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Management of Myelodysplastic Syndrome Relapsing after Allogeneic Hematopoietic Stem Cell Transplantation: A Study by the French Society of Bone Marrow Transplantation and Cell Therapies

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A B S T R A C T

To find out prognostic factors and to investigate different therapeutic approaches, we report on 147 consecutive patients who relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for myelodysplastic syndrome (MDS). Sixty-two patients underwent immunotherapy (IT group, second allo-HSCT or donor lymphocyte infusion), 39 received cytoreductive treatment alone (CRT group) and 46 were managed with palliative/supportive cares (PSC group). Two-year rates of overall survival (OS) were 32%, 6%, and 2% in the IT, CRT, and PSC groups, respectively ($P < .001$). In multivariate analysis, 4 factors adversely influenced 2-year rates of OS: history of acute graft-versus-host disease (hazard ratio [HR], 1.83; 95% confidence interval [CI], 1.26 to 2.67; $P = .002$), relapse within 6 months (HR, 2.69; 95% CI, .82 to 3.98; $P < .001$), progression to acute myeloid leukemia (HR, 2.59; 95% CI, 1.75 to 3.83; $P < .001$), and platelet count < 50 G/L at relapse (HR, 1.68; 95% CI, 1.15 to 2.44; $P = .007$). A prognostic score based on those factors discriminated 2 risk groups with median OSs of 13.2 versus 2.4 months, respectively ($P < .001$). When propensity score, prognostic score, and

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treatment strategy were included in Cox model, immunotherapy was found to be an independent factor that favorably impacts OS (HR, .40; 95% CI, .26 to .63; $P < .001$). In conclusion, immunotherapy should be considered when possible for MDS patients relapsing after allo-HSCT.

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INTRODUCTION

Myelodysplastic syndrome (MDS) represents a group of clonal myeloid stem cell disorders with a heterogeneous spectrum of presentations, ranging from an indolent course over several years to rapid progression to acute myeloid leukemia (AML). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only available curative approach for patients with higher risk MDS [1-4]. However, despite the beneficial effects of allo-HSCT, these patients are at substantial risk of relapse after transplantation [5-8]. Additionally, the risk of relapse remains high despite various pretransplant "debulking" strategies with the aim of controlling the disease and reducing the incidence of post-transplant relapse. Indeed, in a previous study [9], we observed a 3-year cumulative incidence of relapse of 37% in patients who received either induction-type chemotherapy or demethylating agents (DMAs) before transplantation.

The prognosis of post-transplant relapse is poor, leading to a rapidly progressive disease with a fatal outcome. The management of patients with MDS who relapse after allo-HSCT is still controversial. In addition, no prognostic factor, which may guide therapeutic intervention, has yet been described, and the optimal treatment for relapse has yet to be determined.

As a result of the lack of well-established data, the management of patients relapsing after allo-HSCT is challenging and consists of many disparate strategies. Several studies have addressed the issue of post-transplant relapse in MDS patients. Except in cases where palliative or supportive care is the only feasible option, cytoreductive treatment (CRT), using either DMAs or induction-type chemotherapy, has been used with differing degrees of success, as well as immunotherapeutic strategies, with donor lymphocyte infusion (DLI) or second allo-HSCT, either alone or in combination with CRT [10-17]. However, the number of patients evaluated in these studies was limited, and interpretation of their data is confounded by the inclusion of both MDS and AML. To identify factors predictive of survival after relapse and to investigate the impact of different therapeutic strategies on outcome, we report a multicenter retrospective study of 147 consecutive patients with MDS who relapsed after allo-HSCT.

METHODS

This study was approved by the board of the Société Française de Greffe de Moelle et de Thérapie Cellulaire and was conducted according to the Declaration of Helsinki.

