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ORIGINAL REPORT

Impact of Azacitidine Before Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes: A Study by the Société Française de Greffe de Moelle et de Thérapie-Cellulaire and the Groupe-Francophone des Myélodysplasies

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ABSTRACT

Purpose
To investigate the impact of prior-to-transplantation azacitidine (AZA) on patient outcome after allogeneic stem-cell transplantation (alloSCT) for myelodysplastic syndrome (MDS).

Patients and Methods
Of the 265 consecutive patients who underwent alloSCT for MDS between October 2005 and December 2009, 163 had received cytoreductive treatment prior to transplantation, including induction chemotherapy (ICT) alone (ICT group; n = 98), AZA alone (AZA group; n = 48), or AZA preceded or followed by ICT (AZA-ICT group; n = 17). At diagnosis, 126 patients (77%) had an excess of marrow blasts, and 95 patients (58%) had intermediate-2 or high-risk MDS according to the International Prognostic Scoring System (IPSS). Progression to more advanced disease before alloSCT was recorded in 67 patients. Donors were sibling (n = 75) or HLA-matched unrelated (10/10; n = 88). They received blood (n = 142) or marrow (n = 21) grafts following either myeloablative (n = 33) or reduced intensity (n = 130) conditioning.

Results
With a median follow-up of 38.7 months, 3-year outcomes in the AZA, ICT, and AZA-ICT groups were 55%, 48%, and 32% ($P = .07$) for overall survival (OS); 42%, 44%, and 29% ($P = .14$) for event-free survival (EFS); 40%, 37%, and 36% ($P = .86$) for relapse; and 19%, 20%, and 35% ($P = .24$) for nonrelapse mortality (NRM), respectively. Multivariate analysis confirmed the absence of statistical differences between the AZA and the ICT groups in terms of OS, EFS, relapse, and NRM.

Conclusion
With the goal of downstaging underlying disease before alloSCT, AZA alone led to outcomes similar to those for standard ICT.

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INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (alloSCT) remains the only potentially curative available therapeutic approach in patients with myelodysplastic syndrome (MDS). Despite the beneficial effects of alloSCT, these patients are at substantial risk of relapse after transplantation, especially in case of reduced-intensity conditioning (RIC). Whether a treatment should be administered before transplantation and the type of such treatment are still controversial. In particular, acute myeloid leukemia (AML) induction chemotherapy (ICT) has been recommended in young patients when MDS was associated with more than 5% marrow blasts,[1,2] but this approach is associated with toxicities that could prohibit proceeding to transplantation and may interfere with the transplantation outcome.

Demethylating agents or DNMTi (DNA methyltransferase inhibitors), including azacitidine (AZA)

and decitabine, have emerged as new therapeutic approaches that significantly prolong overall survival (OS) and are considered the current standard of care for most patients with intermediate-2 and high-risk MDS, although they have no curative potential.[3,4] DNMTi have a good toxicity profile compared with ICT, appear to be active in MDS with unfavorable karyotype, and may therefore be of interest if used before transplantation. Nevertheless, their role in this MDS setting has not yet been established.

The aim of this study was to assess the impact of treatment prior to transplantation with AZA on survival, relapse, and nonrelapse mortality (NRM). We report an analysis of 163 patients with MDS who underwent alloSCT following different prior treatments.

PATIENTS AND METHODS

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

Patient Selection

Transplantation modalities were made as homogeneous as possible by using the following inclusion criteria: patients older than age 18 years referred for first alloSCT with the source of stem cells being marrow or blood from either a sibling or an HLA-A–, -B–, -Cw–, -DR–, or –DQ–identical unrelated donor at the allele level (so-called 10/10). Patients who received alloSCT 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 by using a computerized search for discrepancy errors and vigorous on-site data verification of each file. HLA matching was cross-checked with the data of the French Bone Marrow Donor Registry, as previously described.[5]

Consequently, 265 consecutive patients with MDS who underwent alloSCT between October 2005 and December 2009 in 24 French and Belgian centers were identified, of whom 28 were excluded because their files lacked at least one of the following: initial French-American-British (FAB)/WHO category and International Prognostic Scoring System (IPSS) score, treatment prior to transplantation, or disease status at transplantation.

Because the main objective of this study was to investigate the impact of therapy prior to transplantation on alloSCT outcome, especially pretreatment with AZA compared with ICT, 74 other patients were excluded because they had received only best supportive care, including blood transfusion, hormones, growth factors (erythropoietin, granulocyte colony-stimulating factor), immunosuppressive treatment, and antibiotics. The remaining 163 patients were divided into three groups according to treatment received prior to transplantation as follows: ICT alone (ICT group; n = 98), AZA alone (AZA group; n = 48), and AZA preceded or followed by ICT (AZA-ICT group; n = 17), corresponding to patients for whom either treatment failed and who received the other treatment (Fig 1). Of note, choice of pretransplantation treatment was based on local physicians' decisions.

