Biol Blood Marrow Transplant 20 (2014) 1349–1355

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Upfront Allogeneic Stem Cell Transplantation after Reduced-Intensity/Nonmyeloablative Conditioning for Patients with Myelodysplastic Syndrome: A Study by the Société Française de Greffe de Moelle et de Thérapie Cellulaire

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Article history:
Received 2 February 2014
Accepted 4 May 2014

Key Words:
Transplantation
Azacitidine
Best supportive care
MDS

A B S T R A C T

Cytoreduction before allogeneic stem cell transplantation (allo-SCT) for patients with myelodysplastic syndromes remains a debatable issue. After excluding patients who had received preconditioning induction chemotherapy, we analyzed 128 consecutive patients with myelodysplastic syndrome who received reduced-intensity or nonmyeloablative conditioning (RIC/NMA) allo-SCT. Among them, 40 received azacitidine (AZA) before transplant (AZA group) and 88 were transplanted up front (best supportive care [BSC] group). At diagnosis, 55 patients had intermediate 2 or high-risk scores per the International Prognostic Scoring System and 33 had a high cytogenetic risk score. Progression to a more advanced disease before allo-SCT was recorded in 22 patients. Source of stem cells were blood (n = 112) or marrow (n = 16) from sibling (n = 78) or HLA-matched unrelated (n = 50) donors. With a median follow-up of 60 months, 3-year overall survival, relapse-free survival, cumulative incidence of relapse, and nonrelapse mortality were, respectively, 53% versus 53% ($P = .69$), 37% versus 42% ($P = .78$), 35% versus 36% ($P = .99$), and 20% versus 23% ($P = .74$), for the AZA group and BSC group, respectively. Multivariate analysis confirmed the absence of statistical differences in outcome between the AZA and BSC groups, after adjusting for potential confounders using the propensity

Financial disclosure: See Acknowledgments on page 1355.
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1083-8791/$ – see front matter
http://dx.doi.org/10.1016/j.bbmt.2014.05.010

score approach. The absence of cytoreduction before RIC/NMA allo-SCT did not seem to alter the outcome. However, our results emphasize the need to perform prospective protocols to delineate the role of debulking strategy and to identify subsets of patients who may benefit from this approach.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-SCT) remains the only potentially curative therapeutic approach in patients with myelodysplastic syndrome (MDS).

Because the disease affects more often elderly than young patients, reduced-intensity or nonmyeloablative conditioning (RIC/NMA), which gives similar results to myeloablative conditioning with less toxicity, appeared to be more convenient in this category of patients. Despite the beneficial effects of allo-SCT, these patients are at substantial risk of relapse after transplant, especially in cases of RIC/NMA [1]. High disease burden at transplant has been shown to be correlated with poor outcome and may increase the post-transplant relapse risk [2-4].

Pretransplant induction-type chemotherapy has been recommended in young patients when MDS was associated with more than 5% marrow blasts [5]. The benefit of induction chemotherapy before allo-SCT is not well established, however. Although some studies suggested that upfront allo-SCT with no prior cytoreduction gave the same results as those in patients who received induction chemotherapy [6-8], other studies suggested a beneficial effect of induction chemotherapy before transplant [2,4,9]. Thus, there is no definitive evidence of a survival benefit associated with cytoreductive treatment before allo-SCT in MDS. We and others showed that demethylating agents, which have emerged as the current standard of care for most patients with intermediate 2 and high-risk MDS, were a valid “debulking” approach and showed similar outcomes when compared with induction chemotherapy [10-13].

The aim of the current study was to assess the impact of best supportive care (BSC) compared with before transplant treatment with azacitidine (AZA) on patient outcome after allo-SCT following RIC/NMA for MDS. To perform this retrospective study, we used a propensity score-based approach that can control for potentially confounding biases.

METHODS

The study was approved by the French Society of Bone Marrow Transplantation and Cell Therapy board and conducted according to the Declaration of Helsinki.

Patient Selection

Transplantation modalities were made as homogeneous as possible using the following inclusion and exclusion criteria: (1) patients older than 18 years referred for first allo-SCT after RIC or NMA according to the standard definition published by Bacigalupo et al. [14] and (2) source of stem cell was marrow or blood from either a sibling or an HLA-A, -B, -Cw, -DR, and -DQ identical unrelated donor at the allelic level (so-called 10/10). Patients who received allo-SCT from an HLA-mismatched donor, cord blood, or T cell–depleted graft and patients with chronic myelomonocytic leukemia were excluded.