Selection Criteria

The medical records of patients who received allo-HSCT for MDS were comprehensively reviewed. Data were made as homogeneous as possible by using the following inclusion criteria: first allo-HSCT from either a sibling or an unrelated donor HLA identical at the allele level (termed 10/10). Patients who received allo-HSCT from an HLA-mismatched donor, from cord blood, or from a T cell–depleted graft and those with chronic myelomonocytic leukemia or aged <18 years were excluded. MDS relapse was defined as the presence of ≥5% and <20% of marrow blasts and/or the reappearance of major myelodysplastic features associated with cytopenias or evidence of autologous reconstitution when chimerism was available. Relapse as progression to AML was defined as the presence of ≥20% of marrow blasts.

Consequently, 461 consecutive patients with MDS who underwent allo-HSCT between March 1999 and December 2011 in 24 French and Belgian centers were identified, of whom 17 (3.7%) were excluded for missing data. Of the 444 remaining patients, 147 had experienced relapse or progression to AML and were included in this study. Table 1 summarizes patients and donor characteristics and transplantation modalities.

Treatment of Relapse and Response Evaluation

As shown in Figure 1, patients were divided into 3 groups according to the main salvage therapeutic strategy as decided by physicians in charge of patients: palliative supportive care alone (PSC group, n = 46), CRT alone including DMAs or AML-like intensive chemotherapy (CRT group, n = 39), and immunotherapy (IT) with DLI (primarily $CD3^+$) and/or second allo-HSCT (same donor for half of patients) (IT group, n = 62). Some patients of the latter group received other treatment in addition to IT. Thus, patients in the IT group received DLI alone (n = 24; 16%) or second allo-HSCT alone (n = 7; 5%), CRT with DLI (n = 18; 12%), or CRT plus DLI and second allo-HSCT (n = 13; 9%). To investigate clinical factors that influenced physicians' decision in cases where a more intensive therapy was not selected (CRT or IT for PSC group, IT for CRT group), we requested several items: (1) patient characteristics (poor performance status, infections, other comorbidities, many prior therapeutic lines), (2) disease characteristics (too advanced stages, proliferative relapse, early relapse), (3) availability of allogeneic source, (4) patient decision, and (5) other.

Preallogeneic and postrelapse treatment responses were assessed using the 2006 International Working Group criteria [18]. Only an overall response rate that included complete and partial remission, complete marrow remission, and hematologic improvement was considered for statistical analysis.

Statistical Analyses

The analyses were performed on the reference date of June 1, 2013. The tests were 2-sided, with a Type I error set at $\alpha = .05$. Baseline characteristics were presented as the median (interquartile range) for continuous data (assumption of normality assessed using the Shapiro-Wilk test) and as the number of patients and associated percentages for categorical parameters. Comparisons of patient characteristics between the 3 treatment groups (PSC, CRT, and IT) were made using the chi-square or Fisher's exact tests for categorical variables and using analysis of variance or the Kruskal-Wallis test for quantitative parameters (homoscedasticity verified using Bartlett's test).

Overall survival (OS) was defined as the interval from relapse after allo-HSCT to death, regardless of the cause of death. Disease-free survival was not reported here given that International Working Group 2006 criteria are difficult to address in a confident way in the setting of a retrospective analysis including patients undergoing therapies that also can induce bone marrow failure and dysplastic changes by itself. OS curves and estimates were constructed using the Kaplan-Meier method. The log-rank test was used in a univariate analysis to test the prognostic value of patient characteristics at transplantation for the occurrence of an event.

Cox proportional hazards regression was used to investigate prognostic factors in a multivariate situation by backward and forward stepwise analysis of the factors considered significant in univariate analysis (entered into the model if $P < .1$) and according to clinically relevant parameters [19,20]. The proportional hazard hypotheses were verified using Schoenfeld's test and plotting residuals. The interactions between possible prognostic factors were also tested. Results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). A prognostic score for survival was designed using the variables from the multivariate model and according to the rounded HRs values. Risk categories derived from this score were compared using log-rank test.