Patients were also categorized according to the first treatment received before alloSCT (ie, AZA or ICT, irrespective of whether the other treatment was also administered before transplantation). Therefore, 51 received AZA as their first treatment (intent-to-treat AZA group), and 112 received ICT as their first treatment (intent-to-treat ICT group).

Patient and Donor Characteristics and Transplantation Modalities

Morphologic classification, according to FAB and WHO classifications,[6,7] was documented as a separate variable at initial diagnosis and at time of transplantation. IPSS score at diagnosis was calculated,[8] and possible progression to more advanced disease between diagnosis and transplantation was recorded. Responses to treatment and disease status at transplantation were reevaluated according to International Working Group (IWG) 2006 criteria.[9]

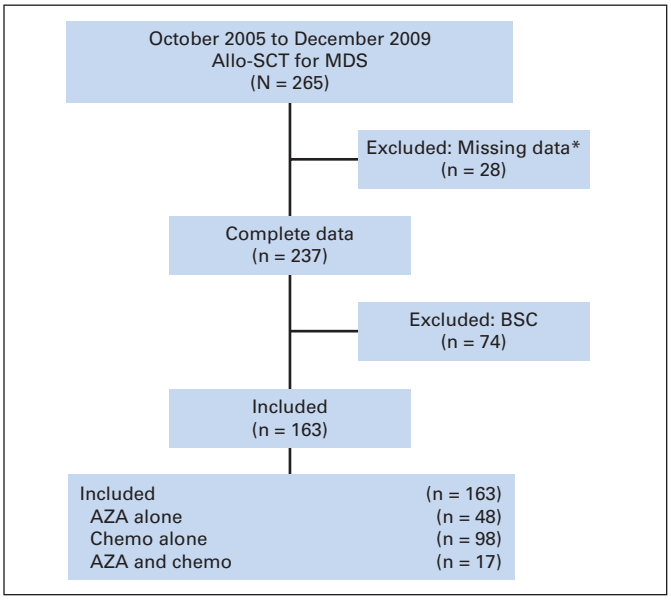

Fig 1. Flow chart for patient selection strategy. (*) Patients whose files were missing data for at least one of the following were excluded: initial French-American-British/WHO diagnosis, International Prognostic Scoring System score at diagnosis, prior-to-transplantation treatment, WHO criteria, and disease status at transplantation. Allo-SCT, allogeneic stem-cell transplantation: AZA, azacitidine; BSC, best supportive care; Chemo, chemotherapy; MDS, myelodysplastic syndrome.

At diagnosis (Table 1), 24 (15%) of the 163 patients had refractory anemia, refractory anemia with ringed sideroblasts, or refractory cytopenia with multilineage dysplasia; 52 patients (32%) had refractory anemia with excess of blasts (RAEB-1); 74 patients (45%) had RAEB-2; and 13 patients (8%) had RAEB in transformation/acute myeloid leukemia (RAEB-T/AML; with marrow blasts between 20% and 30%). Cytogenetic analysis according to IPSS classification was favorable, intermediate, or poor risk in 93, 32, and 37 patients, respectively; IPSS was low or intermediate-1 in 68 patients (lower-risk category, 42%) or intermediate-2 or high in 95 patients (higher-risk category, 58%). In AZA-treated groups, the drug was started after a median time from diagnosis of 150 days (range, 38 to 941 days) and stopped at a median of 60 days before transplantation (range, 6 to 438 days). The median number of cycles was four (range, one to 26 cycles). According to IWG 2006 criteria,[9] 119 patients (73%) at transplantation were in complete remission, partial remission, or marrow complete remission, including 33 patients (69%) in the AZA group, 77 patients (78%) in the ICT group, and nine patients (53%) in the AZA-ICT group. Forty-four patients (27%) were nonresponders, including four who achieved stable disease with hematologic improvement, 19 who achieved stable disease without hematologic improvement, and 21 who had progressive disease. Overall, 67 (41%) of the 163 patients had progressed to more aggressive disease before transplantation.

Transplantation modalities according to treatment prior to transplantation are listed in Table 2. Median time from diagnosis to transplantation was 10.0 months (range, 1.2 to 260.2 months). There were 101 men and 62 women with a median age of 57 years (range, 18 to 69 years) at alloSCT. The donor was an HLA sibling for 75 patients and an HLA-matched unrelated donor for 88 patients. In 33 patients, a myeloablative conditioning (MAC) regimen was used, and in 130 patients, nonmyeloablative conditioning (RIC) was used. Peripheral blood stem cells were used in 87% and bone marrow stem cells were used in 13% of the patients.

