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Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes

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In this multicenter retrospective study, the outcomes of 836 patients with myelodysplastic syndrome (MDS) who underwent transplantation with a human leukocyte antigen (HLA)–identical sibling donor were analyzed according to 2 types of conditioning: reduced-intensity conditioning (RIC) in 215 patients, and standard myeloablative (or high-dose) conditioning (SMC) in 621 patients. In multivariate analysis, the 3-year relapse rate was significantly increased after RIC (hazard ratio [HR], 1.64; 95% confidence interval [95% CI], 1.2-2.2; *P* = .001), but the 3-year nonrelapse mortality (NRM) rate was decreased in the RIC group (HR, 0.61; 95% CI, 0.41-0.91; *P* = .015). The 3-year probabilities of progression-free and overall survivals were similar in both groups (39% after SMC vs 33% in RIC; multivariate *P* = .9; and 45% vs 41%, respectively; *P* = .8). In conclusion, the lower 3-year NRM after RIC is encouraging, since these patients were older (age > 50 years in 73% RIC vs 28% in SMC, *P* < .001) and had more adverse pretransplantation variables. However, based on the higher risk of relapse, patients with no contraindications for SMC should not receive RIC outside of prospective randomized trials, which are needed to establish the position of RIC-based transplantation in the treatment of patients with MDS. (Blood. 2006;108:836-846)

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative treatment option for patients with myeloid malignancies, including high-risk myelodysplastic syndromes (MDS) and secondary acute myelogenous leukemia (sAML). Standard myeloablative conditioning (SMC) regimens for patients with myeloid malignancies usually consist of the combination of cyclophosphamide and high-dose total body irradiation (TBI) or high-dose busulphan.[1-9] A serious limitation of these regimens is the associated toxicity that requires intense supportive care and predisposes debilitated and elderly patients to a high risk of nonrelapse mortality (NRM) from direct organ toxicity, infections, and graft-versus-host disease (GVHD).[10-12] Recipient age, disease-related risk factors, and the intensity of the conditioning regimen, among other variables, are important predictors of post-HSCT outcome.[12,13] Specifically, the high NRM in elderly and debilitated patients precludes the use of SMC regimens in many patients with high-risk MDS or sAML. Less-toxic conditioning regimens, collectively referred to as reduced-intensity conditioning (RIC) regimens, have been developed by using lower doses of alkylating agents or TBI, usually in combination with fludarabine.[14-26] A large number of RIC regimens have been described in small and heterogeneous groups of patients with MDS, and thus currently the "optimal" RIC regimen is unknown. Current data suggest that RIC regimens do reduce the early morbidity and NRM in high-risk patients while allowing sustained engraftment of allogeneic hematopoietic stem cells not only from matched-related donors but also from unrelated donors.[14-26] On the other hand, the incidence of disease relapse in MDS and AML may increase if the dose intensity of the conditioning is reduced.[17,18,27,28] It is obvious that the final result of these opposite effects of RIC regimens on the outcome of HSCT for MDS is extremely relevant.

In this retrospective, multicenter study, we evaluated the role RICs and SMC regimens in the outcome of patients receiving human leukocyte antigen (HLA)–identical sibling HSCT for MDS and sAML.

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A list of the transplantation centers and investigators of the European Blood and Marrow Transplantation Group appears in the "Appendix."

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Patients, materials, and methods

Patient and transplantation characteristics and definitions

Patient details are shown in Table 1. Included in the study were 993 patients from 128 centers, with a primary diagnosis of MDS (refractory anemia [RA], RA with ring sideroblasts [RARS], RA with excess of blasts [RAEB], RAEB in transformation [RAEB-t], unclassified MDS, or secondary and therapy-related AML [sAML]), while patients with chronic myelomonocytic leukemia were excluded. Only patients who underwent a first allogeneic transplantation between January 1997 and December 2001 with HLA-genoidentical siblings and who were registered in the European

Table 1. Patient characteristics

	Standard myeloablative conditioning	Reduced-intensity conditioning	*P*
No. (%)	621 (74.3)	215 (25.7)	
Period of transplantation, no. (%)			
1997-1998	268 (43.2)	30 (14)	
1999-2001	353 (56.8)	185 (86)	
Male sex, no. (%)	340 (54.8)	121 (56.3)	
Median age, y (range)	45 (18-67)	56 (27-72)	< .001
35 y or younger, no. (%)	135 (21.7)	5 (2.3)	
36-50 y, no. (%)	315 (50.7)	54 (25.1)	
Older than 50 y, no. (%)	171 (27.5)	156 (72.6)	
Male patient-female donor, no. (%)	132 (21.3)	50 (23.3)	
CMV risk group, no. (%)			< .005
Patient^{+}/donor$^{+/-}$ (high risk)	275 (44.3)	107 (50)	
Patient^{-}/donor$^{+/-}$ (intermediate-low risk)	70 (11.3)	28 (13)	
Patient^{-}/donor^{-} (low risk)	128 (20.6)	21 (9.8)	
Last FAB disease classification, no. (%)			.007
Secondary or therapy-related AML	198 (37.4)	75 (41.4)	
RA or RARS	72 (13.6)	20 (11.1)	
RAEB	126 (23.8)	59 (32.6)	
RAEB-t	134 (25.3)	27 (14.9)	
Unclassified MDS	91 (14.7)	34 (15.8)	
Response to chemotherapy at transplantation, no. (%)			.02
Untreated	234 (37.7)	90 (41.9)	
First complete remission (CR-1)	211 (34)	66 (30.7)	
Non-CR-1	176 (28.3)	59 (27.4)	
More than 10% blasts in BM at transplantation, no (%)	73 (11.8)	31 (14.4)	.04
IPSS risk group, peak (% of cases with known IPSS)*			
Intermediate-1	125 (34)	38 (31)	.5
Intermediate-2	99 (27)	30 (25)	
High	140 (39)	54 (44)	
Cytogenetics, no. (%)†			
Poor risk	147 (59)	41 (66)	.3‡
Other (nonpoor risk)	102 (41)	21 (34)	
Not available	372	153	
Mo from diagnosis			.4
Less than 3	289 (46.5)	89 (41.4)	
3 to 6	192 (30.9)	69 (32.1)	
More than 6	140 (22.5)	57 (26.5)	
Prior autologous HSCT, no. (%)	68 (11)	54 (25)	< .01
Disease phase at transplantation, no. (%)			.3
Early	281 (45.2)	85 (39.5)	
Nonearly	227 (36.6)	84 (39.1)	
Not available	113 (18.2)	46 (21.4)	
Stem cell source, no. (%)			< .001
BM	305 (49.1)	27 (12.6)	
PBSCs	316 (50.9)	188 (87.4)	
CD34^{+} cells/kg cell dose infused, by stem cell source, no. (%)			
PBSCs	316	188	
Below the median§	112 (23)	60 (32)	.9
Above the median§	113 (36)	67 (36)	
Not available	91 (29)	61 (32)	
Bone marrow, no. (%)	305	27	
Below 2.2 × 10^{6}/kg§	69 (23)	6 (22)	.8
Above 2.2 × 10^{6}/kg§	91 (30)	8 (30)	
Not available	145 (47)	13 (48)	
Median mo follow-up in survivors (N/%)	50 (269/43)	38 (93/43)	< .05