To evaluate the impact of postrelapse treatment strategy, propensity score matching was used in an attempt to reduce the effect of potential bias in this cohort. This method allowed balancing of all relevant measured variables between the treatment groups. The covariates included in the propensity score model were known to be clinically relevant: age (as continuous variable), World Health Organization diagnosis, International Prognostic Scoring System (high versus low risk), progression to more aggressive disease before allo-HSCT, treatment before allo-HSCT, response status before allo-HSCT, conditioning (myeloablative

Table 1
Demographics, Disease Characteristics, and Transplantation Modalities of the 147 Patients

	Total (n = 147)	PSC Group (n = 46)	CRT Group (n = 39)	IT Group* (n = 62)	*P*
Median age at transplant, yr (range)	56 (18-69)	55 (32-69)	57 (24-64)	55 (18-69)	.415
Patient sex, n (%)					.418
Male	87 (60)	27 (59)	20 (51)	40 (65)	
Female	60 (40)	19 (41)	19 (49)	22 (35)	
FAB/WHO at diagnosis, n (%)					.965
RA/RARS/RCMD	38 (26)	11 (24)	11 (28)	16 (26)	
RAEB-1	39 (26)	13 (28)	11 (28)	15 (24)	
RAEB-2	63 (43)	19 (41)	15 (39)	29 (47)	
RAEB-t/AML	7 (5)	3 (7)	2 (5)	2 (3)	
IPSS at diagnosis, n (%)					.102
Low/intermediate-1	65 (44)	15 (33)	17 (44)	33 (53)	
Intermediate-2/high	82 (56)	31 (67)	22 (56)	29 (47)	
Progression to more aggressive disease before transplant, n (%)					.080
No	92 (63)	23 (50)	25 (64)	44 (71)	
Yes	55 (37)	23 (50)	14 (36)	18 (29)	
Year of transplant, n (%)					<.001
≤2005	73 (50)	34 (74)	8 (21)	31 (50)	
>2005	74 (50)	12 (26)	31 (79)	31 (50)	
Marrow blasts at transplant, n (%)					.942
<5%	13 (9)	4 (9)	3 (8)	6 (10)	
≥5%	134 (91)	42 (91)	36 (92)	56 (90)	
Disease status at transplant, n (%)					.030
Responders	64 (44)	14 (30)	23 (59)	27 (44)	
Nonresponders	83 (56)	32 (70)	16 (41)	35 (56)	
Treatment before allo-HSCT, n (%)					.012
Yes	92 (63)	29 (63)	31 (79)	32 (52)	
No	55 (37)	17 (37)	8 (21)	30 (48)	
Donor type, n (%)					.864
Sibling	96 (65)	29 (63)	25 (64)	42 (68)	
HLA-matched unrelated	51 (35)	17 (37)	14 (36)	20 (32)	
Stem cell source, n (%)					.008
Marrow	44 (30)	13 (28)	5 (13)	26 (42)	
PBSCs	103 (70)	33 (72)	34 (87)	36 (58)	
Conditioning, n (%)					.127
Myeloablative	41 (28)	15 (33)	6 (15)	20 (32)	
Reduced intensity	106 (72)	31 (67)	33 (85)	42 (68)	
ATG, n (%)					.013
No	75 (51)	31 (67)	14 (36)	30 (48)	
Yes	72 (49)	15 (33)	25 (64)	32 (52)	
TBI, n (%)					.005
No	93 (63)	22 (48)	32 (82)	39 (63)	
Yes	54 (37)	24 (52)	7 (18)	23 (37)	
GVHD before relapse, n (%)					
Acute	68 (46)	23 (50)	18 (46)	27 (44)	.802
Chronic	30 (20)	10 (22)	12 (31)	8 (13)	.092

FAB/WHO indicates French-American-British classification/World Health Organization classification; RA/RARS/RCMD, refractory anemia/refractory anemia with ringed sideroblasts/refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transformation; IPSS, International Prognostic Score System; PBSCs, peripheral blood stem cells; ATG, antithymocyte globulin; TBI, total body irradiation.