Statistical Analyses

The analysis was performed on the reference date of April 1, 2011. OS was defined as the interval from alloSCT to death, regardless of the cause of death.

Table 1. Patient Demographic and Clinical Characteristics at Diagnosis

Characteristic	Total (N = 163) No.	%	AZA Alone (n = 48) No.	%	ICT Alone (n = 98) No.	%	AZA-ICT (n = 17) No.	%	P
Sex									.16
Male	101	62	27	56	60	61	14	82	
Female	62	38	21	44	38	39	3	18	
FAB/WHO category									.97
RA/RARS/RCMD	24	15	7	15	14	14	3	18	
RAEB-1	52	32	17	35	31	32	4	24	
RAEB-2	74	45	21	44	45	46	8	47	
RAEB-t/AML	13	8	3	6	8	8	2	12	
IPSS score									.35
Low/intermediate-1	68	42	16	33	45	46	7	41	
Intermediate-2/high	95	58	32	67	53	54	10	59	
Cytogenetics									.07
Favorable	93	57	23	48	58	59	12	71	
Intermediate	32	20	9	19	18	19	5	29	
High risk	37	23	16	33	21	22	0		
Interval from diagnosis to transplantation, months									.08
< 6.2	31	19	4	8	26	27	1	5	
6.2-9.9	47	29	16	34	27	28	4	24	
10.0-21.2	49	30	17	35	24	24	8	47	
> 21.2	36	22	11	23	21	21	4	24	

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; FAB, French-American-British [classification]; ICT, induction chemotherapy; IPSS, International Prognostic Scoring System; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-t, RAEB in transformation; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia.

Table 2. Patient Characteristics at Transplantation and Transplantation Modalities

Characteristic	Total (n = 163) No.	%	AZA (n = 48) No.	%	ICT (n = 98) No.	%	AZA-ICT (n = 17) No.	%	P
Recipient age, years									.07
Median	57		60		57		58		
Range	18-69		30-68		18-69		32-67		
Sex mismatch*	39	24	10	21	24	25	5	29	.75
Progression to more aggressive disease									< .001
No	96	59	41	85	48	49	7	41	
Yes	67	41	7	15	50	51	10	59	
Marrow blasts, %									.01
< 5	120	74	32	67	79	81	9	53	
≥ 5	43	26	16	33	18	19	8	47	
Disease status									.06
Responders†	119	73	33	69	77	78	9	53	
Nonresponders	44	27	15	31	21	22	8	47	
Donor type									.77
Sibling	75	46	20	42	48	47	8	47	
HLA-matched unrelated	88	54	28	58	52	51	9	53	
Stem-cell source									.64
Marrow	21	13	8	17	11	11	2	12	
PBSCs	142	87	40	83	87	89	15	88	
Karnofsky score at transplantation									.73
80-100	131	80	39	83	78	80	14	82	
50-70	16	10	4	9	11	11	1	6	
Missing	16		5		9		2		
Reason for RIC									.55
Age > 50 years	96	74	30	75	59	79	9	60	
Comorbidities	15	11	4	10	8	11	2	13	
Protocol driven	14	11	5	13	5	7	3	20	
Missing	5		1		3		1		
Conditioning									.41
MAC	33	20	8	17	23	23	2	12	
RIC	130	80	40	83	75	77	15	88	
ATG									.11
No	56	34	18	37	36	37	2	12	
Yes	107	66	30	63	62	63	15	88	
TBI									.41
No	125	77	38	79	73	75	14	82	
Yes	38	23	10	21	25	25	3	18	

Abbreviations: ATG, antithymocyte globulin; AZA, azacitidine; ICT, induction chemotherapy; MAC, myeloablative conditioning; PBSC, peripheral blood stem cell; RIC, reduced-intensity conditioning; TBI, total-body irradiation.

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

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

Event-free survival (EFS) 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 and evidence of autologous reconstitution when chimerism was available. 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 (aGVHD) and neutrophil and platelet engraftment.

For continuous variables, medians and ranges were determined. The assumption of normality was assessed by using the Shapiro-Wilk test. Categorical variables were described by frequencies and percentages. The three prior-to-transplantation treatment groups (AZA, ICT, and AZA-ICT) were compared by using the χ^2 or the Fisher's exact tests for categorical data. For continuous variables, the analysis of variance or Kruskal-Wallis test was applied according to the distribution of the studied variable.

All censored criteria were calculated from the time of transplantation. 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 transplantation for the occurrence of the event. Prior-to-transplantation treatment and variables having a significance level of $P < .15$ from the univariate analyses were introduced in a multivariable Cox regression, with backward selection at level $P < .15$. Prior-to-transplantation treatment was always included in the selection, whatever its significance level in univariate analysis. Adjusted hazard ratios (HRs) and 95% CIs were computed, and $P \leq .05$ was considered statistically significant.

