity score to reduce baseline imbalances, the only factor influencing overall and progression-free survival was still cytogenetic risk at transplantation. **Conclusion:** Overall survival appears to be similar with the 3 conditioning regimens. The only factor influencing survival is cytogenetic risk at transplantation, suggesting that new promising drugs in the conditioning and/or early interventions after transplantation are needed to improve outcomes in these patients.

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Keywords: Myelodysplastic syndrome, Allogeneic stem cell transplantation, Conditioning regimen, Overall survival, Covariate adjustment using the propensity

Introduction

Myelodysplastic syndromes (MDS) constitutes a group of heterogeneous clonal hematopoietic stem cell disorders.[1, 2] Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) remains the only potentially curative therapy.[3, 4] This procedure improves overall survival (OS) in patients with high-risk MDS.[5, 6] If the stem cell source and donor type have no impact on transplant outcomes,[7, 8] lower blast medullar infiltration seems to be associated with better outcomes.[9, 10] The impact of the conditioning regimen intensity is still debated.[11-16] Standard myeloablative conditioning (MAC) combining busufan (Bu 12.8 mg/kg) and cyclophosphamide (Cy 120 mg/kg; BuCy) or cyclophosphamide (120 mg/kg) and 12 gray total body irradiation (Cy/TBI)[17-19] for MDS patients in a frail condition has been replaced by reduced intensity conditioning (RIC), such as FluBu2[20, 21] (fludarabine and 6.4 mg/kg busulfan) or FluBu1 (fludarabine and 3.2 mg/kg busulfan) with no impact of busulfan dose intensity on recipient outcomes.[22] RIC (with FluBu2[23] or 2 Gy TBI ± fludarabin[13] ± cladribin[24]) compared to standard MAC is associated with reduced non-relapse mortality (NRM) but an increased risk of relapse. A recent meta-analysis[25] included 2 main prospective studies considering MDS and acute myeloid leukemia.[14, 15] In subgroup analyses, the OS observed with RIC was inferior to the OS obtained with MAC for intermediate-risk MDS,[15] but there was only a trend of better OS with MAC than RIC for high-risk MDS patients.[14] Therefore, myeloablative reduced toxicity conditioning (RTC) based on intermediate doses of intravenous Bu (9.6 and 12.8 mg/kg)[26] or melphalan (80 or 140 mg/m^2)[27] have been investigated to reduce NRM in allografted MDS patients, with similar results.[28] Finally, a sequential conditioning regimen developed for very high-risk diseases, such as relapsed or refractory acute myeloid leukemia (AML) and secondary AML,[29] has been poorly investigated for patients with MDS.[30] In this study, we investigated the impact of these various intermediate intensity conditioning regimens on patient outcomes.

Material and Methods

Study Design and Data Collection

This retrospective multicenter study was approved by the board of the Société Francophone de Greffe de Moelle et Thérapie Cellulaire (SFGM-TC) and conducted according to the Declaration of Helsinki. We included patients allografted in France between 2007 and 2016. Participating centers were asked to verify the data recorded for each patient and provide additional information. The methodology of the study is presented in the supplementary figure.

Inclusion criteria were MDS defined according to the 2008 WHO classification, including refractory anemia with excess blasts in transformation/acute myeloid leukemia (RAEB-T/AML) with marrow blasts between 20% and 30%; high-risk classical International Prognostic Scoring System (IPSS) at diagnosis (≥1.5) [31] regardless of the revised IPSS (R-IPSS); age ≥18 years; Karnofsky ≥ 80% and HCT comorbidity index ≤ 4; and first allo-HSCT with a sibling donor or matched-unrelated donor. Conditioning regimen, hematopoietic stem cell source, and graft versus host disease (GVHD) prophylaxis were administered according to center policy. Patients with prophylactic donor lymphocyte infusions (DLIs) planned at the same moment as the conditioning regimen decision were included.

Exclusion criteria were patients who received allo-HSCT from an alternative donor (HLA-mismatched donor, haplo-identical donor, or umbilical cord blood) and patients who received prophylactic treatment for relapse (eg, hypomethylating agents) after allo-HSCT.