* IT group includes DLI and/or second allo-HSCT.

versus reduced-intensity conditioning), antithymocyte globulin as part of the conditioning regimen, total body irradiation as part of the conditioning regimen, type of donor (sibling versus unrelated), source of stem cells (blood versus marrow), graft-versus-host disease (GVHD) prophylaxis (cyclosporine plus methotrexate versus cyclosporine plus other drugs), occurrence of acute GVHD before relapse, interval between transplantation and relapse (<6 versus ≥6 months), peripheral blood blasts (absent versus present), progression to AML and platelet count (<50 versus ≥50 g/L), and year of transplant (before/during versus after 2005). Patients in the PSC and CRT groups had a similar outcome in terms of 2-year OS; therefore, these patients were analyzed as 1 group and compared with the IT group in multivariate analyses. Statistical analysis was performed using Stata 12 software (StataCorp LP, College Station, TX).

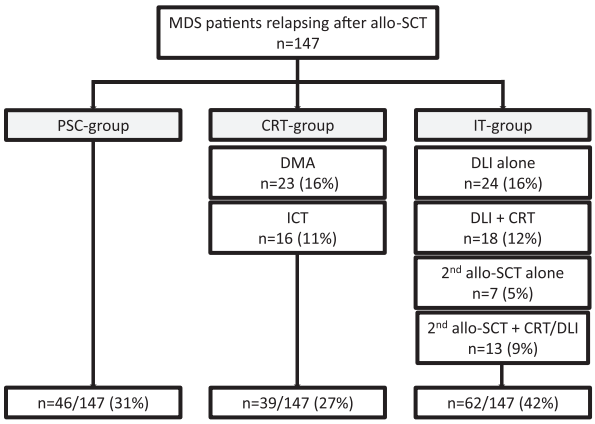
RESULTS

Relapse Characteristics

Post-transplant relapse occurred at a median time of 6 months (range, 1 to 100). Patient characteristics at relapse are summarized in Table 2. The median age was 57 years (range, 19 to 70). Relapse was revealed by the presence of circulating blasts in 73 patients (50%), and more than a third of the patients presented with progression to AML. Median hemoglobin level, platelet count, and leukocyte count were 9.5 g/dL (range, 6.7 to 16.2), 40 g/L (range, 2 to 1155), and 2.8 g/L (range, .2 to 46), respectively. International Prognostic Scoring System cytogenetic risk group at relapse was recorded as good (33%), intermediate (18%), or poor (49%) in the 76 assessable patients (52%). When compared with patients without available cytogenetics (n = 71), these patients harbored significantly less aggressive features (less frequent progression to a more advanced disease before allo-HSCT, more delayed relapse, higher hemoglobin and platelets count) (Supplementary Table 1).

Outcomes

The median follow-up duration from relapse was 33 months. Thirty-three of 124 assessable patients (27%) had developed GVHD after a median time of 47 days (range, 1 to 502). The estimated 2-year rate of OS was 16% for the whole population. At 2 years, relapse or progression to AML remained the main cause of death (86% of patients). Other



Abbreviations: MDS, myelodysplastic syndrome; allo-SCT, allogeneic hematopoietic stem cell transplantation; PSC, palliative-supportive care; CRT, cytoreductive therapy; IT, immunotherapy including donor lymphocyte infusion and/or second allogeneic hematopoietic stem cell transplantation; DMA, demethylating agents; ICT, intensive chemotherapy; DLI, donor lymphocyte infusion.

Figure 1. Distribution of the 147 patients with MDS according to the salvage therapy received for relapse after allo-HSCT.

causes of death included infection (9%), GVHD (3%), second cancer (1%), and undetermined in 1%.

Prognostic Factors for OS and Scoring System

As shown in Table 3, univariate analysis revealed that 2-year OS was influenced by the type of post-relapse salvage therapy ($P < .001$), pretransplant therapeutic strategies ($P = .008$), development of acute GVHD before relapse ($P = .022$), interval time from transplant to relapse ($P < .001$), progression to AML ($P < .001$), platelet count ($P < .001$), and peripheral blood circulating blasts ($P < .001$) at relapse. In multivariate analysis, developing acute GVHD before relapse (HR, 1.83; 95% CI, 1.26 to 2.67; $P = .002$), relapsing within 6 months of transplantation (HR, 2.69; 95% CI, 1.82 to 3.98; $P < .001$), progression to AML at relapse (HR, 2.59; 95% CI, 1.75 to 3.83; $P < .001$), and platelets < 50 G/L at relapse (HR, 1.68; 95% CI, 1.15 to 2.44; $P = .003$) adversely influenced 2-year OS (Table 4).