The occurrence of relapse, NRM, and chronic GVHD (cGVHD) were 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 by using the Kalbfleish and Prentice method.[10] The individual prognostic value of each variable was assessed by the Gray test (bivariate analyses were performed for comparison of cumulative incidence curves). Prior-to-transplantation treatment and variables having a significance level of $P < .15$ in the univariate analyses were introduced in a multivariate Fine and Gray model. Adjusted HRs and 95% CIs were computed. Statistical analyses were performed by using SAS software (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/).

Table 3. Univariate Analysis by Key Subsets: 3-Year OS and EFS, Relapse Mortality Rates, and NRM

Characteristic	No. of Patients	3-Year OS %	3-Year OS *P**	3-Year EFS %	3-Year EFS *P**	Relapse %	Relapse *P*†	NRM %	NRM *P*†
Sex			.18		.32		.68		.33
Male	101	43		39		38		24	
Female	62	55		49		35		17	
Age, years			.53		.49		.98		.35
< 57.6	80	47		46		36		19	
≥ 57.6	83	49		40		38		23	
FAB/WHO			.60		.71		.32		.72
RA/RARS/RCMD	24	54		54		22		25	
RAEB-1	52	34		27		48		26	
RAEB-2	74	53		46		38		16	
RAEB-t/AML	13	57		53		23		24	
IPSS			.38		.34		.10		.24
Low/intermediate-1	68	52		40		35		27	
Intermediate-2/high	95	46		43		40		17	
Cytogenetics			< .001		< .001		< .001		.71
Favorable	93	60		49		27		24	
Intermediate	32	44		50		37		17	
High risk	37	21		22		59		19	
Sex mismatch			.88		.82		.65		.71
No	123	46		44		35		22	
Yes	39	52		38		45		18	
Progression to more aggressive disease			.84		.46		.86		.84
No	96	48		42		38		21	
Yes	67	48		42		36		21	
Marrow blasts, %			.25		.12		.25		.84
< 5	135	48		44		36		21	
≥ 5	27	43		33		45		22	
Treatment prior to alloSCT									
AZA alone *v* ICT alone			.65		.67		.78		.76
AZA alone	48	58		52		40		17	
ICT alone	98	51		45		35		19	
AZA alone *v* AZA plus ICT			.032		.038		.31		.041
AZA alone	48	58		52		40		17	
AZA plus ICT	17	35		29		37		35	
Interval from diagnosis to transplantation, months			.90		.84		.42		.18
< 10	81	49		44		39		16	
≥ 10	82	54		46		29		24	
Disease status			.07		.07		.67		.18
Responders	119	49		45		37		19	
Nonresponders	44	42		36		38		27	
Donor age, years			.06		.08		.91		.08
< 44.9	81	40		67		40		27	
≥ 44.9	80	56		47		33		16	
Donor type			.10		.11		.74		.04
Sibling	75	51		51		37		14	
HLA-matched unrelated	88	44		36		37		27	
Stem-cell source			.24		.48		.47		.91
Marrow	21	38		38		43		19	
PBSCs	142	49		43		36		21	

(continued in next column)

Table 3. Univariate Analysis by Key Subsets: 3-Year OS and EFS, Relapse Mortality Rates, and NRM (continued)

Characteristic	No. of Patients	3-Year OS %	3-Year OS *P**	3-Year EFS %	3-Year EFS *P**	Relapse %	Relapse *P*†	NRM %	NRM *P*†
Recipient CMV serostatus			.60		.79		.99		.64
Negative	73	45		40		39		22	
Positive	90	50		45		35		20	
Donor CMV serostatus			.16		.07		.05		.86
Negative	85	41		33		46		22	
Positive	78	55		55		26		19	
Conditioning			.40		.63		.74		.76
MAC	33	50		45		37		18	
RIC	130	47		42		37		22	
ATG			.79		.69		.59		.84
No	56	48		43		34		22	
Yes	107	48		42		38		20	
TBI			.13		.18		.49		.35
No	125	51		46		36		19	
Yes	38	36		31		42		27	

Abbreviations: alloSCT, allogeneic stem-cell transplantation; AML, acute myeloid leukemia; ATG, antithymocyte globulin; AZA, azacitidine; CMV, cytomegalovirus; EFS, event-free survival; FAB, French-American-British [classification]; ICT, induction chemotherapy; IPSS, International Prognostic Scoring System; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OS, overall survival; PBSC, peripheral blood stem cell; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-t, RAEB in transition; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RIC, reduced-intensity conditioning; TBI, total-body irradiation.