Participating centers were asked to verify the data recorded for each patient in the French Bone Marrow Transplantation Registry and to provide additional information. Quality of the data was controlled using a computerized search for discrepancy errors and vigorous onsite data verification of each file. HLA matching was cross-checked with the data from the French Bone Marrow Donor Registry as previously described [15].

Consequently, 283 consecutive patients with MDS who underwent allo-SCT between January 1999 and December 2009 in 24 French and Belgian centers were identified. Twenty-seven patients were excluded because their files lacked at least 1 of the following: initial French-American-British (FAB)/World Health Organization (WHO) category or International Prognostic Scoring System (IPSS) classification, treatment before transplantation, and disease status at transplant. In addition, we excluded 128 patients who received induction-type chemotherapy or cytoreduction treatment other than AZA. Based on local physicians' decisions, the 128 remaining patients received either best supportive care (BSC group, n = 88), which included blood transfusion, hormones, growth factors (erythropoietin, granulocyte colony-stimulating factor), and immunosuppressive treatment, or AZA alone (AZA group, n = 40) (Figure 1).

Patient and Donor Characteristics and Transplantation Modalities

Morphological classification, according to FAB and WHO classifications [16,17], was documented as a separate variable at initial diagnosis and at time of transplantation. IPSS at diagnosis was calculated [18], and all progressions to more advanced disease between diagnosis and transplantation were recorded. Responses to treatment and disease status at transplant were reevaluated according to International Working Group 2006 criteria [19].

At diagnosis (Table 1), 42 of 128 patients (33%) had refractory anemia, refractory anemia with ringed sideroblasts, or refractory cytopenia with multilineage dysplasia, 46 (36%) patients had refractory anemia with excess of blasts (RAEB-1), 34 patients (26%) had RAEB-2, and 6 patients (5%) had RAEB in transformation/acute myeloid leukemia (with marrow blasts between 20% and 30%). Cytogenetic analysis was, according to IPSS classification [18], favorable, intermediate, and poor risk in 65 (51%), 30 (23%), and 33 patients (26%), respectively. IPSS was low or intermediate 1 in 73 patients (lower risk category, 57%) or intermediate 2 and high in 55 patients (higher risk category, 43%). Patients in the AZA group had significantly higher IPSS at diagnosis compared with the BSC group ($P = .003$).

In the AZA group, the drug was started after a median time from diagnosis of 192 days (range, 38 to 941) and discontinued at a median time of 54 days before transplant (range, 6 to 438 days). The median number of AZA cycles was 4.5 (range, 2 to 26). The median time from diagnosis to transplant was 22.8 months. Thirty-three patients (26%) were transplanted before 7.3 months, 63 (49%) received allo-SCT between 7.3 and 22.8 months after diagnosis, and 32 (25%) were transplanted after 26.7 months.

Table 2 depicts patients' characteristics at transplant and transplantation modalities according to treatment group before allo-SCT. Thus, median age at transplant was higher in the AZA group compared with the BSC group (60 versus 56 years; $P = .0001$). Overall, 22 of 128 patients (17%) had progressed to a more aggressive disease before transplantation: 7 patients (17.5%) in the AZA group and 15 (17%) in the BSC group. According to International Working Group 2006 criteria [19], 29 patients (23%) were responders (including complete remission, partial remission, or marrow complete remission): 26 patients (65%) in the AZA group and 3 (3%) in the BSC group ($P = .0001$).

Patients of the AZA group received more allo-SCT from an HLA-matched unrelated donor than those of the BSC group ($P = .0001$). There was no

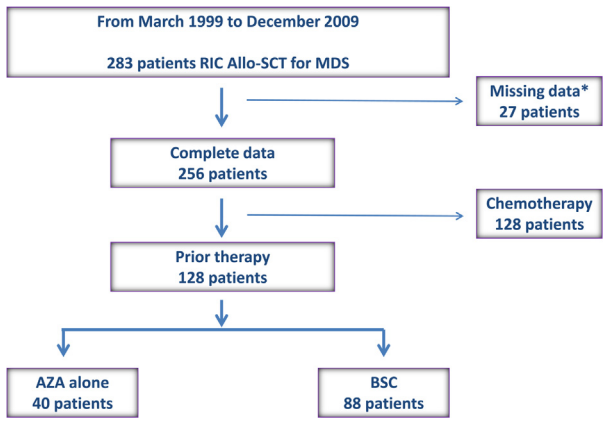

Figure 1. Flow chart for patient selection strategy. Patients whose files were missing at least 1 of the following data were excluded: initial FAB/WHO diagnosis, IPSS at diagnosis, before-transplantation treatment, WHO criteria, and disease status at transplant.