*The IPSS risk group was not available in 257 (41%) and 92 (43%) patients in the standard myeloablative and reduced-intensity conditioning groups, respectively.
†Available in detail in 311 patients.
‡Refers to the comparison of cytogenetic risk group in the 311 patients with available data.
§CD34^{+} cell dose below and above the median (defined as 5.5 × 10^{6}/kg) for each stem cell source are classified as low and high cell dose infused, respectively.

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Group for Blood and Marrow Transplantation (EBMT) registry were included in this analysis. SMC included cyclophosphamide plus high-dose TBI (≥ 8 Gy) or cyclophosphamide plus high-dose busulphan (16 mg/kg total dose by mouth or the equivalent intravenous dose), with or without other high-dose cytotoxic agents and/or antithymocyte globulin (ATG) or alemtuzumab. RIC included fludarabine plus intermediate doses of 1 or 2 alkylating agents or low-dose TBI (2 to 4 Gy), with or without ATG or alemtuzumab. Conditioning regimens are detailed in Table 2. Intermediate doses of alkylating agents consisted of busulphan (8 to 10 mg/kg orally), intravenous melphalan (80 to 140 mg/m^2), intravenous cyclophosphamide (600 to 120 mg/m^2), or intravenous thiotepa (5-10 mg/kg). In 157 patients, the exact doses of cytotoxic drugs and/or TBI were not available; we defined them as an "unknown" type of conditioning regimen, and their impact on outcomes was analyzed as detailed in "Statistical methods." Unless otherwise specified, results refer to the 836 patients with a well-classified type of conditioning regimen.

For GVHD prophylaxis, in vitro T-cell depletion was more common in the SMC group (22% in the SMC vs 5% in the RIC regimens; $P < .01$). Among non–T-cell–depleted transplants, the combination of cyclosporine A (CsA) plus methotrexate (MTX) was more common in the SMC, while CsA alone was more common in the RIC group (Table 2). The use and dosage of alemtuzumab or ATG was reported in only 5% and 23% of the study cohorts, respectively. This variable was not uniformly entered into the EBMT database in most patients, and thus the impact on transplantation outcomes of these commonly used antibodies in many RIC regimens published cannot be performed in the current study.

As expected, baseline patient characteristics differed between the 2 study groups. For instance, median recipient age at transplantation was 45 years for the SMC group and 56 years for the RIC group ($P < .001$). Other relevant differences are shown in Table 1. We were able to collect sufficient data on cytogenetics or cytopenias in order to calculate the international prognostic scoring system (IPSS) for MDS in about 50% of patients in both transplantation groups[29] (as shown in Table 1). Disease morphology was classified according to the French-American-British (FAB) classification, and the worst FAB type before HSCT was considered for the analyses. For classifying the disease status at transplantation, we took into account whether complete remission (CR) was achieved with AML-type chemotherapy prior to the transplant conditioning, or if the patient did not receive such treatment, or was refractory to chemotherapy or no longer in CR. A number of patients (324) did not receive AML-type (ie, remission-induction) chemotherapy before HSCT, and they accounted for the "untreated group," which represented similar proportions of patients in both study groups (38% in the SMC regimens vs 42% in the RIC regimens). Additionally, the proportion of patients in first CR after chemotherapy was similar (34% vs 31%, respectively). The remaining 235 patients accounted for the "treated, not in first CR" group because they were in second or later CR or were either refractory, in partial response, or with progressive disease after chemotherapy (28% vs 27%, respectively). Detailed results of cytogenetic data were available in 311 (37%) patients (40% in the SMC regimens vs 29% in the RIC regimens; $P = .008$). Among these patients, high-risk karyotypes, as previously defined,[30] were equally observed in both study groups (147 [59%] of 249 in the SMC regimens vs 41 [66%] of 62 in the RIC regimens).

Disease phase at transplantation (not disease status, as described) was defined as early phase (≤ 5% marrow blasts: untreated RA/RARS or RAEB, RAEB-t, and sAML in first CR with intensive chemotherapy) or non–early phase (> 5% marrow blasts). The source of stem cells was peripheral blood stem cells (PBSCs) in 51% in the SMC regimens vs 87% in the RIC regimens ($P < .001$). Due to the retrospective nature of the study, the reason(s) for inclusion in a RIC protocol and exclusion from a SMC in each transplantation group were not known. In the EBMT database, acute and chronic GVHD (aGVHD and cGVHD, respectively) are graded using established criteria.[30]

Informed consent was obtained locally in accordance with the principles laid out in the Declaration of Helsinki and according to the local and national approvals according to the specific trial followed by each center.