Patient and Transplant Characteristics

IPSS[31] and R-IPSS[32] were calculated at diagnosis and checked for all patients. Possible progression to more advanced disease between diagnosis and transplantation was recorded. Progressive disease was defined by an increase of >50% in the bone marrow blast percentage before allo-HSCT.

Patients undergoing sequential conditioning received FLAMSA, which consisted of fludarabine, amsacrine, and aracytine followed by RIC with 6.4 mg/kg Bu or 4 Gy Cy/TBI followed by allo-HSCT.

Patients undergoing non-sequential conditioning received FluBu2, FluBu3, or FluBu4. FluBu2 consisted of fludarabine (total dose 150-160 mg/m^2) combined with intravenous (iv) Bu (3.2 mg/kg daily) for 2 days (total dose 6.4 mg/kg). FluBu3 and FluBu4 consisted of fludarabine (total dose 150-160 mg/m^2) combined with iv Bu (3.2 mg/kg daily) for 3 days (total dose 9.6 mg/kg) or 4 days (total dose 12.8 mg/kg), respectively.

Statistical Analysis

Patient and disease characteristics were reported using descriptive statistics. Relapse was defined by standard hematological criteria.[34] Acute[33] and chronic[34] GVHD were diagnosed and graded using established criteria. The primary endpoints of the study were 3-year overall survival (OS) and 3-year progression-free survival (PFS).

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OS was defined as the time from stem-cell transplantation to death from any cause or end of follow-up. PFS was defined as the time from stem-cell transplantation to relapse, disease progression, death from any cause, or end of follow-up. The log-rank test was used to compare Kaplan-Meier curves. The secondary endpoints included the incidence and severity of acute and chronic GVHD, relapse incidence (RI), NRM, and GVHD relapse-free survival (GRFS). Cumulative incidence functions (CIFs) were used to estimate RI and NRM, which were analyzed as competing risks. The cumulative incidence of grade II-IV acute GVHD at 100 days and chronic GVHD at 2 years were estimated considering death as a competing event. GRFS was defined as survival without grade III-IV acute GVHD, without chronic GVHD requiring systemic immunosuppressive treatment for severe chronic GVHD, and without relapse.[35]

Covariate adjustment using the propensity: 2 separate analyses compared the FLAMSA-RIC and RIC groups (group 1) and the RTC and RIC groups (group 2). Pre-transplantation factors included in each model: recipient age at transplantation, time from diagnosis to transplantation, number of treatment lines before transplantation, disease status at transplantation, percentage of marrow blast at transplantation, and prophylactic DLIs planned with the conditioning regimen. The following variables were considered as potential predictors for each model and for each event: conditioning regimen, cytogenetic prognosis, CMV risk, stem cell source, HLA matching, risk level, and in vivo T-cell depletion. Multivariable analysis was performed using the Cox proportional hazard regression model. A stepwise selection procedure was applied using the criteria for variable selection, $P = .20$ for variable entry and $P = .1$ for variable removal, with the propensity variable forced in all models. Statistical analyses were performed in SAS 9.4 software (SAS Institute).

Results

Patients and Treatment

A total of 427 patients with high-risk MDS were included in this study. Seventy-two patients (16.9%) received sequential FLAMSA-RIC, 270 (63.2%) received FluBu2 RIC, and 85 (19.9%) received FluBu3/FluBu4 RTC. The median age at the time of the transplant for the entire cohort was 59.9 years (range 27.1-71.9) and recipient age at transplantation significantly differed between the groups, with older recipients in the RIC group. Detailed characteristics of the patients are summarized in Table 1 .

At the time of transplantation, there was a significant difference between the 3 groups in the percentage of blasts (Table 1). We observed that MDS with excess of blast 2 (MDS-EB2) and progressive MDS were more frequent in the FLAMSA-RIC group. We found no difference between the 3 groups in regards to the IPSS or cytogenetic risk at diagnosis. However, significant differences were found between the 3 groups in the stem cell source, in vivo T-cell depletion (no ATG for 6 patients in the FLAMSA-RIC group only), and GVHD prophylaxis (Table 1).