Table 1
Patient Demographics and Clinical Characteristics at Diagnosis

	Total (n = 128)	AZA Alone (n = 40)	BSC (n = 88)	*P*
Sex, n (%)				.36
Male	78 (61)	22 (55)	56 (64)	
Female	50 (39)	18 (45)	32 (36)	
FAB/WHO, n (%)				.028
RA/RARS/RCMD	50 (39)	8 (20)	42 (48)	
RAEB-1	35 (27)	14 (35)	21 (24)	
RAEB-2	37 (29)	15 (38)	22 (25)	
RAEB-t/AML	6 (5)	3 (8)	3 (3)	
IPSS, n (%)				.003
Low/int-1	73 (57)	15 (36.5)	58 (66)	
Int-2/high	55 (43)	25 (62.5)	30 (34)	
Cytogenetics, n (%)				.11
Favorable	65 (51)	20 (50)	45 (51)	
Intermediate	30 (23)	6 (15)	24 (27)	
High risk	33 (26)	14 (35)	19 (22)	
Interval from diagnosis to transplant, n (%)				.03
<7.3 mo	33 (26)	6 (15)	27 (31)	
7.3-12.9 mo	31 (24)	15 (37.5)	16 (18)	
12.9- 26.7 mo	32 (25)	12 (30)	20 (23)	
≥26.7 mo	32 (25)	7 (17.5)	25 (28)	

RA indicates refractory anemia; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; int, intermediate.

difference between the 2 groups regarding the intensity of conditioning because about 75% of patients received RIC in both groups and no patient received 200-cGy total body irradiation alone.

Statistical Analyses

The analysis was performed on the reference date of November 22, 2012. Overall survival (OS) was defined as the interval from allo-SCT to death, regardless of the cause of death. Relapse-free survival (RFS) was defined as survival with no evidence of relapse. Relapse was defined as the presence of more than 5% marrow blasts and/or reappearance of major myelodysplastic features associated with cytopenia (or worsening of previous cytopenia) and evidence of autologous reconstitution when chimerism was available. Nonrelapse mortality (NRM) was defined as death resulting from the graft procedure without evidence of relapse. Estimated 3-year event rates were reported because the number of events beyond 3 years was insufficient for accurate estimates. Estimated 100-day event rates were assessed for acute graft-versus-host disease (GVHD) and neutrophil and platelet engraftment.

For continuous variables, results were expressed as means and standard deviations in cases of normal distribution and as medians and ranges otherwise. The assumption of normality was assessed using the Shapiro-Wilk test. Categorical variables were described by the frequencies and percentages. The 2 before-transplant treatment groups (AZA and BSC) were compared using the chi-square or the Fisher exact tests for categorical data. For continuous variables, the ANOVA or Kruskal-Wallis test were applied according to the distribution of the studied variable.

All censored criteria were calculated from the time of transplantation. For OS, RFS, and acute GVHD, distributions over time were estimated by the Kaplan-Meier product limit method. The log-rank statistic was used to test the prognostic value of patient characteristics at transplant for the occurrence of the event. Before-transplant treatment and variables having a significance level (*P* value) less than .15 from the bivariate analyses were introduced in a multivariable Cox regression, with backward selection at level $P < .15$. Before-transplant treatment was always included in the selection whatever its significance level in bivariate analysis. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were computed, and $P \leq .05$ was considered statistically significant.

The occurrence of relapse, NRM, and chronic GVHD was studied by using competing risk methodology. For the events of relapse and GVHD, death without experiencing the event was considered as a competing event. For NRM, the competing event was relapse. The cumulative incidence of each event was estimated using the Kalbfleish and Prentice method [20]. The individual prognostic value of each variable was assessed by the Gray test (comparison of cumulative incidence curves: bivariate analyses). Before-transplant treatment and variables with $P < .15$ in the bivariate analyses were introduced in a multivariate Fine and Gray model. Adjusted HR and 95% CIs were computed.