*Log-rank.

†Gray (cumulative incidence).

RESULTS

At the date of analysis (April 1, 2011), median follow-up was 38.7 months (range, 15.2 to 65.6 months). All but seven patients had obtained neutrophil engraftment after a median time of 16 days (range, 0 to 70 days). Fifty-three patients (33%) had developed grade 2 to 4 aGVHD, including 21 patients (13%) with grade 3 to 4. Of the 143 evaluable patients who survived more than 100 days, 75 (52%) had developed cGVHD, including 44 (31%) with extensive cGVHD. For the whole patient group, median 3-year OS, EFS, relapse, and NRM were 48%, 42%, 37%, and 21%, respectively.

Univariate Analysis

As expected, among all at diagnosis and/or at transplantation characteristics that were studied, high-risk cytogenetic profile adversely influenced OS, EFS, and relapse $P < .001$ for all). Patients who received grafts from cytomegalovirus-seropositive donors tended to relapse more often than other patients ($P = .05$), although those who received alloSCT from an HLA-matched unrelated donor had a lower NRM rate ($P = .04$).

Grade 2 to 4 aGVHD was correlated more positively with bone marrow stem cells (52%) than with peripheral blood stem cells (29%; $P = .03$). The type of conditioning, either MAC or RIC, affected also the rate of aGVHD (58% *v* 28%; $P = .01$).

As depicted in Table 3, none of the following variables seemed to influence the outcome of alloSCT: recipient age and sex, sex mismatch, donor age, stem-cell source, recipient and conditioning regimen type (ie, intensity, antithymoglobulin, or total-body irradiation), initial FAB/WHO subgroups, IPSS at diagnosis, progression to more advanced disease at time of transplantation, time between diagnosis and transplantation, and marrow blasts at transplantation. Of note, disease status at transplantation tended to influence OS and EFS, with *P* values of .07 for each.

Outcome According to Prior-to-Transplantation Treatment

In patients treated with AZA alone and ICT alone before transplantation, 3-year OS was 58% versus 51% ($P = .65$), 3-year EFS was 52% versus 45% ($P = .67$), cumulative incidence of relapse was 40% versus 37% ($P = .76$), and NRM was 19% versus 20% ($P = .78$), respectively (Fig 2). Conversely, when compared with patients in the AZA group, those who received AZA plus ICT had lower rates of 3-year OS (35%; $P = .035$), EFS (29%; $P = .038$), and NRM (35%; $P = .041$).

The type of treatment before alloSCT had no significant impact on the incidence and severity of aGVHD (data not shown). However, higher cumulative incidence of extensive cGVHD was observed in the AZA-ICT group (57%) compared with the ICT-alone group (26%) and AZA-alone group (31%; $P = .049$).

Outcome According to First Prior-to-Transplantation Treatment

In the intent-to-treat AZA and intent-to-treat ICT groups, 3-year OS was 58% versus 49% ($P = .39$), 3-year EFS was 52% versus 43% ($P = .40$), relapse rate was 41% versus 37% ($P = .71$), and NRM was 16% versus 23% ($P = .39$), respectively.

Multivariate Analysis

Multivariate analysis confirmed the absence of significant differences between AZA and ICT groups in terms of OS (HR, 1.41; 95% CI,