Engraftment and GVHD

Engraftment was comparable between the three conditioning regimens. Secondary graft rejection occurred only in 4 patients from the RIC and RTC groups (Table 2). In the entire cohort, grade II–IV and grade III–IV acute GVHD 100 days after allo-HSCT was 27.7% and 12.3%, respectively, with no significant difference between the three groups. However, extensive chronic GVHD significantly differed between the three groups (Table 2). Cumulative incidence of chronic GVHD 24 months after allo-HSCT was 43.6% (95% CI, 29.8-56.6) in the FLAMSA-RIC group, 48.7% (95% CI, 41.2-55.9) in the RIC group, and 45.7% (95% CI, 31.0-59.3) in the RTC group ($P = .78$).

Overall Outcomes

In the entire cohort, the 3-year OS and the 3-year PFS were 50.4% (95% CI, 45.1%-56.1%) and 43.0% (95% CI, 37.8%-48.5%), respectively. The 3-year NRM and relapse cumulative incidences were 24.2% (95% CI, 19.3%-29.5%) and 40.9% (95% CI, 35.2-46.6), respectively. We found no significant difference between the FLAMSA-RIC, RIC, and RTC groups (Table 3). In the same way, the 2-year cumulative incidence of GRFS was not significantly different according to conditioning regimen (Table 3 and Figure 1). In subgroup analysis, the 3-year OS of patients with RAEB-T/AML at diagnosis (n = 17) was 40,1% [19,1%-71,1%] versus 50,9% [45,5%-56,6%] for patients with MDS (n = 410) with no statistical difference between the 2 groups ($P = .388$).

Multivariate Analyses After Propensity Score (FLAMSA-RIC Vs. RIC (group 1) and RTC Versus. RIC (group 2))

Patient and transplantation characteristics for the propensity score analysis is described in Supplementary Table 1 and Supplementary Table 2, respectively. Factors associated with event occurrence are summarized in Table 4 and Table 5 for group 1 and group 2, respectively. Briefly, poor cytogenetic prognosis (group 1, $P = .005$ and group 2, $P = .002$) and matched-unrelated donor (group 1, $P = .047$ and group 2, $P = .055$) were associated with increased mortality. In both groups, poor cytogenetic prognosis status was a prognostic factor associated with increased treatment failure (group 1, $P = .029$ and group 2, $P = .008$), and matched-unrelated donor was a prognostic factor for NRM (group 1, $P = .002$ and group 2, $P = .003$). An impact of the intensity of the conditioning regimen on NRM was observed for FLAMSA-RIC ($P = .053$) and on relapse incidence was observed for FLAMSA-RIC ($P = .007$) and RTC ($P = .048$). In both groups, poor cytogenetic prognosis status was an independent prognostic factor for relapse (group 1, $P = .010$ and group 2, $P = .005$). The use of a matched-unrelated donor was associated with an increased risk of death because of relapse and/or grade III-IV acute GVHD and/or extensive chronic GVHD occurrence (group 1, $P = .017$ and group 2, $P = .001$).

Discussion

In the absence of a randomized trial, no definitive recommendation is available for the conditioning intensity in allo-HSCT for MDS. Most studies have been retrospective and included patients with MDS and AML.[13] Studies comparing RTC (FluBu4) and RIC (FluBu2) have mostly been conducted in patients with various stages of AML or MDS with distinct ages at transplantation.[16,36] Only one study of 248 patients with AML or MDS has considered

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Table 1 Patient and Transplant Characteristics (N = 427)