We designed a scoring system based on the 4 characteristics of relapse that were identified by multivariate analysis in 141 assessable patients: 2 points were attributed to history of acute GVHD before relapse and platelets count < 50 G/L at relapse and 3 points to progression to AML at relapse and relapse onset ≥ 6 months. Such a scoring system allowed patients to be segregated into 2 risk groups according to statistical distribution: low score (<5 points) or high score (≥5 points). Median 2-year OS was 2.4 months in the high-risk group (n = 73) and 13.2 months in the low-risk group (n = 68; $P < .001$) (Figure 2).

Impact of Postrelapse Treatment Strategy

One hundred nineteen patients were assessable for response. The best overall response rates were 4%, 17%, and 57% in the PSC, CRT, and IT groups, respectively ($P < .001$). In addition, overall response rate was higher in patients who developed postrelapse GVHD compared with those who did not (63% versus 23%, respectively; $P < .001$).

Two-year OS rates were 2%, 6%, and 32% in the PSC, CRT, and IT groups, respectively ($P < .001$) (Figure 3). Of note, IT was performed in responding patients to before CRT in 18% of cases. DLI provided similar OS compared with second allo-HSCT, and both groups were well balanced concerning relevant factors (Supplementary Table 2). Similar observations were noted when comparing second allo-HSCT from the same versus other donor (data not shown).

The multivariate Cox model that included treatment strategy (IT versus CRT/PSC), scoring system (high versus low risk), and propensity score matching showed that IT was independently associated with better 2-year OS outcomes (HR, .40; 95% CI, .26 to .63; $P < .001$). Of note, 2-year OS rates were 40.5% for low-risk IT patients, 8% for high-risk IT patients, 7.4% for low-risk SC/CRT patients, and 0% for low-risk SC/CRT patients ($P < .001$) (Supplementary Figure 1). The investigation of the factors that influenced the physicians' decision in cases where a more intensive therapy was not selected (CRT or IT for the PSC group, IT for the CRT group) revealed that for both PSC and CRT groups, disease characteristics were the main cause (43.5% and 46%, respectively) followed by patient characteristics (26% for both), availability of stem cell source (11% and 7.5%,

Table 2
Relapse Characteristics of the 147 Patients

	Total (n = 147)	PSC Group (n = 46)	CRT Group (n = 39)	IT Group (n = 62)	*P*
Median age, yr (range)	57 (19-70)	56 (32-70)	59 (24-70)	55 (19-70)	.381
Interval from transplantation to relapse, n (%)					.052
<6 mo	74 (50)	30 (65)	17 (44)	27 (44)	
≥6 mo	73 (50)	16 (35)	22 (56)	35 (56)	
Median hemoglobin, g/dL (range)	9.5 (6.7-16.2)	9 (6.7-12.5)	9.6 (7.2-13.8)	10 (6.8-16.2)	.019
Platelets, n (%)					.001
<50 G/L	80 (54)	35 (76)	19 (49)	26 (42)	
≥50 G/L	67 (46)	11 (24)	20 (51)	36 (58)	
Circulating blasts,* n (%)					.568
Yes	73 (51)	24 (54)	21 (55)	28 (46)	
No	70 (49)	20 (46)	17 (45)	33 (54)	
Progression to AML†					.017
No	91 (62)	26 (63)	19 (49)	46 (77)	
Yes	49 (38)	15 (37)	20 (51)	14 (23)	
IPSS cytogenetics,‡ n (%)					.442
Good	25 (33)	6 (32)	4 (22)	15 (38.5)	
Intermediate	14 (18)	5 (26)	2 (11)	7 (18)	
Poor	37 (49)	8 (42)	12 (67)	17 (43.5)	

* Patients assessable for circulating blasts: 143 (97%).
† Patients assessable for marrow blasts percentage: 141 (96%).
‡ Patients assessable for cytogenetics: 76 (52%).