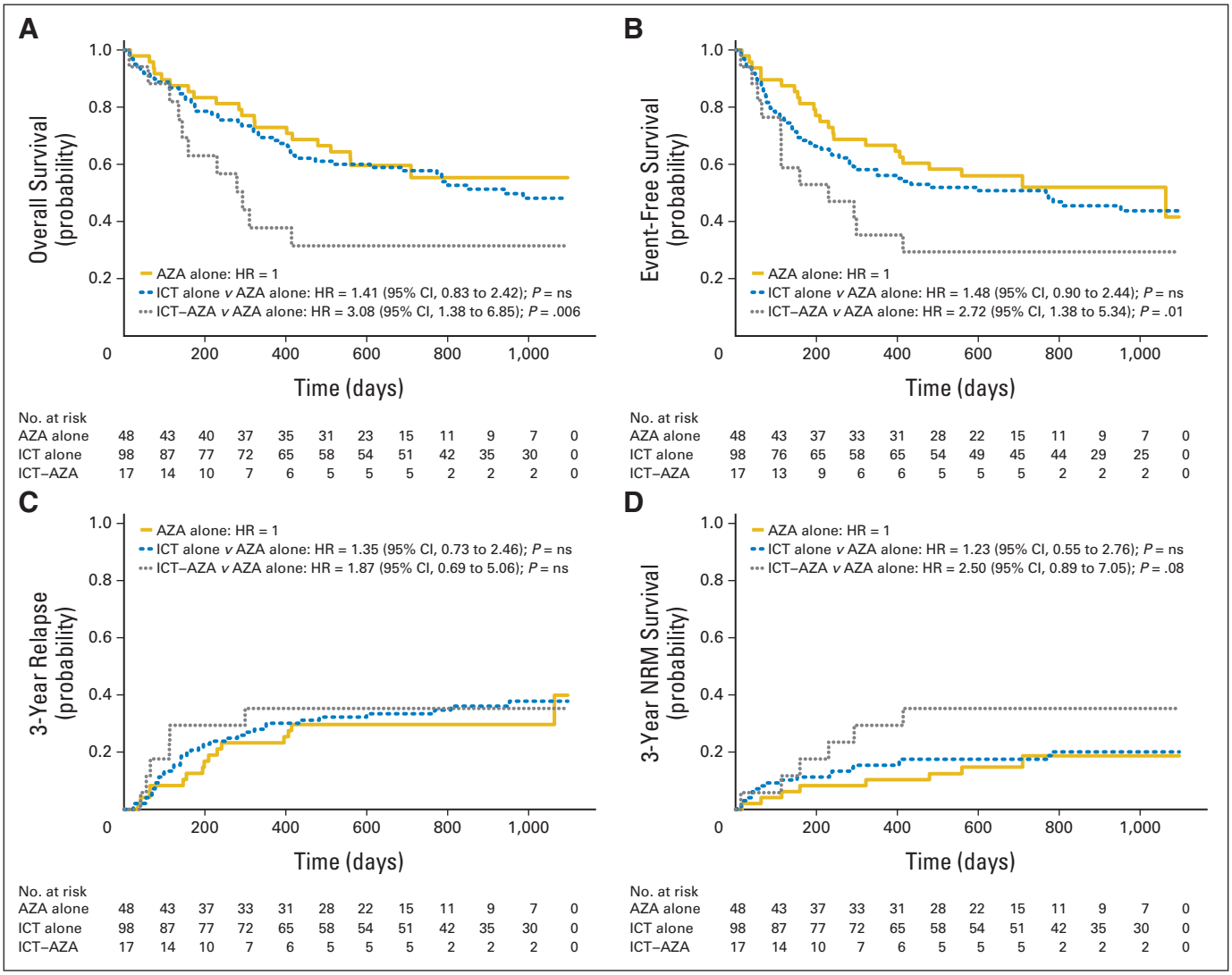

Fig 2. Kaplan-Meier estimates of (A) 3-year overall survival, (B) 3-year event-free survival, (C) cumulative incidence of 3-year relapse, and (D) nonrelapse mortality (NRM) in 163 patients, according to the prior-to-transplantation treatment received. AZA, azacitidine; HR, hazard ratio; ICT, induction chemotherapy; ns, not significant.

0.83 to 2.42; $P = .202$), EFS (HR, 1.48; 95% CI, 0.90 to 2.44; $P = .127$), cumulative incidence of relapse (HR, 1.35; 95% CI, 0.73 to 2.46; $P = .340$), and NRM (HR, 1.23; 95% CI, 0.55 to 2.76; $P = .610$). However, receiving sequential treatment of AZA followed or preceded by ICT was found to adversely influence both OS (HR, 3.08; 95% CI, 1.38 to 6.86; $P = .006$) and EFS (HR, 2.72; 95% CI, 1.38 to 5.34; $P = .014$). In addition, there was a trend toward a negative impact of AZA-ICT on NRM (HR, 2.50; 95% CI, 0.89 to 7.05; $P = .082$). NRM was also influenced by HLA-matched unrelated donor (HR, 2.17; 95% CI, 1.05 to 4.49; $P = .036$).

When intent-to-treat groups were considered, multivariate analyses confirmed the absence of differences between intent-to-treat AZA and intent-to-treat ICT groups in terms of OS (HR, 1.67; 95% CI, 0.93 to 2.65; $P = .091$), EFS (HR, 1.44; 95% CI, 0.89 to 2.44; $P = .137$), cumulative incidence of relapse (HR, 1.38; 95% CI, 0.76 to 2.51; $P = .291$), and NRM (HR, 1.41; 95% CI, 0.63 to 3.14; $P = .400$).

As expected, high-risk cytogenetic profile had a detrimental impact on OS (HR, 1.93; 95% CI, 1.45 to 2.57; $P < .001$), EFS (HR, 1.82; 95% CI, 1.39 to 2.38; $P < .001$), and relapse (HR, 1.87; 95% CI, 1.36 to 2.57; $P < .001$). EFS was also influenced by donor age 44.9 years or older (HR, 1.59; 95% CI, 1.02 to 2.44; $P = .042$). Results for OS, EFS, relapse, and NRM are summarized in Table 4.