Characteristic	FLAMSA-RIC (n = 72)		RIC (n = 270)		RTC (n = 85)		*P*-value
Median recipient age at transplantation, years (range)	59.0	(27.1-67.8)	62.3	(30.6-71.9)	59.2	(38.4-69.3)	**<.001**
Median time from diagnosis to transplant, months (range)	28.4	(7.7-471)	26.6	(3.75-763.3)	22.7	(4.8-525)	.29
Median follow-up, months (range)	41.8	(2.3-186.2)	49.9	(1.1-307.9)	48.5	(0.0-181.2)	.21
Number of treatment lines before transplant							**<.001**
0	27	(37.5)	74	(27.4)	27	(25.9)	
1 or 2	45	(62.5)	196	(72.6)	58	(68.2)	
Treatment before transplant							**.133**
Azacytidine	22	(48.9)	118	(60.2)	28	(48.3)	
Chemotherapy (+/- Aza)	23	(51.1)	78	(39.8)	30	(51.7)	
Median time (in days) of treatment before transplant (range)							
Azacytidine	252	(178-323)	207	(160-322)	217	(182.5-281)	**.759**
Chemotherapy (+/-Aza)	131.5	(84-202)	151.5	(118-209)	152	(94-201.5)	**.466**
Percentage of blasts at transplantation							**<.001**
<10%	36	(51.4)	218	(83.8)	64	(77.1)	
≥10%	34	(48.6)	42	(16.2)	19	(22.9)	
Missing	2		10		2		
IPSS at diagnosis							.58
Intermediate-2 (1.5)	51	(70.8)	206	(76.3)	62	(72.9)	
High (>1.5)	21	(29.2)	64	(23.7)	23	(27.1)	
Cytogenetic prognosis at diagnosis							.93
Very good	1	(1.6)	4	(1.6)	2	(2.4)	
Good	26	(41.3)	114	(46.0)	39	(47.6)	
Intermediate	16	(25.4)	56	(22.6)	20	(24.4)	
Poor	15	(23.8)	57	(23.0)	13	(15.9)	
Very poor	5	(7.9)	17	(6.9)	8	(9.8)	
Missing	9		22		3		
Disease status at transplantation							**<.001**
Progressive	30	(41.7)	32	(11.9)	14	(16.5)	
Stable	19	(26.4)	45	(16.7)	26	(30.6)	
In response	23	(31.9)	193	(71.5)	45	(52.9)	
Stem cell source							**.03**
Bone marrow	6	(8.3)	7	(2.6)	6	(7.1)	
Peripheral blood	66	(91.7)	263	(97.4)	79	(92.9)	
Type of donor							.42
Identical sibling	33	(45.8)	115	(42.6)	43	(50.6)	
Matched unrelated	39	(54.2)	155	(57.4)	42	(49.4)	
CMV risk							.20
High-risk (donor negative to recipient positive)	18	(25.4)	76	(28.3)	17	(20.5)	
Low-risk (donor negative to recipient negative)	29	(40.8)	76	(28.3)	28	(33.7)	
Intermediate-risk (donor positive)	24	(33.8)	117	(43.5)	38	(45.8)	
Missing	1		1		2		
In vivo T-cell depletion							**<.001**
No	6	(8.3)	0	(0.0)	0	(0.0)	
ATG	66	(91.7)	270	(100.0)	85	(100.0)	
GVHD prophylaxis							**<.001**
Cyclosporin/Tacrolimus	5	(6.9)	86	(31.9)	36	(42.4)	

(*continued on next page*)

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Table 1 (*continued*)

Characteristic	FLAMSA-RIC (n = 72)		RIC (n = 270)		RTC (n = 85)		*P*-value
Cyclosporin/Tacrolimus + MMF	53	(73.6)	116	(43.0)	26	(30.6)	
Cyclosporin/Tacrolimus + MTX	11	(15.3)	63	(23.3)	18	21.2)	
Other	3	(4.2)	5	(1.9)	5	(5.9)	

Data are given as n (%) unless otherwise noted. Abbreviations: ATG, anti-thymocyte globulin; CMV, cytomegalovirus; GVHD, graft versus host disease; IPSS, International Prognostic Scoring System; RIC, restricted-intensity conditioning; RTC, restricted toxicity conditioning
*P<0.05

Table 2 Patient Outcomes (N = 427)