Table 3
Univariate Analysis for 2-Year OS from Relapse

Variable	No. of Patients	2-Year OS		*P*
		Percent	Standard Deviation	
FAB/WHO at diagnosis				.827
RA/RARS/RCMD	38	23	7	
RAEB-1	39	13	5	
RAEB-2	63	16	5	
RAEB-t/AML	7	14	13	
IPSS at diagnosis				.073
Low/intermediate-1	65	19	5	
Intermediate-2/high	82	13	4	
Progression to more aggressive disease before transplant				.054
No	92	17	4	
Yes	55	14	5	
Year of transplant				.987
≤2005	73	15	4	
>2005	74	15	4	
Treatment before allo-HSCT				.008
Supportive care	55	24	6	
CRT	92	11	3	
Disease status at transplant				.638
Responders	64	16	5	
Nonresponders	83	15	4	
Donor type				.165
Sibling	96	19	4	
HLA-matched unrelated	51	10	4	
Stem cell source				.143
Marrow	44	25	7	
PBSCs	103	12	3	
Conditioning				.922
Myeloablative	41	16	6	
Reduced intensity	106	16	4	
ATG				.215
No	75	13	4	
Yes	72	19	5	
TBI				.081
No	93	19	4	
Yes	54	11	4	
GVHD prophylaxis				.050
CSA + MTX	56	22	6	
CSA + other drugs	96	13	4	
Acute GVHD before relapse				.022
No	79	21	5	
Yes	68	10	4	
Chronic GVHD before relapse				.349
No	117	16	3	
Yes	30	13	6	
Interval from transplantation to relapse				<.001
≥6 mo	73	25	5	
<6 mo	74	7	3	
Peripheral blood blasts at relapse				<.001
No	74	23	5	
Yes	73	9	3	
Platelet count at relapse				<.001
≥50 G/L	67	23	5	
<50 G/L	80	10	3	
Progression to AML				<.001
No	92	23	4	
Yes	49	5	3	
IPSS cytogenetics at relapse				.731
Good	25	27	9	
Intermediate	14	21	11	
Poor	36	23	7	

CSA indicates cyclosporine A; MTX, methotrexate.

respectively), and patient refusal (2% and 5%). Other causes were reported in 17.5% and 15.5%, respectively (Supplementary Table 3).

Table 4
Multivariate Analysis for 2-Year OS from Relapse

Prognostic Factors	HR	95% CI	*P*
Acute GVHD before relapse	1.83	1.26-2.67	.002
Interval from transplantation to relapse <6 mo	2.69	1.82-3.98	<.001
Progression to AML at relapse	2.59	1.75-3.83	<.001
Platelet count < 50 G/L at relapse	1.68	1.15-2.44	.007

DISCUSSION

To the best of our knowledge, this is the largest study to investigate factors influencing survival after relapse and treatment strategies in patients relapsing after allo-HSCT for MDS. To make the study population as homogeneous as possible, we only included patients who received allo-HSCT from an HLA-matched sibling or an HLA-allele matched unrelated donor (10/10). Donor–recipient HLA matching was verified from the database of the French National Donor Registry as previously described [21]. In addition, data were meticulously cross-checked using several different methods of verification (matching several sources of data, onsite verification, and a computerized search for discrepancies). Because of the retrospective nature of our study, missing data remained regarding marrow blast percentage, presence of circulating blasts, cytogenetics, evaluation of response to postallogeneic salvage therapy, and occurrence of GVHD after relapse in 4%, 2.7%, 48%, 19%, and 16% of cases. As shown for cytogenetic evaluation, we believe less invasive management as well as less strict follow-up was done for these patients with very poor prognosis.

Our study highlights factors that could aid the identification of patients who may benefit from salvage intervention. Relapse characteristics were the most important of these factors. Relapses occurring earlier than 6 months after allo-HSCT and those associated with a high tumor burden (ie, circulating blasts and a high percentage of marrow blasts) were strongly associated with poor survival. A high tumor burden at relapse and the development of acute GVHD before relapse are reportedly risk factors for poor OS in patients relapsing after allo-HSCT for AML or acute lymphoblastic leukemia [22-26].