Table 2
Patient Characteristics at Transplant and Transplantation Modalities

	Total (n = 128)	AZA (n = 40)	BSC (n = 88)	*P*
Recipient age, median (range)	58 (24-69)	60 (47-68)	56 (24-69)	.0001
Donor age, median (range)	48 (19-77)	46 (19-68)	50 (21-77)	.07
Sex mismatch,* n (%)	26 (20)	8 (20)	18 (20)	.95
Progression to more advanced disease, n (%)				.95
No	106 (83)	33 (82.5)	73 (83)	
Yes	22 (17)	7 (17.5)	15 (17)	
Marrow blasts, median (range)	5 (0-38)	3.8 (0-26)	6 (0-38)	.18
Marrow blasts, n (%)				.04
<5%	57 (45)	24 (60)	33 (38)	
≥5%	65 (51)	16 (40)	49 (56)	
Missing	6 (4)	0	6 (7)	
Disease status, n (%)				.0001
Responders†	29 (23)	26 (65)	3 (3)	
Nonresponders	99 (77)	14 (35)	85 (97)	
Donor type, n (%)				.0001
Sibling	78 (61)	14 (35)	64 (73)	
HLA-matched unrelated	50 (39)	26 (65)	24 (27)	
Stem cell source, n (%)				.06
Marrow	16 (12.5)	2 (5)	14 (16)	
PBSC	112 (87.5)	38 (95)	74 (84)	
ATG, n (%)				.17
No	43 (34)	10 (25)	33 (37)	
Yes	85 (66)	30 (75)	55 (63)	
TBI, n (%)				.89
No	97 (76)	30 (75)	67 (76)	
Yes	31 (24)	10 (25)	21 (24)	
Conditioning, n (%)				.66
NMA	29 (23)	10 (25)	19 (22)	
RIC	99 (77)	30 (75)	69 (78)	
GVHD prophylaxis, n (%)				.66
CSA + MTX	32 (25)	11 (27)	21 (24)	
CSA + other drugs	96 (75)	29 (73)	67 (76)	

PBSC indicates peripheral blood stem cells; ATG, antithymocyte globulin; TBI, total body irradiation; CSA, cyclosporine A; MTX, methotrexate.

* Sex mismatch is defined as a male recipient who received graft from a female donor.

† Responders included patients with complete or partial remission or marrow complete remission.

Because our study was not randomized, we used a propensity score to adjust *P* values for patients who received BSC and those who received AZA [21]. The propensity score model included variables that might have influenced the outcome of allo-SCT; these included age of recipient, IPSS, cytogenetic risk groups, percentage of marrow blast and disease status at transplant, donor type, donor age, stem cell source, time interval between the diagnosis and the transplant, use of total body irradiation, and GVHD prophylaxis. In multivariable analyses, *P* values for before-transplant treatment are presented with and without propensity score adjustment. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, NC). For the Fine and Gray model the R package "cmprsk" was used (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

RESULTS

At the date of analysis (November 22, 2012), median follow-up was 60 months (range, 36 to 143). All but 4 patients had obtained neutrophil engraftment after a median of 17 days (range, 0 to 70). Forty-four patients (34%) had developed grades II to IV acute GVHD, including 16 patients (13%) with grades III to IV. Of the 113 assessable patients who survived more than 100 days, 60 (47%) had developed chronic GVHD, including 36 (28%) with extensive grade. For the whole patient group (n = 128), the 3-year OS, RFS, relapse rate, and NRM were 53%, 41%, 37%, and 22%, respectively.

Bivariate Analysis

Among all studied characteristics, at diagnosis, at transplant, and transplantation modalities, the FAB/WHO classification, the interval from diagnosis to transplant, and the donor type adversely impacted OS, with *P* values of .03, .009 and .04, respectively. RFS was adversely influenced by the cytogenetic risk ($P = .02$) as well as by the time interval between the diagnosis and transplant ($P = .003$), which also impacted the NRM ($P = .01$). The IPSS at diagnosis negatively affected the relapse risk ($P = .04$) and tended to influence OS ($P = .05$). Cytogenetics adversely impacted the relapse risk ($P = .003$).