DISCUSSION

In this series, which to the best of our knowledge is the largest study on the use of AZA before transplantation in patients with MDS, we found post-transplantation outcome (in terms of OS, EFS, cumulative incidence of relapse, and NRM) in patients who received AZA alone before transplantation comparable to that of patients treated with ICT alone before alloSCT. The same results were observed when the first treatment received before alloSCT was considered.

The study was started in October 2005, corresponding to the date when AZA became available in France, and stopped on December 2009, which permitted more than 1 year of follow-up. We did not include patients who received transplantation before October 2005 because transplantation modalities and patient outcomes changed over time.[11-13] To make the study population as homogeneous as possible, we included only patients who received alloSCT from an HLA sibling or HLA allelically matched unrelated donor (10/10).

Single-agent therapy with AZA may be of value in stabilizing the disease or even reverting it to an earlier stage and allowing time for patients to reach transplantation since, in our study, only 15% of patients referred to alloSCT after AZA alone had progressed to more advanced disease before transplantation compared with 51% of those who had received ICT alone. Lübbert et al[14] suggested that, outside the alloSCT setting, decitabine could be a valid alternative to standard chemotherapy in elderly patients with MDS/AML before alloSCT. Furthermore, in a larger retrospective study comparing decitabine agents with ICT in patients with AML or MDS, Kantarjian et al[15] showed better OS in the patients treated with decitabine compared with historic controls receiving ICT because of lower early mortality rather than response rate. Nevertheless, the retrospective nature of those studies does not allow any firm conclusion regarding a beneficial effect of DNMTi.

Table 4. Multivariate Analyses

Characteristics	3-Year OS			3-Year EFS			3-Year Relapse			3-Year NRM		
	HR	95% CI	P*	HR	95% CI	P*	HR	95% CI	P*	HR	95% CI	P*
Recipient age, years												
< 57.6	1			—			—			—		
≥ 57.6	0.63	0.37 to 1.07	.089									
Cytogenetics												
Low/intermediate	1			1			1			—		
High risk	1.93	1.45 to 2.57	< .001	1.82	1.39 to 2.38	< .001	1.87	1.36 to 2.57	< .001			
Prior treatment												
AZA alone	1			1			1			1		
ICT alone *v* AZA alone	1.41	0.83 to 2.42	.202	1.48	0.90 to 2.44	.127	1.35	0.73 to 2.46	.340	1.23	0.55 to 2.76	.610
ICT-AZA *v* AZA alone	3.08	1.38 to 6.86	.006	2.72	1.38 to 5.34	.014	1.87	0.69 to 5.06	.220	2.50	0.89 to 7.05	.082
Disease status at transplantation												
Responders	1			1			—			—		
Nonresponders	1.37	0.83 to 2.45	.215	1.36	0.86 to 2.17	.193						
Donor age, years												
< 44.9	—			1			—			—		
≥ 44.9				1.59	1.02 to 2.44	.042						
Donor type	—			1						1		
Sibling HLA-matched unrelated				1.31	0.77 to 2.22	.320	—			2.17	1.05 to 4.49	.036
Donor CMV serostatus												
Negative	—			1			1			—		
Positive				0.79	0.51 to 1.22	.287	0.63	0.36 to 1.10	.110			

NOTE. Prior-to-transplantation treatment and variables having a significance level of $P < .15$ in the univariate analyses were introduced in a multivariate model.
Abbreviations: AZA, azacitidine; CMV, cytomegalovirus; EFS, event-free survival; HR, hazard ratio; ICT, induction chemotherapy; NRM, nonrelapse mortality; OS, overall survival.

Few studies have investigated DNMTi before alloSCT.[14,16-18] Field et al,[17] in a retrospective series of 30 patients with MDS and patients without MDS treated with AZA alone or in association with chemotherapy or other drugs before alloSCT and compared with 24 patients who did not receive AZA, showed a comparable 1-year OS and EFS in the two groups. They also found a trend toward lower incidence of relapse in the AZA group. The population heterogeneity as well as the heterogeneity of treatment received before alloSCT in the group that was not treated with AZA (13 patients received transplantation without prior treatment) may be an explanation for the lower relapse rate in patients who received AZA. In this study, we did not observe any difference in relapse rate between patients treated with AZA and those treated with ICT.

Although never studied in a prospective manner, relapse is thought to be more likely to occur after RIC.[19] In this study, and in agreement with what has been reported by Buchholz et al,[20] there was a lower rate of relapse after RIC than after MAC. The explanation for this result may be that all the patients in our study received a cytoreductive treatment prior to transplantation.