Although disease status at transplantation and cytogenetics are determining risk factors for post-transplant relapse [9-27], these parameters did not appear to influence the outcome after relapse in our study. Our results are in line with previous studies in patients with AML [22]. However, only 52% of patients were assessable and presented with significantly less aggressive features. More invasive diagnostic management was then proposed to the patients with expected better outcome, which is consistent with routine practice. Such bias might also impair the evaluation of the cytogenetics prognostic impact. The recent description of the MDS mutational spectrum has been shown to be of prognostic relevance, which could also be relevant in the setting of relapse after allo-HSCT [28].

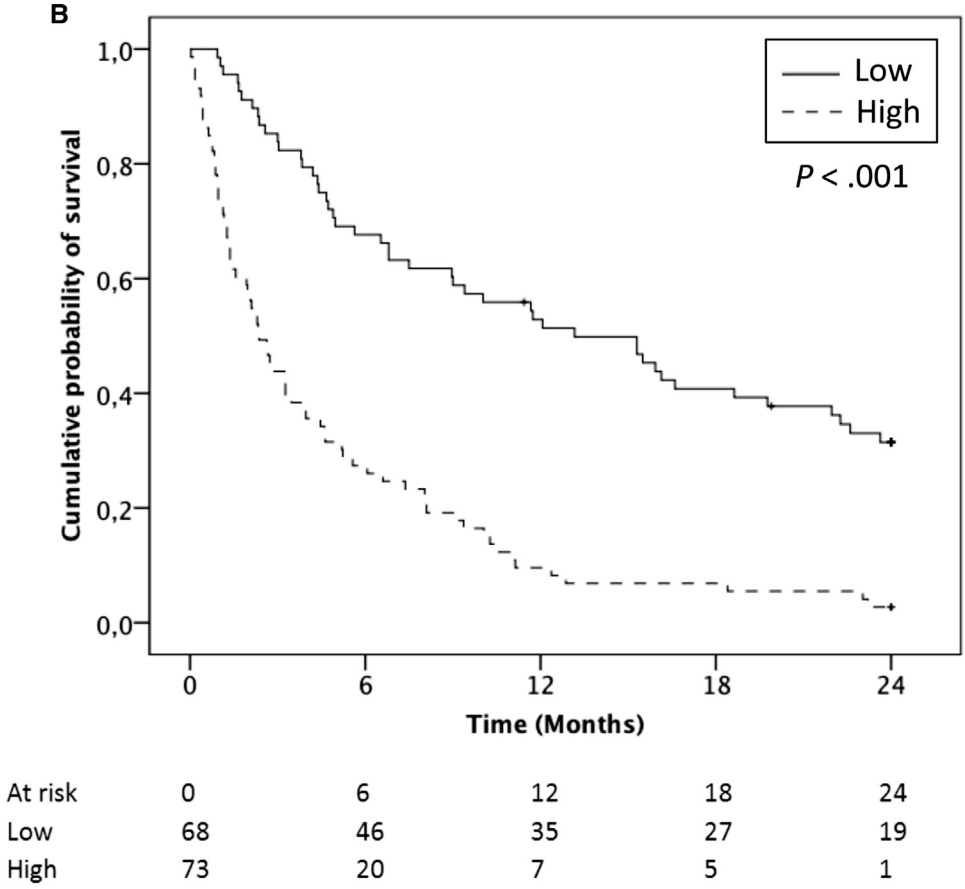
The major finding of this study was that IT was associated with improved OS for patients with MDS relapsing after allo-HSCT who received such strategy as believed appropriate by treating physicians. Several studies have discussed the management of post-transplant relapse [10-17]. However, the interpretation of their results is complicated, because none of these studies restricted their inclusion criteria to either 1 underlying disease or to allo-HSCT from HLA-matched donors only.