End-point definitions

End points were assessed on the date of last patient contact, and the final database was updated in December 2005. Median follow-up time from transplantation for the patients alive at last update was longer in the SMC group (50 months vs 38 months in the RIC regimens; $P < .05$) Analysis focused on hematopoietic recovery, aGVHD and cGVHD, NRM, disease relapse (REL) or progression, progression-free survival (PFS), and overall survival (OS). The date of neutrophil recovery was defined as the first of 3 consecutive days with an absolute neutrophil count higher than 0.5×10^9/L, while the date of platelet recovery was defined as the first of 7

Table 2. Conditioning regimens and GVHD prophylaxis

	Standard myeloablative conditioning	Reduced-intensity conditioning
Conditioning regimens, no. (%)*		
Standard myeloablative conditioning	621	—
TBI-based + cyclophosphamide/others	273 (44)	—
Chemotherapy only	348 (56)	—
Busulphan-cyclophosphamide	212 (34)	—
Busulphan-cyclophosphamide + other(s)	136 (22)	—
Reduced-intensity conditioning	—	215
Fludarabine + single alkylating agent	—	96 (45)
Fludarabine + busulphan	—	61
Fludarabine + melphalan	—	14
Fludarabine + other	—	21
Fludarabine + low-dose TBI (0.2 Gy)	—	13 (6)
Fludarabine + other agents (except single alkylating agent)	—	106 (49)
Alemtuzumab or ATG-containing	32 (5)	50 (23)
None or not specified	589 (95)	165 (77)
GVHD prophylaxis (excluding alemtuzumab or ATG), no. (%)†		
Non-T-cell depletion	439 (70.7)	180 (84)
CsA + MTX	356 (57.3)	71 (33)
CsA alone	22 (3.5)	69 (32.1)
CsA + other drugs (non-MTX)	61 (9.8)	40 (18.6)
In vitro T-cell depletion + CsA (± MTX)	138 (22.2)	10 (4.7)
Not detailed	44 (7.1)	25 (11.6)

— indicates not applicable.

*Doses detailed in "Patient and transplantation characteristics and definitions."

†$P < .001$.

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consecutive days with a platelet count higher than 50×10^9/L. Analysis of cGVHD included patients who had neutrophil recovery and survived without disease progression for more than 90 days after transplantation; cases were coded as absent, limited, or extensive. Transplantation outcomes were analyzed at 3 years after transplantation, although outcomes at earlier time points are shown in Table 3.

Statistical methods

The probabilities of PFS and OS were estimated from the time of transplantation using Kaplan-Meier curves. Groups were compared using the 2-tailed log-rank test. The hematopoietic recovery and occurrence of GVHD, NRM, and disease relapse or progression were calculated using cumulative incidence estimates, taking into account the competing risk structure.[31,32] Univariate analyses of these latter outcomes were performed using univariate Cox regression models. In addition to the type of conditioning regimen used before HSCT (main study variable), the following covariates were analyzed in univariate analysis: recipient age at transplantation (continuous covariate; 50 years and younger vs older than 50 years for display purposes), year of transplantation (1998-2000 vs 2001-2002), time interval between diagnosis and transplantation (continuous covariate; 3 months and less vs more than 3 months for display purposes), recipient sex, disease type at last disease evaluation (MDS vs sAML), cytogenetics (high-risk karyotypes[29] vs other karyotypes), marrow blast percentage before transplantation (continuous covariate; $< 10\%$ vs 10% or more for display purposes), disease stage at transplantation (first CR vs untreated disease vs treated but not in first CR), disease status or risk group at transplantation (early vs nonearly, as defined previously), recipient-donor sex match (female donor to male recipient vs others), ex vivo T-cell depletion, speed of neutrophil recovery (continuous covariate; 14 days or less vs more than 14 days for display purposes), cytomegalovirus (CMV) risk group (donor and recipient seronegative vs other), $CD34^+$ cell dose infused (continuous covariate categorized as $> 6 \times 10^6$/kg and more vs less), GVHD prophylaxis (CsA + MTX vs CsA alone vs other) and stem cell source (PBSC vs bone marrow [BM]). The IPSS score was only available for about 50% of the patients and thus was not included as a covariate, as previously indicated. For multivariate analyses, the main covariates were first entered into the model; then, covariates found not to be significant at the .10 level were removed from the Cox proportional hazards model in a stepwise backward way. Type of conditioning regimen was held in the model at each step. Potential interactions between the covariate type of conditioning regimen and the other remaining covariates were tested, adding cross-product terms to the model in a forward stepwise way. Grades II to IV aGVHD were introduced in the final models for NRM, relapse, PFS, and OS as a time-dependent covariate. Departure from the proportional

Table 3. Engraftment and transplantation outcomes (acute GVHD, chronic GVHD, NRM, relapse, PFS, and OS), with univariate impact of transplantation group

	No. evaluated	Standard myeloablative conditioning	No. evaluated	Reduced-intensity conditioning	*P*
Hematologic reconstitution and engraftment	621		215		
No hematologic recovery	621	25 (4)	215	12 (5.6)	.3
Not evaluable (death < day +15)	621	11 (1.8)	215	5 (2.3)	
Primary graft failure	610	14 (2.8)	210	7 (3.2)	
Secondary graft failure	599	4 (0.6)	203	4 (1.9)	
Stable engraftment	621	581 (93.6)	215	194 (90.2)	
D to more than 0.5×10^9/L neutrophils (range)	599	16 (0-90)	203	14 (1-59)	.001
D to more than 50×10^9/L platelets (range)	599	23 (5-90)	203	16 (0-90)	< .001
GVHD					
Acute GVHD, any grade (% of all cases)	621	362 (58)	215	92 (43)	< .001*
No		259 (42)		123 (57)	
Grade I		148 (27)		39 (20)	
Grade II		127 (23)		22 (11)	
Grade III		58 (11)		15 (7)	
Grade IV		29 (5)		16 (8)	
D onset acute GVHD, median (range)		15 (1-31)		13 (1-31)	
Chronic GVHD (%)	400		132		.15*
No		190 (48)		73 (55)	
Limited		109 (27)		31 (24)	
Extensive		101 (25)		28 (21)	
NRM (cumulative incidence, 95% CI)†	621		215		
3 mo		0.20 (0.17-0.23)		0.15 (0.11-0.21)	
1 y		0.28 (0.25-0.32)		0.20 (0.15-0.26)	.04
3 y		0.32 (0.28-0.36)		0.22 (0.17-0.28)	
Disease progression/relapse (cumulative incidence, 95% CI)‡	621		215		
3 mo		0.08 (0.06-0.10)		0.14 (0.11-0.20)	
1 y		0.22 (0.19-0.25)		0.35 (0.30-0.43)	< .01
3 y		0.27 (0.24-0.31)		0.45 (0.38-0.53)	
Progression-free survival (cumulative incidence, 95% CI)§	621		215		
3 mo		0.72 (0.74-0.80)		0.76 (0.69-0.81)	
1 y		0.50 (0.46-0.54)		0.45 (0.38-0.52)	.1
3 y		0.41 (0.37-0.45)		0.33 (0.27-0.40)	
Overall survival (cumulative incidence, 95% CI)§	621		215		
3 mo		0.82 (0.79-0.85)		0.84 (0.79-0.89)	
1 y		0.58 (0.54-0.62)		0.57 (0.49-0.63)	.7
3 y		0.45 (0.41-0.49)		0.41 (0.35-0.47)	