Seventeen patients received AZA preceded (n = 15) or followed (n = 2) by ICT. These patients had worse outcomes in terms of OS and EFS than other patients who received AZA alone or ICT alone before transplantation. This inferior outcome could result from the fact that patients who required both treatments had more resistant disease with more frequent relapse post-transplantation and/or to the fact that they had increased NRM because they received more treatment before transplantation. It is of note that 50% of patients treated with both AZA and ICT were responders at transplantation and none of them had a high-risk cytogenetic profile at diagnosis. In addition, they had similar rates of post-transplantation relapse compared with the other groups of patients. In contrast, there was a trend toward higher NRM rate ($P = .082$) and more extensive cGVHD compared with patients belonging to the other groups. These results are in line with our previous finding that intensification of the conditioning regimen before alloCST in patients with therapy-related MDS or AML experienced a detrimental effect on post-transplantation outcome without reduction in the relapse rate.[1]

In conclusion, for the purpose of reducing the tumor burden before alloSCT, azacitidine seems to be a valid therapeutic approach and showed comparative OS, EFS, relapse incidence, and NRM when compared with ICT. AlloSCT in patients who required both AZA and ICT had less satisfactory outcomes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Yakoub-Agha I, de La Salmonière P, Ribaud P, et al: Allogeneic bone marrow transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia: A long-term study of 70 patients—Report of the French Society of Bone Marrow Transplantation. J Clin Oncol 18:963-971, 2000
2. de Witte T, Hagemeijer A, Suciu S, et al: Value of allogeneic versus autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia: Final results of a prospective randomized European Intergroup Trial. Haematologica 95:1754-1761, 2001
3. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al: Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study. Lancet Oncol 10:223-232, 2009
4. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al: Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 28:562-569, 2010
5. Yakoub-Agha I, Mesnil F, Kuentz M, et al: Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: A prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. J Clin Oncol 24:5695-5702, 2006
6. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the acute leukaemias: French-American-British (FAB) co-operative group. Br J Haematol 33:451-458, 1976
7. Swerdlow S, Campo E, Harris NL, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue. Lyon, France, International Agency for Research on Cancer, 2008
8. Greenberg P, Cox C, LeBeau MM, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 89:2079-2088, 1997
9. Cheson BD, Greenberg PL, Bennett JM, et al: Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 108:419-425, 2006
10. Kalbfleisch JD, Prentiss R: The Statistical Analysis of Failure Time Data (ed 2). Hoboken, NJ, John Wiley & Sons, 2002
11. Boehm A, Walcherberger B, Sperr WR, et al: Improved outcome in patients with chronic myelogenous leukemia after allogeneic hematopoietic

stem cell transplantation over the past 25 years: A single-center experience. Biol Blood Marrow Transplant 17:133-140, 2011

12. Remberger M, Ackefors M, Berglund S, et al: Improved survival after allogeneic hematopoietic stem cell transplantation in recent years: A single-center study. Biol Blood Marrow Transplant 17:1688-1697, 2011

13. Vicente D, Lamparelli T, Gualandi F, et al: Improved outcome in young adults with de novo acute myeloid leukemia in first remission, undergoing an allogeneic bone marrow transplant. Bone Marrow Transplant 40:349-354, 2007

14. Lübbert M, Bertz H, Rüter B, et al: Non-intensive treatment with low-dose 5-aza-2′-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. Bone Marrow Transplant 44:585-588, 2009

15. Kantarjian HM, O'Brien S, Huang X, et al: Survival advantage with decitabine versus intensive chemotherapy in patients with higher risk myelodysplastic syndrome: Comparison with historical experience. Cancer 109:1133-1137, 2007

16. Cogle CR, Imanirad I, Wiggins LE, et al: Hypomethylating agent induction therapy followed by hematopoietic cell transplantation is feasible in patients with myelodysplastic syndromes. Clin Adv Hematol Oncol 8:40-46, 2010

17. Field T, Perkins J, Huang Y, et al: 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 45:255-260, 2010

18. Kim DY, Lee JH, Park YH, et al: Feasibility of hypomethylating agents followed by allogeneic hematopoietic cell transplantation in patients with myelodysplastic syndrome. Bone Marrow Transplant 47:374-379, 2011

19. Horwitz ME: Reduced intensity versus myeloablative allogeneic stem cell transplantation for the treatment of acute myeloid leukemia, myelodysplastic syndrome and acute lymphoid leukemia. Curr Opin Oncol 23:197-202, 2011

20. Buchholz S, Dammann E, Stadler M, et al: Cytoreductive treatment with clofarabine/ara-C combined with reduced-intensity conditioning and allogeneic stem cell transplantation in patients with high-risk, relapsed, or refractory acute myeloid leukemia and advanced myelodysplastic syndrome. Eur J Haematol 88:52-60, 2012

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