As shown in Table 3, none of the following variables seemed to influence the outcome of patients: gender and recipient age, sex mismatch, donor age, stem cell source, recipient and conditioning regimen modalities (i.e. antithymoglobulin or total body irradiation), GVHD prophylaxis, donor/recipient cytomegalovirus status, progression to more advanced disease at time of transplant, marrow blasts, or disease status at transplant.

Outcome According to Before-Transplant Treatment

In patients treated with AZA and patients transplanted upfront after BSC, 3-year OS was 53% versus 53% ($P = .69$), 3-year RFS was 37% versus 42% ($P = .78$), cumulative incidence of relapse was 35% versus 36% ($P = .99$), and NRM was 20% versus 23% ($P = .74$), respectively (Figure 2).

Multivariate Analysis

Because treatment with AZA or management of patients with BSC before allo-SCT was not allocated through randomization, we used a propensity score-based approach for the comparison of outcomes between patients in the AZA and BSC groups as described above in Statistical Analyses. The time interval between diagnosis and transplant was found to have an impact on outcome. Therefore, being transplanted after more than 26.7 months adversely influenced OS (HR = 2.28; 95% CI, 1.31 to 3.95; $P = .003$), RFS (HR = 2.39; 95% CI, 1.44 to 3.96; $P = .0007$), and NRM (HR = 2.55; 95% CI, 1.18 to 5.39; $P = .017$). As expected, high-risk cytogenetics had a detrimental impact on RFS (HR = 1.99; 95% CI, 1.18 to 3.38; $P = .01$) and cumulative incidence of relapse (HR = 3.05; 95% CI, 1.68 to 5.53; $P = .0002$). Unrelated donor had a detrimental impact on OS (HR = 1.78; 95% CI, 1.01 to 3.14; $P = .044$) and NRM (HR = 2.30; 95% CI, 1.01 to 5.24; $P = .047$). Disease status (nonresponders versus responders) at transplant adversely influenced NRM (HR = 3.29; 95% CI, 1.13 to 9.58; $P = .029$).

The type of treatment before allo-SCT had no impact on the incidence and severity of either acute or chronic GVHD. Donor type was the only factor that influenced acute GVHD development (HR = 1.66; 95% CI, 1.03 to 2.69; $P = .037$).

Multivariate analysis confirmed the absence of significant differences between AZA and BSC groups in terms of OS (HR = 1.27; 95% CI, .78 to 2.34; $P = .445$), RFS (HR = 1.04; 95% CI, .61 to 1.75; $P = .897$), relapse (HR = 1.15; 95% CI, .62 to 2.13; $P = .653$), and NRM (HR = 1.56; 95% CI, .64 to 3.85; $P = .325$). As shown in Table 4, the same results were obtained after propensity adjustment.

DISCUSSION

In this series, patients with MDS who underwent upfront RIC allo-SCT without prior cytoreduction had similar outcomes compared with those who received AZA as a preconditioning treatment in terms of OS, RFS, cumulative incidence of relapse, and NRM. These results were confirmed after adjustment with propensity score that included main patients and disease characteristics and transplantation modalities.

To our knowledge, our study is the first to investigate the effect of AZA before transplant as compared with BSC in patients undergoing RIC/NMA allo-SCT for MDS. Few studies have addressed the impact of pretransplant AZA in MDS patients [11,13]. In these studies, data interpretation is difficult because of the heterogeneity of pretransplant characteristics regarding the treatment (AZA and/or chemotherapy or BSC) or the conditioning regimens that were either myeloablative or RIC/NMA according to standard definitions [14].

The incidence of post-transplant relapse appears to be higher after RIC/NMA than after myeloablative conditioning [5,22-24]. Because reducing the bulk of the disease before transplant is thought to be a strategy to decrease the incidence of post-transplant relapse [4,5,25], we deliberately chose to restrict our study to patients who received a RIC/NMA regimen, hypothesizing that before-transplant treatment could have a significant impact on outcome in this setting. We also wanted to specifically investigate the impact of AZA before transplant compared with BSC given that AZA showed similar outcomes when compared with induction chemotherapy [10-13].