*Test for linear association in a 2*k table, where k was the number of treatment groups compared.

†Cumulative incidence with disease progression as competing risk; univariate likelihood ratio test from Cox model = log-rank from Kaplan-Meier.

‡Cumulative incidence with NRM as competing risk; univariate likelihood ratio test from Cox model = log-rank from Kaplan-Meier.

§(1 − sum of NRM and relapse incidence) by definition; identical to Kaplan-Meier estimate; log-rank test.

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hazards assumption was assessed using methods based on partial residuals and a graphical approach. If the proportional hazards assumption did not hold for a covariate, stratified or extended Cox models with time-dependent covariates were considered to assess whether the estimate of the main risk factor (conditioning regimen) would be biased due to a model misspecification. If this was not the case, we accepted a small deviation from the proportional hazards assumption in secondary covariates.

When groups were compared according to continuous covariates, the Mann-Whitney *U* test or Kruskal-Wallis 1-way analysis of variance on ranks test were used for differences in medians. According to the group sizes, a chi-square analysis or Fisher exact test was used to compare categorical covariates. SPSS version 11 (SPSS, Chicago, IL) was used for all statistical analyses. All the analyses described were first executed in the entire patient cohort (n = 993, including the 157 patients with an undefined type ["missing"] of conditioning regimen), and then in the 836 patients with a clearly defined type of conditioning regimen (because the other covariate patterns might be influenced by the group of 157 patients, and hence correction for confounding might be different). In both approaches the condition regimen was used as a factor, in the first with 3 levels, and in the second analysis with only 2 levels. This separate analysis was intended to identify whether the "missing" group of patients had any different outcomes that would suggest a selection bias. Since the results from this group did not differ from the other 836 patients, and did not influence the final multivariate models, the analyses will refer to the comparison of SMC and RIC conditioning regimens, unless specified otherwise.

Results

Hematopoietic recovery

Neutrophil recovery occurred in all but 37 patients (4% in the SMC group and 6% in the RIC group; $P = .3$), with a median time to reach an absolute neutrophil count higher than 0.5×10^9/L of 16 days in the SMC group and 14 days in the RIC group ($P = .001$). Median time to achieve a platelet count higher than 50×10^9/L was 23 and 16 days, respectively ($P < .001$). The reported frequency of graft failure (primary plus secondary) was similar between groups, as shown in Table 3.

GVHD

aGVHD developed in 362 (58%) of 621 patients in the SMC group and 92 (43%) of 215 in the RIC group, resulting in a 100-day cumulative incidence of 65% and 46%, respectively ($P < .001$). The number of each grade of aGVHD is shown in Table 3. The median day of onset of aGVHD was +15, without differences between groups. cGVHD developed within 1 year after transplantation in 210 (52%) of 400 evaluable patients in the SMC group (109 limited and 101 extensive cGVHD) and 59 (45%) of 132 RIC patients (31 limited and 28 extensive forms).

NRM

The 3-month and 3-year incidences of NRM were 20% and 32% in the SMC, and 15% and 22% in the RIC group, respectively ($P = .04$) (Table 3 and Figure 1). In univariate analysis, the variables that were associated with an increased 3-year NRM were (1) use of SMC regimens ($P = .03$); (2) patient age older than 50 years ($P = .004$); (3) low $CD34^+$ cell dose infused ($P = .04$); (4) not being in first CR at transplantation ($P < .001$); (5) BM as stem cell source ($P = .05$); and (6) non–poor-risk karyotype ($P = .05$). In multivariate analysis, the variables that increased the NRM are shown in Table 4, and the use of RIC showed a statistically significant impact toward reducing 3-year NRM ($P = .015$). The cumulative incidence of NRM in patients older than 50 years was

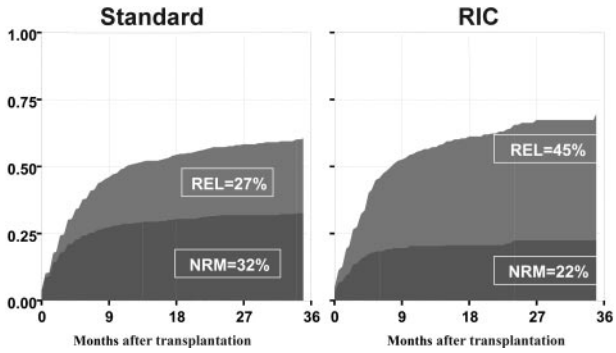

Figure 1. NRM and REL cumulative incidence estimates (36-month) from a competing risk model, estimated separately for both conditioning regimens. STANDARD myeloablative and RIC.

57% in the SMC versus 32% in the RIC group ($P = .01$). In addition, the 3-year NRM was higher with SMC in all disease statuses at transplantation, as shown in detail in Figure 2.