	FLAMSA-RIC N = 72 (16.9%)		RIC N = 270 (63.2%)		RTC N = 85 (19.9%)		
	N	%	N	%	N	%	*P*-Value*
Engraftment/Hemopoietic chimerism							.21
Full donor	52	76.5	154	63.1	57	71.3	
Mixed	16	23.5	87	35.7	22	27.5	
Graft rejection	0	0.0	3	1.2	1	1.3	
Missing	4		26		5		
Acute GVHD							.78
Grade 0-I	49	69.0	197	73.2	60	72.3	
Grade II-IV	22	31.0	72	26.8	23	27.7	
Grade III-IV	8	11.3	34	12.6	10	12.0	
Missing	1		1		2		
Chronic GVHD							.40
No	47	65.3	169	62.6	60	70.6	
Yes	25	34.7	101	37.4	25	29.4	
Extension of chronic GVHD							**.002**
Limited	8	33.3	59	62.6	20	83.3	
Extensive	16	66.7	37	37.4	4	16.7	
Missing	1		5		1		
Cause of death							**.02**
Disease related	18	54.5	80	64.0	13	38.2	
GVHD	10	30.3	38	30.4	19	55.9	
Infection	3	9.1	3	2.4	0	0.0	
Rejection/poor graft function	0	0.0	1	0.8	1	2.9	
Hemorrhage	0	0.0	2	1.6	1	2.9	
Multiple organ failure	2	6.1	1	0.8	0	0.0	

Abbreviations: RIC = restricted-intensity conditioning; RTC = restricted-toxicity conditioning; GVHD = graft versus host disease.
*P<0.05

the fundamental difference in age criteria between MAC (FluBu4 and 4 Gy TBI) and RIC (FluBu2+ 2 Gy TBI) and performed a propensity score matching analysis. After adjustments, they found 42 case-control pairs and no significant differences in OS, NRM, or the relapse rate between the 2 groups. An interesting finding was a trend of a higher cumulative incidence of chronic GVHD at 1 year in the RIC arm (64.8% vs. 39.3% in the MAC arm).[37] Only a few prospective studies have been published on the comparison of RIC and MAC for MDS. One prospective study compared standard myeloablative conditioning with high toxicity (eg, BuCy and Cy/TBI) to reduced intensity conditioning (eg, FluBu2),[15] and one prospective study compared myeloablative conditioning (standard and with reduced toxicity, such as FluBu4) to reduced intensity conditioning (eg, FluBu2 or Flu/Mel with melphalan $\leq$150 mg/m^2).[14] These 2 main studies included patients with AML and MDS; the MDS subgroup analysis showed that OS may be better with MAC than RIC. In 2005, Schmid et al.[29] published the results of FLAMSA-RIC with prophylactic DLI in 75 consecutive patients having high-risk AML/MDS. The 2-year OS and LFS were 42% and 40%, respectively. Interestingly, neither cytogenetics