To make the study population as homogeneous as possible, we included only patients who received allo-SCT from an HLA sibling or HLA-allelically matched unrelated donor (10/10). This donor selection may explain in part the higher survival rate observed in the BSC group when compared with the findings reported by Lim et al. [26], for instance. Indeed, the population of this latter study was different from ours in that Lim et al. included 25% of patients with secondary acute myeloid leukemia, 34% were more than 60 years old, and some patients had received allo-SCT from unrelated mismatched donors. Of note, the OS rate observed in our current study is similar to that previously reported in allo-SCTs from sibling [6,7,15] or HLA-matched unrelated donors [15].

Given the retrospective nature of our study, we used propensity score adjustment to accurately identify the impact of BSC and AZA on patient outcome by balancing the covariates in the 2 groups and reducing bias when treatment assignment was not random [21]. After adjustment, OS, RFS, cumulative incidence of relapse, and NRM were not statistically different between the 2 groups of patients.

In an attempt to identify a subset of patients that could benefit from AZA, we analyzed the 3-year OS in the AZA group according to disease status at transplant. Although the difference in OS did not reach the significance threshold, responders to AZA (n = 26) seemed to do better than nonresponders (n = 14) (62% versus 36%, respectively; $P = .08$). Therefore, if there is an indication for stabilizing the disease while waiting for the transplant, we suggest restricting the use of AZA to patients who are likely to respond to this drug. Indeed, some factors have been identified to influence the response to AZA, such as age, cytogenetics, molecular abnormalities, and hyperferritinemia [27-30]. New therapeutic strategies combining AZA and other drugs known to have an effect in MDS have been suggested [31,32]. However, this latter approach is to be used with caution in candidates for allo-SCT because the combination of AZA and induction-type chemotherapy as debulking treatment was reported to lead to less satisfactory outcomes in a retrospective study [10].

Table 3
Bivariate Analysis by Key Subsets: 3-Year OS and Event-Free Survival, Relapse, and NRM Rates and *P* Values

	No. of Patients	OS		RFS		Relapse		NRM	
		%	*P* (Log-rank)	%	*P* (Log-rank)	%	*P* (Gray [Cumulative Incidence])	%	*P* (Gray [Cumulative Incidence])
Sex			.84		.83		.46		.70
Male	78	52.6		41.9		33.3		23.1	
Female	50	54.0		40.8		40.0		20.0	
Patient age			.30		.08		.27		.68
≤58 yr	64	57.8		49.6		31.3		20.3	
>58 yr	64	48.4		33.5		40.6		23.4	
FAB/WHO			.03		.21		.10		.77
RA/RARS/RCMD	50	71.4		56.5		22		25	
RAEB-1	35	39.1		35.3		16		25	
RAEB-2	37	52.9		33.6		41		17	
RAEB-t/AML	6	33.3		25.0		33		33	
IPSS			.05		.12		.04		.43
Low/int-1	73	60.3		47.9		28.8		24.6	
Int-2/high	55	43.6		32.9		45.5		18.2	
Cytogenetics			.07		.02		.0003		.13
Favorable/int	95	57.9		47.6		27.4		25.3	
High risk	33	39.4		22.2		60.6		12.1	
Sex mismatch*			.91		.58		.41		.89
No	102	52.9		41.3		37.3		21.6	
Yes	26	53.9		41.5		30.8		23.1	
Progression to more advanced disease			.76		.67		.32		.68
No	106	53.8		41.6		34.0		22.6	
Yes	22	50		40.9		45.5		18.2	
Marrow blasts			.23		.14		.10		.71
<5%	57	57.9		44.3		28.1		24.6	
≥5%	63	47.6		37.3		42.9		20.6	
Treatment before allo-SCT			.69		.78		.99		.74
BSC	88	53.4		42.0		36.4		22.7	
AZA alone	40	52.5		36.5		35.0		20.0	
Interval from diagnosis to transplant			.009		.003		.38		.01
<26.7 mo	96	59.4		49.6		33.3		16.7	
≥26.7 mo	32	34.4		17.0		43.8		37.5	
Disease status†			.48		.36		.91		.26
Responders	29	62.1		34.6		34.5		13.8	
Nonresponders	99	50.5		40.4		36.4		24.2	
Donor age			.47		.07		.06		.81
<48 yr	64	57.8		51.4		28.1		21.9	
≥48 yr	63	49.2		32.5		44.4		20.6	
Donor type			.04		.57		.31		.07
Sibling	78	59.0		43.0		39.7		16.7	
HLA-matched unrelated	50	44.0		39.3		30.0		30.0	
Stem cell source			.23		.31		.81		.63
Marrow	16	62.5		50.0		37.5		18.8	
PBSC	112	51.8		39.9		35.7		22.3	
GVHD prophylaxis			.40		.23		.59		.11
CSA + MTX	32	56.2		45.5		40.6		12.5	
CSA + other drugs	96	52.1		40.1		34.4		25	
CMV recipient serostatus			.73		.54		.17		.36
Negative	56	50		39.6		42.9		17.9	
Positive	72	55.6		43.3		30.6		25.0	
CMV donor serostatus			.80		.60		.32		.53
Negative	61	54.1		42.2		32.8		24.6	
Positive	67	52.2		41.0		38.8		19.4	
ATG			.28		.36		.37		.52
No	43	44.1		36.8		41.8		25.6	
Yes	85	57.6		44.1		32.9		20	
TBI			.14		.24		.26		.85
No	97	55.7		43.4		34.0		21.6	
Yes	31	45.2		36.0		41.9		22.6	