Disease REL or progression

Nearly one-fourth (161 [26%]) of patients in the SMC group and 87 (40%) in the RIC group progressed or relapsed, resulting in a 3-year cumulative incidence of 27% and 45%, respectively ($P < .01$ in univariate analysis), as shown in Table 3 and Figure 1. In univariate analysis, the variables that were associated with an increased 3-year incidence of REL were (1) use of RIC regimens ($P < .01$); (2) disease status not in first CR after chemotherapy at transplantation ($P < .001$); (3) pharmacologic GVHD prophylaxis with ATG or alemtuzumab versus other(s) ($P < .05$); (4) advanced disease phase at transplantation ($P < .05$); (5) poor-risk karyotype ($P < .001$); and (6) time interval from diagnosis to transplantation other than 3 to 6 months ($P = .03$). Table 5 shows in detail results of the multivariate analysis, which identified 4 variables to be associated with increased 3-year REL risk, including the use of RIC regimens ($P = .001$). The cumulative incidences of REL in patients aged younger than or older than 50 years old were higher in the RIC group (age > 50 years, 38% in the SMC group vs 59% in the RIC group; and in < 50 years, 28% vs 51%, respectively). As shown in Figure 3, the 3-year incidence of transplantation failure (NRM + REL) was nearly identical with both types of conditioning regimens in all age categories because a lower NRM in the RIC group was counterbalanced by higher REL. In addition, the REL was lower with SMC in all disease statuses at transplantation, as shown in detail in Figure 2. The largest difference is in the chemorefractory group (treated with AML type but not achieved first CR at transplantation), with a 3-year REL incidence of 37% versus 65%, respectively.

Survival

As shown in Table 3, the type of transplantation conditioning had no impact on the 3-year probabilities of OS and PFS; the 3-year OS was 45% in the SMC group and 41% in the RIC group ($P = .7$), while PFS was 41% and 33%, respectively ($P = .4$).

PFS. In univariate analysis, the variables that decreased the 3-year PFS probability were (1) sAML versus other MDS types ($P = .03$); (2) disease status not in first CR at transplantation ($P < .001$); (3) age older than 50 years ($P = .05$); (4) poor-risk karyotype ($P = .03$); (5) time interval from diagnosis to transplantation other than 3 to 6 months ($P = .03$); (6) BM as stem cell source ($P = .04$); and (7) donor or recipient seropositive for CMV before transplantation ($P = .06$). Table 6 shows in detail results of

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Table 4. Multivariate analysis of 36-month nonrelapse mortality in a Cox model

Variable	No. evaluable	Hazard ratio on NRM (95% CI)*	*P* (overall) contrast†
Transplantation group			
Standard myeloablative conditioning‡	621	(1)	
Reduced-intensity conditioning	215	0.61 (0.41-0.91)	.015
Patient age			
50 y or younger‡	508	(1)	
Older than 50 y	326	1.4 (1.1-1.8)	.04
Response to AML-type chemotherapy			(.025)
First complete remission‡	276	(1)	
Untreated	235	1.5 (1.04-2.1)	.03
Treated, but not in CR1	241	1.6 (1.1-2.2)	.01
CD34$^+$ cell dose infused§			(.1)
Low‡	247	(1)	
High	278	0.7 (0.5-0.98)	.04
Interval from diagnosis to transplantation			
3 to 6 mo‡	192	(1)	
Other than 3 to 6 mo‖	429	1.4 (1.03-1.9)	.03

Other variables with nonsignificant trends toward increasing NRM (*P* value, .06-0.1): (1) Bone marrow as stem cell source ($P = .08$).

*A hazard ratio less than 1.0 indicates that the variable leads to a reduction of NRM, while a value above 1.0 indicates that it leads to an increase in NRM.

†Some risk factors in the Cox model contain a category for "unknown" to avoid loss of information; the overall *P* value between brackets denotes the *P* value of the complete risk factor; the individual *P* values denote the *P* values of the given contrasts to the reference category. For clarity, the "unknown" categories as well as the nonsignificant risk factors have been omitted from the table.

‡Reference group.

§See Table 1 for details.

‖$P = .1$

the multivariate analysis, in which 3 variables were found to decrease the 3-year probability of PFS: (1) sAML versus other MDS types; (2) disease status not in first CR at transplantation; and (3) age older than 50 years; RIC, however, showed no influence on PFS ($P = .9$).

OS. In univariate analysis, variables that decreased the 3-year OS were (1) patient age older than 50 years ($P = .009$); (2) disease status not in first CR at transplantation ($P < .001$); (3) sAML versus other MDS types ($P = .03$); (4) time interval from diagnosis to transplantation other than 3 to 6 months ($P = .06$); (5) low CD34$^+$ cell dose infused ($P = .04$); and (6) BM as stem cell source ($P = .06$). In multivariate analysis, the variables that decreased OS are shown in Table 7, and RIC had no impact on 3-year OS: (1) patient age older than 50 years; (2) sAML versus other MDS types; and (3) disease status not in first CR at transplantation (detailed in Table 7). Figure 4 shows the adjusted probability of OS by transplantation group and disease status. OS was similar in both transplantation groups in all disease statuses (notably, treated but not in first CR [33% in SMC vs 33% in RIC] and first CR [56% vs 57%, respectively]).

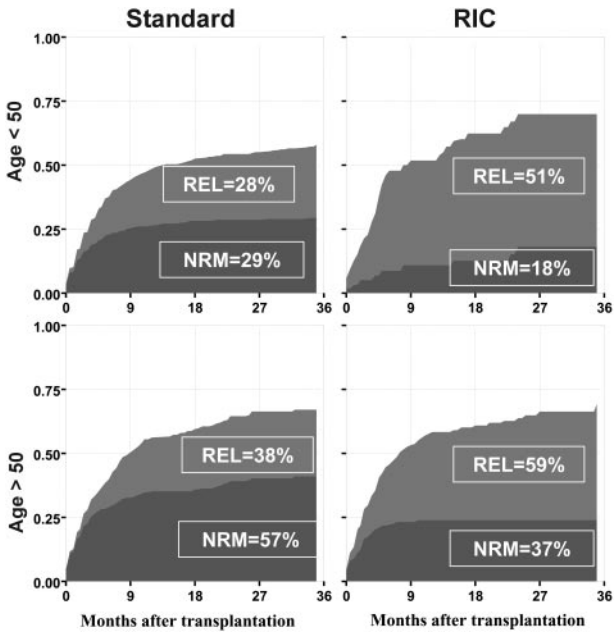

Figure 2. NRM and REL cumulative incidence estimates (36-month) from a competing risk model, estimated separately for both conditioning regimens (standard myeloablative and RIC) and 3 disease status categories at transplantation. The three categories are "untreated," "treated; in CR1," and "treated; not in CR1."

