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Clinical Research

Antithymocyte Globulin before Allogeneic Stem Cell Transplantation for Progressive Myelodysplastic Syndrome: A Study from the French Society of Bone Marrow Transplantation and Cellular Therapy

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A B S T R A C T

We investigated the impact of rabbit antithymocyte globulins (ATG) on patient outcomes after allogeneic stem cell transplantation (allo-SCT) for progressive myelodysplastic syndrome (MDS). Of the 242 consecutive patients who underwent allo-SCT for progressive MDS between October 1999 and December 2009, 93 received ATG (ATG group) at the median dose of 5 mg/kg, whereas 149 patients did not (no-ATG group). Donors were sibling (n = 153) or HLA-matched unrelated (n = 89). Patients received blood (n = 90) or marrow (n = 152) grafts after either myeloablative (n = 109) or reduced-intensity (n = 133) conditioning. Three-year overall and event-free survival, nonrelapse mortality, relapse, and chronic graft-versus-host disease (GVHD) development were not significantly different between the 2 groups. In contrast, acute grade II to IV GVHD occurred more often in the no-ATG group (55% of the patients) than in the ATG group (27%, $P < .0001$). Similar results were observed with acute grade III to IV GVHD (28% and 14% in the no-ATG group and ATG group, respectively; $P = .009$). In multivariate analysis, after adjustment with propensity score, the absence of ATG was the

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strongest parameter associated with an increased risk of acute grade II to IV GVHD (hazard ratio, 2.13; 95% confidence interval, 1.35 to 3.37; $P = .001$]. ATG had no impact on overall and event-free survival or cumulative incidence of the relapse. In conclusion, the addition of ATG to allo-SCT conditioning did not increase the incidence of relapse of patients with progressive MDS. The incidence of acute GVHD was decreased without compromising outcomes.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-SCT) remains the only potentially curative therapeutic approach in patients with myelodysplastic syndrome (MDS). Despite the beneficial effects of allo-SCT, these patients are at a substantial risk of relapse after transplantation [1-4]. Disease status is a major factor that influences patient outcome with an increased risk of relapse, especially in patients with progressive disease [5]. Indeed, disease status at transplantation can be broken down into 2 categories according to the International Working Group 2006 response criteria: (1) responding, for patients with complete, marrow, and partial remission or stable disease with hematological improvement; and (2) progressive disease including refractory, relapsing, progressive and stable disease without hematological improvement [6].

Although significant improvements in HLA matching techniques have been accomplished [7], allo-SCT is still limited by the immunological recognition and destruction of host tissues, termed *graft-versus-host disease* (GVHD). Both in its acute and chronic forms, GVHD continues to be the major source of morbidity and mortality after allo-SCT [8]. Severe acute GVHD has a poor prognosis, with 5-year overall survival of 25% for grade III and 5% for grade IV disease [9].

One of the strategies developed to reduce the risk of GVHD is ex vivo T cell depletion of the graft. Although this has been proven to be very effective to prevent GVHD, this is also associated with a significant increase in graft failure and risk of relapse [10,11]. An alternative strategy is to provide in vivo T cell depletion in blood and lymphoid tissues using antithymocyte globulin (ATG), a set of polyclonal antibodies directed against a wide range of immune cell epitopes [12]. However, the use of ATG, incorporated within the conditioning regimen before allo-SCT, is still controversial, especially for patients with progressive disease. Indeed, the risk of GVHD seems to be reduced in various proportions with ATG [13-20] but a significant increase of disease relapse has also been observed [21,22]. In addition, the impact of ATG on the incidence of relapse is still unknown in the subgroup of patients with progressive disease.

In an attempt to assess the impact on outcomes of rabbit ATG incorporated within the conditioning regimen, we report a multicenter retrospective study of 242 consecutive patients who underwent an allo-SCT for progressive MDS.