RA indicates refractory anemia; RARS, refractory anemia with ring sideroblasts; RAEB, refractory anemia with excess blasts; AML, acute myeloid leukemia; RCMD, refractory cytopenia with multilineage dysplasia; int, intermediate; PBSC, peripheral blood stem cells; CSA, cyclosporine A; MTX, methotrexate; CMV, cytomegalovirus; ATG, antithymocyte globulin; TBI, total body irradiation.

* Sex mismatch is defined as a male recipient who received graft from a female donor.

† Responders included patients with complete or partial remission or marrow complete remission.

Still, prospective studies are warranted to investigate more precisely not only prognostic factors of response but also the optimum schedule of AZA perfusion to enhance response rate and, thus, favorably impact on patient outcome.

In line with what has been already reported [6,25], we observed that delaying the transplant was the foremost independent factor with a detrimental impact on OS, RFS, and NRM. The "wait-and-see" attitude in low-risk IPSS MDS

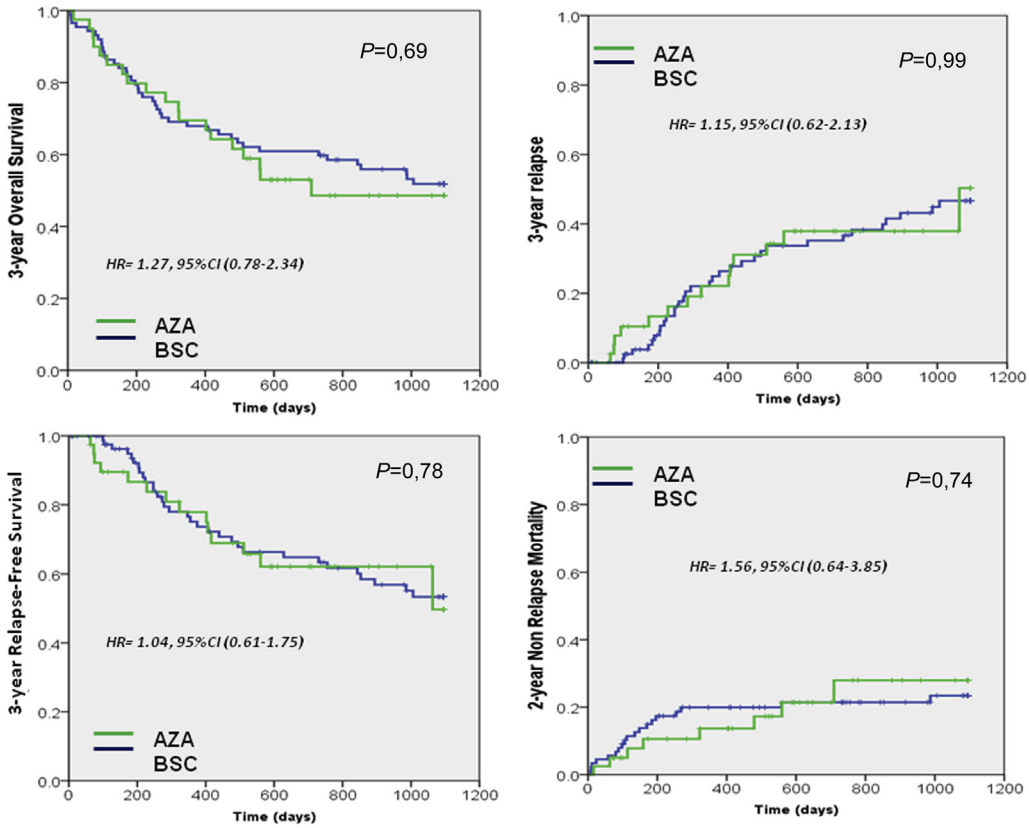

Figure 2. Kaplan-Meier estimates of 3-year OS, RFS, 3-year cumulative incidence of relapse, and NRM in 128 patients, according to treatment received before transplant. (▬) AZA-group, (▬) BSC-group.