Discussion

The current study has confirmed the impact of previously observed risk factors on the outcome of HSCT from an HLA-identical sibling using SMC regimens, including age, disease phase and status at time of transplantation, type of MDS (RA and RARS with a better outcome), the cytogenetic risk category, and, more recently, the source of stem cells and number of CD34$^+$ cells infused.[1-18,33,34] Reports from large international registries and studies from single centers included only patients in the SMC group who received transplants before 1998, with median patient ages of 35 to 40 years, since allogeneic HSCT was rarely done in patients older 50 years of age. In fact, age older than 45 to 50 years was shown to be the major prognostic variable for increased NRM, PFS, and OS in the largest studies published. The EBMT reported a 3-year NRM rate of 43%,[5] while the International Bone Marrow Transplant Registry (IBMTR)[10] and the Seattle group[8] reported NRM rates of 37% and 40%, respectively, even in such young patient groups. In all studies, older age (with few patients > 50 years of age) was the strongest negative predictor of NRM, with a corresponding impact on PFS and OS, but not on MDS relapse. The other most significant variable that had a prognostic impact on outcome in most studies is MDS "risk category." Risk category can be classified by the type of

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Table 5. Multivariate analysis of 36-month disease progression/relapse in a Cox model

Variable	No. evaluable	Hazard ratio of relapse (95% CI)*	*P* (overall) contrast†
Transplantation group (main study variable)			
Standard myeloablative conditioning‡	621	(1)	
Reduced-intensity conditioning	215	1.64 (1.2-2.2)	.001
Response to AML-type chemotherapy			(< .001)
First complete remission‡	276	(1)	
Untreated	235	1.2 (0.5-2.3)	.48
Treated, but not in CR1	241	2.1 (1.1-3.8)	.025
Risk (or disease phase)			(.001)
Early stage‡	365	(1)	
Advanced stage	311	2.2 (1.2-4.1)	.01
Cytogenetics§			(< .001)
Nonpoor risk‡	122	(1)	
Poor risk	188	2.4 (1.5-3.8)	.001

Other variables with a nonsignificant trend toward increasing relapse ($P = .06$-$.1$): (1) pharmacologic GVHD prophylaxis with ATG or alemtuzumab (0.10); and (2) interval from diagnosis to transplantation other than 3 and 6 months ($P = .1$).

*A hazard ratio less than 1.0 indicates that the variable leads to a reduction of disease relapse, while a value above 1.0 indicates that it leads to an increase in relapse.

†Some risk factors in the Cox model contain a category for "unknown" to avoid loss of information; the overall *P* value between brackets denotes the *P* value of the complete risk factor; the individual *P* values denote the *P* values of the given contrasts to the reference category. For clarity, the "unknown" categories as well as the nonsignificant risk factors have been omitted from the table.

‡Reference group.

§See "Patient and transplantation characteristics and definitions" for details.

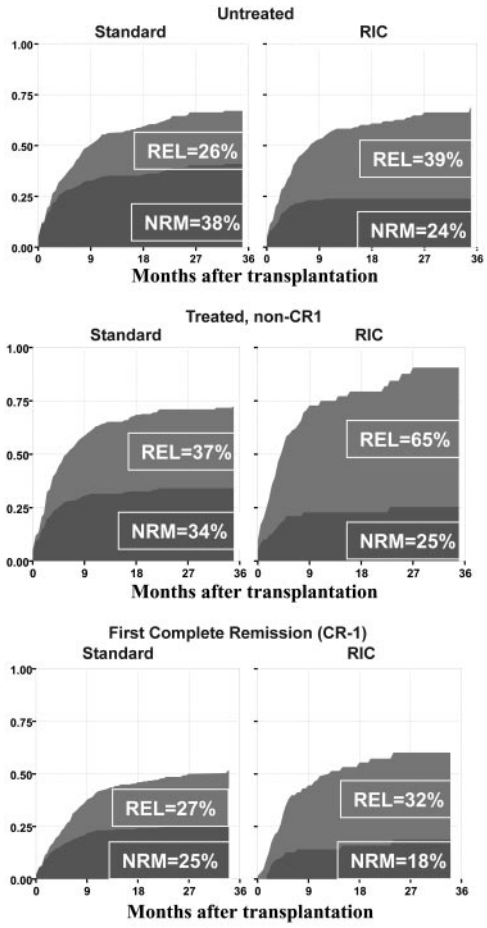

Figure 3. NRM and REL cumulative incidence estimates (36-month) from a competing risk model, estimated separately for both conditioning regimens (standard myeloablative and RIC) and 2 age classes (≤ 50 years and > 50 years).

MDS (with RA and RARS being low-risk, and all other types, especially sAML, being high-risk), the percentage of BM blasts at HSCT, the cytogenetic risk group and/or the IPSS.[10,35] In this regard, our results, which include a large number of patients receiving transplants in a recent period, identified similar prognostic factors. In addition, PBSCs as a stem cell source showed a trend toward reducing the NRM rate, confirming a prior study from the EBMT.[6] Unfortunately, we were unable to test the prognostic impact of the IPSS, since the variables required for calculating the IPSS score were not available for a relatively large proportion of patients, which was similar in both study groups (Table 1). However, the IPSS had no impact in univariate analysis in the 55% of SMC and 57% RIC recipients for whom the IPSS could be estimated (data not shown in detail).