PATIENTS AND 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 homogenous as possible using the following inclusion criteria: patients older than 18 years with MDS who were referred for first allo-SCT. The source of stem cells was the bone marrow or blood from either a sibling or an unrelated donor that was HLA-A, -B, -Cw, -DR, and -DQ identical at allelic level. Patients with chronic myelomonocytic leukemia and those who received allo-SCT from an HLA-mismatched donor or cord blood or a T cell–depleted graft were excluded. Thymoglobuline (Genzyme Corporation, Cambridge, MA) was the only ATG administered to the patients, as this is the only brand approved in France for use in allo-SCT.

Participating centers verified the data recorded for each patient in the French Bone Marrow Transplantation Registry and provided additional information. Quality of the data and HLA matching were controlled by using a computerized search for discrepancy errors. Consequently, 461 consecutive patients who underwent allo-SCT between October 1999 and December 2009 in 24 French and Belgian centers were identified. Thirty-six patients were excluded because their files lacked data. Because the objective of this study was to investigate the impact of ATG on patients with progressive MDS, we excluded the 183 patients who responded to pretransplantation treatment according to International Working Group 2006 criteria [6]. Of the 242 remaining patients, 93 received ATG during conditioning (ATG group) and 149 did not (no-ATG group, n = 149) (Figure 1).

Patient and Donor Characteristics and Transplantation Modalities

Disease morphology was classified according to the French-American-British and World Health Organization (WHO) classifications [23,24] and the International Prognostic Scoring System (IPSS) score was calculated at diagnosis according to Greenberg et al. [25]. Progression to more advanced disease between diagnosis and transplantation, responses, and disease status at transplantation were evaluated according to standard criteria [6,26].

Patient and donor initial characteristics at diagnosis and transplantation are shown in Table 1. The use of ATG was center-based in line with national guidelines [27]. The ATG and no-ATG groups were unbalanced in terms of recipient age, stem cell source, number of $CD34^+$ cells in the graft, conditioning, use of total body irradiation, and GVHD prophylaxis. However, there was no difference between the 2 groups regarding the other patient characteristics, including French-American-British/WHO classification, IPSS score, and cytogenetic risk category at diagnosis. In the ATG group, the drug was delivered at a dose of < 5 mg/kg (n = 6), 5 mg/kg (n = 53, 57%), 7.5 mg/kg (n = 11), or 10 mg/kg (n = 10). ATG was infused over 1 day (n = 6), 2 days (n = 45, 48%), 3 days (n = 19), 4 days (n = 7), or 5 (n = 4) days.

STATISTICAL ANALYSES

The analysis was performed on the reference date of April 1, 2011. Overall survival (OS) was defined as the time elapsed from allo-SCT to death, regardless of the cause of death. 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 evidence of

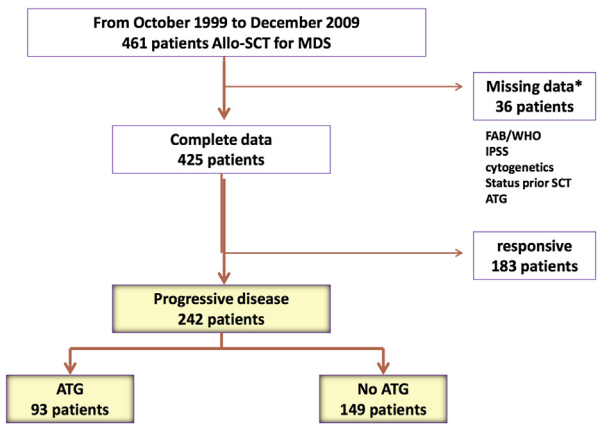

Figure 1. Flow chart for patient selection strategy. *Patients whose files were missing data for at least 1 of the following were excluded: initial French-American-British (FAB)/World Health Organization (WHO) category, International Prognostic Scoring System (IPSS) score and cytogenetic features at diagnosis, disease status before transplantation, and use of antithymocyte globulin (ATG) as part of the conditioning.