A

Characteristics at relapse	Points
prior acute graft-versus-host disease	2
interval from transplantation < 6 months	3
platelet count < 50 G/L	2
Progression to acute myeloid leukemia	3
Total score	*10*

Prognostic group	Score
Low	< 5
High	≥ 5

B

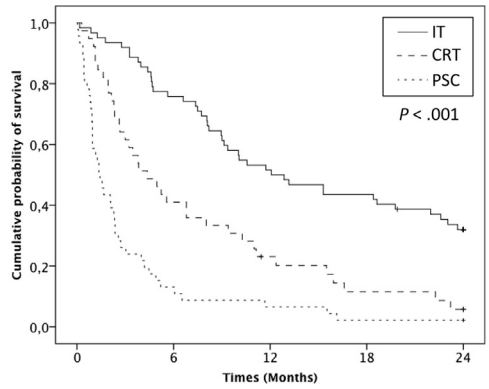


At risk	0	6	12	18	24
Low	68	46	35	27	19
High	73	20	7	5	1

Figure 2. Prognostic score for OS from relapse after allo-HSCT. (A) Prognostic scoring system. The score was computed (for each patient) based on occurrence of acute GVHD (2 points), interval from transplantation to relapse <6 months (3 points), marrow blasts at relapse ≥20% (3 points), and platelet count at relapse <50 g/L (2 points). (B) Kaplan-Meier curves according to the score (high if ≥5 vs. low if <5).

Given the retrospective nature of our study, we used propensity score adjustment to accurately identify the impact of treatment strategies on patient outcome by balancing the covariates in the 2 groups and reducing bias when treatment assignment was not random [29]. Although the propensity score method was originally developed to analyze very large datasets, even in case of more limited studies, it can yield correct estimations of treatment effects [30]. In our work, simulations considering samples size from 1000 to 40 subjects did not substantially alter the Type I error and led to relative biases below 10%. Year of transplantation (before or after 2005) was included in the propensity score because azacitidine, became available in France in 2005 and transplantation modalities and patient outcomes changed over time [31,32].

Despite the use of propensity score matching, the heterogeneity of MDS relapse after allo-HSCT may lead to further bias concerning the therapeutic decision because



At risk	0	6	12	18	24
IT	62	47	32	27	19
CRT	39	16	8	4	2
PSC	46	6	3	1	1

Abbreviations: IT, immunotherapy including donor lymphocyte infusion and/or second allogeneic hematopoietic stem cell transplantation; CRT, cytoreductive therapy; PSC, palliative-supportive care.

Figure 3. Kaplan-Meier estimates of 2-year OS in the 147 patients according to the salvage therapy received for relapse after allo-HSCT.

other factors that are difficult to measure may influence the therapeutic choice. For this reason, we also investigated what finally conditioned physicians' decision to not indicate more intensive therapy. For the both PSC group and CRT group, disease characteristics were the main cause for not indicating more intensive therapy. We then took into account the main factor influencing choice of therapy (ie, disease characteristics) in our analyses. Finally, we deliberately focused on OS instead of disease-free survival, because the latter may be difficult to obtain with confidence. Moreover, it has been observed that an improvement in OS may not be linked to the achievement of a response in patients with MDS [28].

Outside the context of allo-HSCT, DMAs, including 5-azacitidine and decitabine, have emerged as new therapeutic agents that significantly prolong OS and are considered the current standard of care for most patients with intermediate-2 and high-risk MDS, even though they have no curative potential [33,34]. Although not fully satisfactory, DMAs plus DLI have proven effective for the treatment of patients relapsing after allo-HSCT and who are eligible for that type of therapy [10,11,13].

Given the poor prognosis of patients relapsing after allo-HSCT for MDS and to limit the incidence of relapse, prophylactic approaches that include DMAs and DLI immediately after transplantation could represent a valid option. Such a strategy remains contingent on eligibility of the patients and has to be investigated in further prospective protocols. In conclusion, salvage IT (DLI or second allo-HSCT) yields the best results in patients with MDS relapsing after allo-HSCT and should be, whenever possible, especially offered to patients with a low-risk profile.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at 10.1016/j.bbmt.2015.07.037.

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