The results from this large retrospective study show that RIC regimens may reduce the 3-year NRM rate after allogeneic HSCT for MDS when compared to SMC regimens, but with a higher risk of disease relapse and no impact on OS and PFS. The reduction of NRM in multivariate analyses is a promising finding, since patients who received RIC are likely to have serious comorbidities, which led the transplantation center to choose RIC, and surely many of these patients would not have received a HSCT with SMC in most institutions.

In general, the results of allogeneic HSCT have improved over time in all disease categories and donor types. In MDS, the EBMT analyzed the treatment outcome of patients who received transplants in 3 consecutive time periods, showing a progressive improvement in the 3-year OS and PFS, mainly due to a decrease in NRM.[5] Thus, it is important that the current study includes SMC and RIC allografts during the same period (1997 to 2001). Although all transplantations were from an HLA-identical sibling, both transplantation groups were heterogeneous regarding the exact types of conditioning regimens used, and, as previously emphasized, some important disease-related or conditioning-related variables were not available for most cases, especially patients' comorbidities.[36] These handicaps are common to most retrospective registry studies, and can only be partially corrected by the large number of patients analyzed. Other important deleterious variables for many outcomes were confirmed in the current study, mainly high-risk MDS and sAML (especially if not in first CR at

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Table 6. Multivariate analysis of 36-month PFS in a Cox model

Variable	No. evaluable	Hazard ratio of PFS (95% CI)*	*P* (overall) contrast†
Transplantation group (main study variable)			
Standard myeloablative conditioning‡	621	(1)	
Reduced-intensity conditioning	215	1.1 (0.8-1.4)	.9
Disease group			(.088)
Secondary acute leukemia‡	463	(1)	
Myelodysplasia	276	0.78 (0.6-0.98)	.03
Response to AML-type chemotherapy			(< .001)
First complete remission‡	235	(1)	
Untreated	276	1.3 (1.01-1.7)	.04
Treated, but not in CR1	241	2 (1.6-2.5)	< .001
Patient age			
50 y or younger‡	508	(1)	
Older than 50 y	326	1.2 (1-1.5)	.053
Cytogenetics§			(.02)
Nonpoor risk‡	122	(1)	
Poor risk	188	1.1 (0.79-1.5)	.64

Other variables with a nonsignificant trend toward decreasing the PFS (*P,* .06-.1): (1) interval from diagnosis to transplantation other than 3 to 6 months ($P = .07$); and (2) poor-risk cytogenetics ($P = .098$).

*A hazard ratio less than 1.0 indicates that the variable leads to an increase of PFS, while a value above 1.0 indicates that it leads to a reduction of PFS.

†Some risk factors in the Cox model contain a category for "unknown" to avoid loss of information; the overall *P* value between brackets denotes the *P* value of the complete risk factor; the individual *P* values denote the *P* values of the given contrasts to the reference category. For clarity, the "unknown" categories as well as the nonsignificant risk factors have been omitted from the table.

‡Reference group.

§See "Patient and transplantation characteristics and definitions" for details.

transplantation), older age, poor-risk cytogenetics, and low $CD34^+$ cell numbers infused. Nevertheless, only prospective randomized studies with analyses based on the intention-to-treat principle may overcome the multiple possible selection biases inherent in retrospective registry analyses. In this respect, the EBMT MDS subcommittee of the Chronic Leukemia Working Party (CLWP) has launched a prospective randomized study comparing SMC with a homogeneous fludarabine plus busulphan–based RIC.

In the current study transplantations performed from 3 to 6 months after diagnosis showed a trend for a higher OS, and, in general, prior studies showed that a longer duration of MDS before HSCT decreases survival.[1-13,37] These data support the consideration of transplantation early in the course of the disease, but it should be stressed that allogeneic HSCT may be postponed in patients with low-risk MDS in the absence of life-threatening cytopenias. A recent analysis by the Seattle group confirmed that delayed transplantation may result in maximized OS for low and intermediate-1 IPSS groups,[1] waiting for the development of a new cytogenetic abnormality, the appearance of a clinically important cytopenia, or an increase in the percentage of marrow blasts.

In conclusion, the reduction in 3-year NRM after a heterogeneous group of RIC indicates that the goal of reducing early NRM with RICs has been accomplished, but at the cost of a significantly higher risk of relapse. Thus, patients with no contraindications for

Table 7. Multivariate analysis of 36-month OS in a Cox model

Variable	No. evaluable	Hazard ratio of OS (95% CI)*	*P* (overall) contrast†
Transplantation group (main study variable)			
Standard myeloablative conditioning‡	621	(1)	
Reduced-intensity conditioning	215	0.97 (0.76-1.25)	.82
Patient age			
50 y or younger‡	508	(1)	
Older than 50 y	326	1.3 (1.05-1.6)	.02
Disease group			(.02)
Secondary acute leukemia‡	463	(1)	
Myelodysplasia	276	0.72 (0.57-0.92)	.007
Response to AML-type chemotherapy			(< .001)
First complete remission‡	276	(1)	
Untreated	241	1.3 (1.02-1.8)	.04
Treated, but not in CR1	234	1.8 (1.4-2.4)	< .001
Cytogenetics§			(.045)
Non-poor risk‡	122	(1)	
Poor-risk	188	1.1 (0.8-1.5)	.47

*A hazard ratio less than 1.0 indicates that the variable leads to an increase of OS, while a value above 1.0 indicates that it leads to a reduction of OS.

†Some risk factors in the Cox model contain a category for "unknown" to avoid loss of information; the overall *P* value between brackets denotes the *P* value of the complete risk factor; the individual *P* values denote the *P* values of the given contrasts to the reference category. For clarity, the "unknown" categories as well as the nonsignificant risk factors have been omitted from the table.

‡Reference group.

§See "Patient and transplantation characteristics and definitions" for details.

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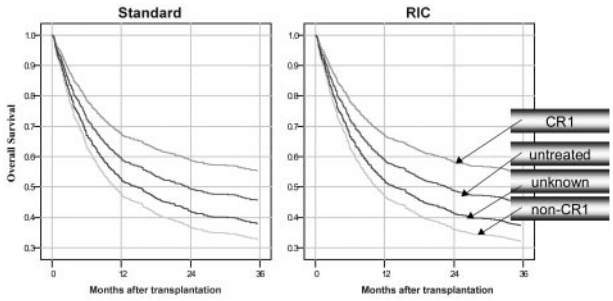

Figure 4. Overall survival (36-month) from a multivariate Cox model, evaluated by conditioning regimen (standard myeloablative and RIC) and 3 statuses at transplantation, adjusted for other relevant risk factors.