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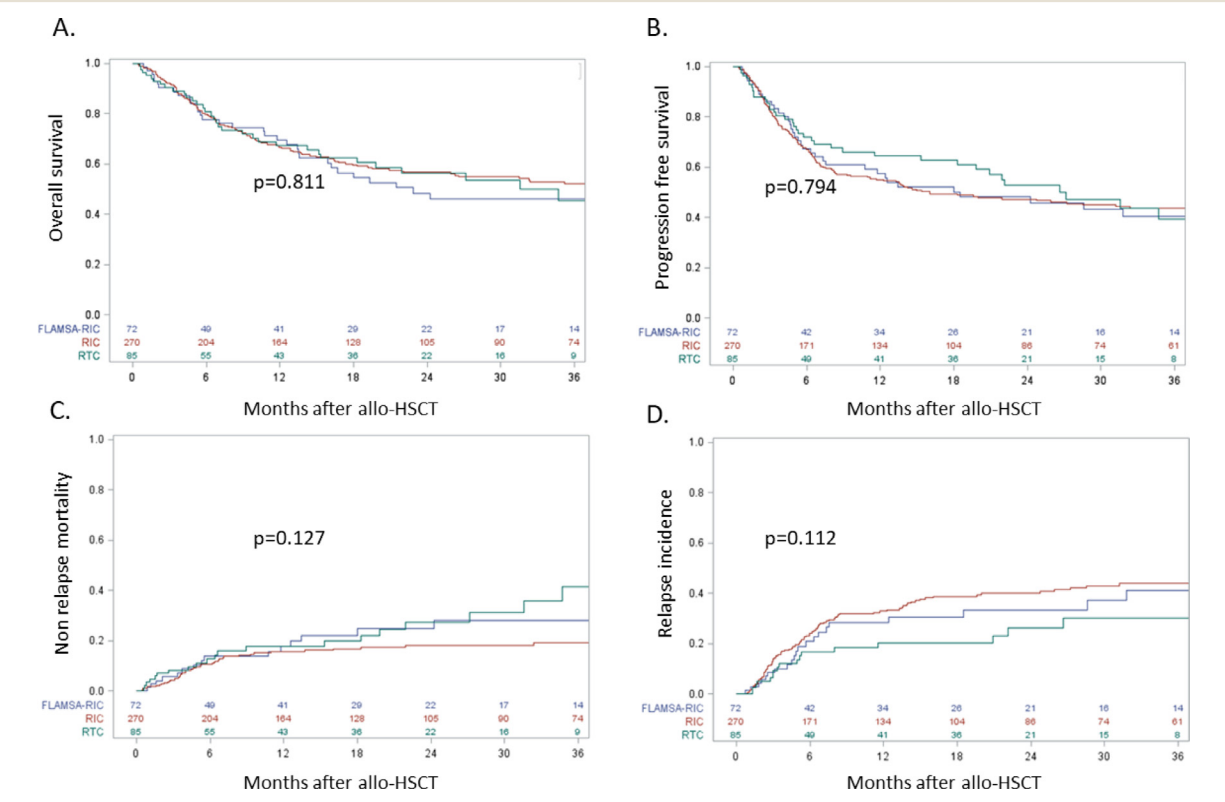
Table 3 Univariate Analysis of 3-Year OS, PFS, and Cumulative Incidence (NRM, RI) and 2-Year Cumulative Incidence (GRFS) According to Conditioning Regimen (N = 427)

	FLAMSA-RIC N = 72 (16.9%)		RIC N = 270 (63.2%)		RTC N = 85 (19.9%)		
	%	95% CI	%	95% CI	%	95% CI	*P*-Value
OS	46.2	[33.9-60.4]	52.2	[45.8-58.9]	45.3	[31.4-62.0]	.81
PFS	40.6	[28.6-55.3]	43.7	[37.5-50.4]	39.5	[26.1-56.5]	.79
GRFS	29.3	[17.3-46.9]	38.3	[31.3-46.3]	41.5	[28.8-57.1]	.80
NRM	28.2	[16.0-41.6]	19.3	[14.1-25.0]	41.7	[23.6-58.8]	.13
RI	41.1	[25.8-55.7]	43.9	[36.9-50.7]	30.1	[17.3-43.9]	.11

Abbreviations: RIC, restricted-intensity conditioning; RTC, restricted-toxicity conditioning; CI, confidence interval; GRFS: GVHD relapse-free survival; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; RI, relapse incidence.
*P <0.05

Figure 1 Transplant outcomes 3 years post-transplantation according to conditioning regimen. (A) Overall survival. (B) Progression-free survival. (C) Cumulative incidence of nonrelapse mortality. (D) Cumulative incidence of relapse. The FLAMSA-RIC group is in blue, RIC in red, and RTC in green.



nor the stage of the disease at transplantation had a significant influence on outcome. Soon after, since 2006 and /or 2007, some centers in France started to perform FLAMSA-RIC with prophylactic DLI to treat all patients with high-risk MDS, especially for patients with progressive or refractory disease. That is why we decided to conduct a retrospective analysis with the SFGM-TC in order to evaluate this strategy compared to the standard FluBu2-RIC and FluBu3/4 RTC.