patients deserves to be revisited [33]. Indeed, factors such as transfusion dependency, cytogenetics, medical comorbidity, and WHO histologic subtype should all be considered when deciding on the role and the timing of transplantation for these patients [34].

A limitation of this study is its retrospective nature with possible selection bias as a result of the impossibility of accounting for patient dropout (either complication from before-transplant treatment in the AZA group or rapid progression to acute myeloid leukemia in both groups). Thus, the result of this homogeneous study, in the absence of data from prospective randomized studies regarding the usefulness of debulking treatment before transplantation in myelodysplastic patients, could represent a first step forward to an accurate answer to this question. Although AZA is thought to have an immunomodulation effect that could influence

Table 4
Multivariate Analyses

Characteristics	3-Year OS			3-Year RFS			3-Year Relapse			3-Year NRM		
	HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**	HR	95% CI	*P**
Cytogenetics												
Low/int				1			1					
High risk				1.99	1.18-3.38	.01	3.05	1.68-5.53	.0002			
Prior treatment												
AZA alone	1		.45	1		.90	1		.65	1		.33
BSC vs AZA alone	1.27	.68-2.34	.64*	1.04	.61-1.75	.99*	1.15	.62-2.13	.75*	1.56	.64-3.85	.97*
Donor type												
Sibling	1									1		
HLA-matched unrelated	1.78	1.01-3.14	.044							2.30	1.01-5.24	.047
Disease status												
Responders										1		
Nonresponders										3.29	1.13-9.58	.029
Interval from diagnosis to transplant												
<26.7 mo	1			1						1		
≥26.7 mo	2.28	1.31-3.95	.003	2.39	1.44-3.96	.0007				2.52	1.18-5.39	.017

Int indicates intermediate; CSA, cyclosporine A; MTX, methotrexate.
Because our study was not randomized, we used a propensity score to adjust *P* values for patients who received BSC and those who received AZA. The propensity score model included variables that might have influenced the outcome of allo-SCT, including age of recipient, IPSS, cytogenetic risk groups, percentage of marrow blast and disease status at transplant, donor type, donor age, stem cell source, time interval between the diagnosis and the transplant, use of total body irradiation, and GVHD prophylaxis. Before-transplant treatment and variables having a significance level of $P < .15$ in the bivariate analyses were introduced in the multivariate model: *P by propensity score.

GVHD development [35], we did not observe any difference between the 2 groups in terms of acute and chronic GVHD.

In conclusion, the absence of cytoreduction by AZA before allo-SCT did not alter the outcome of patients with MDS. However, there is a clear need for prospective trials to identify a subset of patients who may benefit from debulking treatment before allo-SCT according to the newest prognostic factors.

ACKNOWLEDGMENTS

The authors thank Raja Prince for collecting and checking data onsite. Special thanks to Nicole Raus, the French Society of Bone Marrow Transplantation and Cell Therapy data manager. Ibrahim Yakoub-Agha thanks the "Association Capucine" for their support in his research.

Portions of this article were presented at the European Bone Marrow Transplantation Congress, April 1-4, 2013, London, United Kingdom, and at the 12th International Symposium on Myelodysplastic Syndromes (received Tito Bastianello's best abstracts' award), May 8-11, 2013, Berlin, Germany.

Conflict of interest statement: Y.B. is on the Advisory Board of Celgene. M.Mo. and P.F. have received honoraria and research funding from Celgene. I.Y.A. received research funding from Celgene.

Authorship statement: G.D. and I.Y.A. conceived of and designed the study. G.D., A.D., and I.Y.A. performed data review and analysis. All authors wrote the manuscript and gave final approval of the manuscript.

Financial disclosure: The authors have nothing to disclose.

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