SMC should not receive RIC outside of prospective randomized trials. In addition, different RIC approaches should be compared in detail, since the alkylating agent dose intensity and the use of monoclonal antibodies may have an impact on transplantation outcome.[18,22,38-40]

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Appendix

Listed are transplantation centers and responsible coinvestigators who included patients in this study; each center's EBMT Centre Identification Code (CIC) is shown in brackets and is followed by the number of patients included.

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Caballero, Hospital Clinico, Salamanca, Spain [727] 10; D. Blaise, Institut Paoli Calmettes, Marseille, France [230] 9; L. Verdonck, University Medical Centre Utrecht, the Netherlands [239] 9; N. Harhalakis, Evangelismos Hospital, Athens, Greece [622] 9; G. Ehninger, Universitätsklinikum Dresden, Germany [808] 9; P. Ljungman, Huddinge University Hospital, Huddinge, Sweden [212] 8; W. Arcese, University "La Sapienza," Rome, Italy [232] 8; J.-Y. Cahn, Hopital Jean Minjoz, Besancon, France [233] 8; S. McCann, St James Hospital Trinity College, Dublin, Ireland [257] 8; A. Bosi, Ospedale di Careggi, Firenze, Italy [304] 8; J. H. Bourhis, Institut Gustave Roussy, Villejuif, France [666] 8; M. Michallet, Hopital E. Herriot, Lyon, France [671] 8; R. Arnold, Charite, Campus Mitte Med. Klinik, Berlin, Germany [807] 8; F. Guilhot, Hopital La Miletrie, Poitiers, France [264] 7; R. Schwerdtfeger, Deutsche Klinik für Diagnostik, Wiesbaden, Germany [311] 7; D. Niederwieser, University of Leipzig, Germany [389] 7; R. Haas, Heinrich Heine Universität, Düsseldorf, Germany [390] 7; A. Ho, University of Heidelberg, Germany [524] 7; G. Ossenkoppele, Free University Hosp. A'dam, Amsterdam, the Netherlands [588] 7; H. Koc, Ankara University, Ibni Sina Hospital, Ankara, Turkey [617] 7; J. Hansz, K. Marcinkowski, University of Medical Science, Poznan, Poland [730] 7; S. Amadori, University Tor Vergata, St Eugenio Hospital, Rome, Italy [756] 7; M. Martelli, University of Perugia, Italy [794] 7; J. Beck, University of Erlangen, Germany [809] 7; A. Buzyn, Hôpital Necker, Paris, France [160] 6; A. Ferrant, Cliniques Universitaires St Luc, Brussels, Belgium [234] 6; I. Franklin, Glasgow Royal Infirmary, Glascow, Scotland, United Kingdom [244] 6; A. Burnett, University of Wales, Cardiff, Wales, United Kingdom [303] 6; C. Craddock, University Hospital Birmingham NHST Trust, Birmingham, United Kingdom [387] 6; N. 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Chapuis, Hopital Cantonal Universitaire, Geneva, Switzerland [261] 4; B. Labar, University Hospital Centre—Rebro, Zagreb, Croatia [302] 4; W. Linkesch, Karl Franzens University Graz, Austria [308] 4; J. Rowe, Rambam Medical Center, Haifa, Israel [345] 4; G. Lucarelli, Pesaro Hospital, Pesaro, Italy [539] 4; M. Boasson, CHRU, Angers, France [650] 4; J. Besalduch, Hospital Universitari Son Dureta, Palma de Mallorca, Spain [722] 4; B. Rotoli, "Federico II" Medical School/University of Napoli, Italy [766] 4; A. Hellmann, Medical University of Gdansk, Gdansk, Poland [799] 4; M. Hamon, Plymouth Hospitals NHS Trust/Derriford Hospital, Plymouth, United Kingdom [823] 4; H. Tilly, Centre Henri Becquerel, Rouen, France [941] 4; K. Remes, Turku University Central Hospital, Turku, Finland [225] 3; J. Davies, Western General Hospital, Edinburgh, Scotland, United Kingdom [228] 3; F. Jones, Belfast City Hospital, Belfast, Northern Ireland, United Kingdom [268] 3; M. Brune, Sahlgrenska University Hospital, Goeteborg, Sweden [289] 3; B. Hertenstein, Medical School of Hannover, Germany [295] 3; D. Hoelzer, Universität Frankfurt, Germany [297] 3; P. Zachée, AZ Stuivenberg, Antwerp, Belgium, [339] 3; R. Scime, Ospedale V. Cervello, Palermo,

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Italy [392] 3; G. Lucarelli, Pesaro Hospital, Pesaro, Italy [529] 3; H. Sayer, Friedrich-Schiller-Universität Jena, Germany [533] 3; A. Lange, K. Dluski Hospital & Institute of Immunology & Experimental Therapy, Wroclaw, Poland [538] 3; J. de Pablos Gallego, Hospital University Virgen de las Nieves, Granada, Spain [559] 3; A. Schwarer, Alfred Hospital, Melbourne, Australia [595] 3; H. Wandt, Klinikum Nürnberg, Germany [625] 3; R. Schots, University Hospital VUB, Brussels, Belgium [630] 3; M. Sanz, Hospital Universitario La Fe, Valencia, Spain [663] 3; T. Masszi, St László Hospital, Budapest, Hungary [739] 3; G. Juliusson, University Hospital Linköping, Sweden [740] 3; A. Grañena, Institut Catala d'Oncologia, Barcelona, Spain [759] 3; A. Newland, St Batholomew's and the Royal London Hospital, London, United Kingdom [768] 3; R. Giustolisi, University of Catania, Italy [792] 3; G. Mariani, University di Palermo, Italy [814] 3; J. F. 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