The present study confirmed comparable OS and PFS in the 3 different groups in univariate and multivariate analysis, in a cohort of patients with imbalanced characteristics. Among the 4 general methods of propensity scores, [38] we have chosen the covariate adjustment using the propensity score. For this approach, a separate multivariable model is developed, after the propensity score model, in which the study outcome serves as the dependent variable and the conditioning regimen as well as the propensity score serve as predic-

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Table 4 Factors Associated With Event Occurrence in Cohort 1: FLAMSA and RIC (N = 330)

		HR (95% CI)	*P*-Value
Mortality	Cytogenetics		**.005**
(inverse of OS)	Good	1.00	
	Intermediate	1.40 (0.91-2.15)	
	Poor	1.89 (1.29-2.78)	
	Donor type		**.047**
	MRD	1.00	
	MUD	1.41 (1.00-1.97)	
Treatment failure	Cytogenetics		**.029**
(inverse of PFS)	Good	1.00	
	Intermediate	1.24 (0.83-1.84)	
	Poor	1.61 (1.13-2.29)	
NRM	Conditioning regimen		**.053**
	RIC	1.00	
	FLAMSA	1.99 (0.99-4.00)	
	Donor type		**.002**
	MRD	1.00	
	MUD	2.46 (1.38-4.38)	
Relapse	Conditioning regimen		**.007**
	RIC	1.00	
	FLAMSA	0.44 (0.24-0.80)	
	Cytogenetics		**.010**
	Good	1.00	
	Intermediate	1.43 (0.89-2.29)	
	Poor	1.92 (1.26-2.93)	
Mortality due to relapse or GVHD	Donor type		**.017**
(inverse of GRFS)	MRD	1.00	
	MUD	1.38 (1.06-1.80)	

Abbreviations: CI = confidence interval; GVHD = chronic graft-versus host disease; GRFS = graft versus host disease and relapse-free survival; HR = hazard ratio; MRD = matched-related donor; MUD = matched-unrelated donor; NRM = non-relapse mortality; OS = overall survival; PFS = progression-free survival; RI = relapse incidence; RIC = restricted-intensity conditioning; RTC = reduced toxicity conditioning.
*P<0.05

tor variables. This allowed us to estimate the outcome associated with the conditioning intensity while adjusting for the probability of receiving that conditioning, according to 6 independent pretransplant factors, thus reducing confounding but not eliminating it completely. Unadjusted confounding may still exist if unmeasured factors had influenced the conditioning regimen selection. After this propensity score, only patients with a poor cytogenetic prognosis (including poor and very poor according to IPSS-R) had lower OS because of lower PFS, in accordance with other studies.[39-41]

This study highlights that the physicians seem to modulate their therapeutic strategy according to disease status and evolution. Patients with progressive MDS and excess marrow blasts between 10 and 30% more frequently received a FLAMSA-RIC conditioning regimen and were less often treated prior to transplantation. If this conditioning was associated with an acceptable NRM, with no difference in the multivariate analysis for the incidence of acute GVHD (stage II-IV) or severe acute GVHD (stage III-IV), we observed a higher incidence of extensive chronic GVHD in the univariate analysis. Patients in the FLAMSA-RIC group more frequently received DLIs, which were planned per protocol (n = 5) or administered because of mixed chimerism (n = 5) or increased minimal residual disease (MRD) (n = 3). The impact of DLI on GVHD in this group is not clear, as 23% (n = 3) presented with acute grade II-IV GVHD and 15% (n = 2) with chronic GVHD in the FLAMSA-RIC + DLI subgroup versus 32.7% (n = 19) and 38.9% (n = 23) in the FLAMSA-RIC without DLI subgroup (*P* = .74 and *P*= .19, respectively). Moreover, some patients in the FLAMSA-RIC group did not receive in vivo T-cell depletion (ATG), which is an important drug that reduces the incidence of chronic GVHD.[42]

Overall, FluBu2, FluBu3, FluBu4, and FLAMSA-RIC are effective conditioning regimens in the treatment of MDS. The OS and PFS are lower for patients with poor or very poor cytogenetic prognosis, regardless of the intensity of the conditioning regimen. Because early interventions after transplantation to avoid relapse without increasing NRM are disappointing,[43] new promising condi-

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Table 5 Factors Associated With Event Occurrence in Cohort 2: RTC and RIC (N = 335)

		HR (95% CI)	*P*-Value
Mortality	**Cytogenetics**		**.002**
(inverse of OS)	Good	1.00	
	Intermediate	1.73 (1.15-2.61)	
	Poor	1.91 (1.30-2.81)	
	Donor type		**.055**
	MRD	1.00	
	MUD	1.38 (0.99-1.92)	
Treatment failure	**Cytogenetics**		**.008**
(inverse of PFS)	Good	1.00	
	Intermediate	1.47 (1.00-2.15)	
	Poor	1.71 (1.20-2.44)	
	Donor type		**.054**
	MRD	1.00	
	MUD	1.55 (1.01-2.37)	
NRM	**Type of donor**		**.003**
	MRD	1.00	
	MUD	3.46 (1.55-7.58)	
Relapse	**Conditioning regimen**		**.048**
	RIC	1.00	
	RTC	0.56 (0.32-0.99)	
	Cytogenetics		**.005**
	Good	1.00	
	Intermediate	1.44 (0.90-2.32)	
	Poor	2.03 (1.33-3.11)	
Mortality due to relapse or GVHD	**Donor type**		**.001**
(inverse of GRFS)	MRD	1.00	
	MUD	1.54 (1.18-2.00)	

Abbreviations: CI = confidence interval; GVHD = chronic graft-versus host disease; GRFS = graft versus host disease and relapse-free survival; HR = hazard ratio; MRD = matched-related donor; MUD = matched-unrelated donor; NRM = non-relapse mortality; OS = overall survival; PFS = progression-free survival; RI = relapse incidence; RIC = restricted-intensity conditioning; RTC = reduced toxicity conditioning.
∗P<0.05

tioning regimens are still needed. Recently, a prospective phase II trial assessed the efficacy and toxicity of treosulfan, fludarabine, and 2 Gy TBI as conditioning for allo-HCT in patients with MDS. With a median follow-up of 30 months, the 2-year OS, RI, and NRM were very good (73%, 27%, and 8%, respectively).[44] Treosulfan provided effective conditioning for allo-HCT in patients with MDS and unfavorable risk cytogenetics, with low clinical toxicity. Therefore, it represents a promising drug in conditioning for allo-HSCT in high-risk MDS.

Conclusion

In this retrospective study, the disease characteristics (e.g., the cytogenetic risk) at diagnosis, but not the intensity of the conditioning regimen, were the most important factors influencing transplant outcomes. Our study observed a disappointing cumulative relapse incidence at 3 years (>30%) for the entire cohort. New regimens resulting in excellent PFS and minimal toxicity and transplant-related mortality are needed.

Clinical Practice Points

- -Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) remains the only potentially curative therapy for high risk IPSS (≥1.5) MDS
- -No randomized trial compared sequential conditioning (FLAMSA-RIC) to myeloablative with reduced toxicity conditioning (FluBu3/FluBu4) and reduced intensity conditioning (FluBu2) for MDS patients.
- -We conducted a multicenter retrospective analysis of 427 patient records to compare patient outcomes after allo-HSCT according to the intensity of these 3 conditioning regimens.
- -No significant differences in outcomes (overall survival, progression-free survival, non-relapse mortality, relapse incidence,

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and graft versus host disease relapse-free survival) were observed between the 3 groups.

- -Using propensity score analysis to overcome baseline imbalances, the only factor influencing overall and progression-free survival was cytogenetic risk at transplantation.
- -With a 3-year OS of 50.4% (95% CI, 45.1%-56.1%) in the entire cohort, new promising drugs in the conditioning and/or early interventions after transplantation are needed to improve outcomes in these patients.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2021.07.027.

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