Table 1
Patient and Donors Characteristics and Transplantation Modalities

Characteristic	Total (n = 242)	ATG (n = 93)	No-ATG (n = 149)	*P* Value*
At diagnosis				
Gender				.27
Male	151 (62)	62 (67)	89 (60)	
Female	91 (38)	31 (33)	60 (40)	
FAB/WHO				.85
RA/RARS/RCMD	90 (37)	34 (37)	56 (38)	
RAEB-1	82 (34)	30 (32)	52 (35)	
RAEB-2	60 (25)	24 (26)	36 (24)	
RAEB-t/AML	10 (4)	5 (5)	5 (3)	
IPSS				.22
Low/int-1	139 (57)	58 (62)	81 (54)	
Int-2/high	103 (43)	35 (38)	68 (46)	
Cytogenetics				.74
Favorable	115 (47)	47 (50)	68 (46)	
Intermediate	65 (27)	23 (25)	42 (28)	
High risk	62 (26)	23 (25)	39 (26)	
At transplantation				
Recipient age, median (range), yr	52 (20-70)	56 (21-68)	50 (20-70)	<.0001
Gender mismatch†	53 (22)	21 (23)	32 (22)	.83
WBC 10^9/L, median (range)	2.4 (.1-78)	2.3 (.1-33)	2.6 (.1-78)	.36
Hemoglobin gr/dL, median (range)	9.1 (5.2-15.9)	8.8 (5.2-13.8)	9.3 (5.6-15.9)	.24
Platelet 10^9/L, median (range)	55 (1-696)	52 (3-696)	56 (1-600)	.57
Marrow blasts, median (range)	7 (0-64)	7 (0-50)	7 (0-64)	.43
Disease status				.61
Nonresponders	242 (100)	93 (100)	149 (100)	
Pretransplantation progression	67 (28)	25 (26)	43 (29)	
Donor type				.29
Sibling	153 (63)	55 (59)	98 (66)	
HLA-matched unrelated	89 (37)	38 (41)	51 (34)	
Stem cell source				.0001
Marrow	90 (37)	17 (18)	73 (49)	
PBSC	152 (63)	76 (82)	76 (51)	
CD34+ 10^6/kg, median (range)	4.8 (.4-26.8)	5.65 (.8-26.8)	4.2 (.41-19.3)	.003
Conditioning				.0001
MAC	109 (45)	9 (10)	100 (67)	
RIC	133 (55)	84 (90)	49 (33)	
TBI				.0001
No	146 (60)	82 (88)	64 (43)	
Yes	96 (40)	11 (12)	85 (57)	
GVHD prophylaxis				.0001
Cs-A and MTX	119 (50)	23 (25)	96 (64)	
Cs-A and other drugs	120 (50)	67 (75)	53 (36)	

FAB indicates French-American-British classification; WHO, World Health Organization; RA, refractory anemia; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; RAEB-t, RAEB in transformation; AML, acute myeloid leukemia; IPSS, International Prognostic Scoring System; int, intermediate; WBC, white blood cells; PBSC, peripheral blood stem cells; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation; GVHD, graft-versus-host disease; Cs-A, Cysclosporine A; MTX, short course of methotrexate.

Data presented are n (%) unless otherwise indicated.

* Comparison of the ATG and "no-ATG" groups using Mann-Whitney U test, or Chi-squared test, as appropriate.

† Gender mismatch is defined as male recipient who received graft from female donor.

autologous reconstitution when chimerism was available. Nonrelapse mortality (NRM) was defined as death resulting from the transplantation 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 GVHD and neutrophil and platelet engraftment.

For continuous variables, medians and ranges were determined. The assumption of normality was assessed using the Shapiro-Wilk test. Categorical variables were described by frequencies and percentages. The 2 groups of patients (ATG and no-ATG) were compared using the chi-square or the Fisher exact tests for categorical data. For continuous variables, ANOVA or Kruskal-Wallis tests were 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 test was used to test the prognostic value of patient characteristics at transplantation for the occurrence of the event. Variables having a significance level of $P < .10$ from the univariate analyses were introduced in a multivariable Cox regression, with backward selection at level $P < .10$. ATG was always included in the selection, whatever its significance level in univariate analysis. Adjusted hazard ratios and 95% confidence intervals (CI) were computed and $P \leq .05$ was considered statistically significant.

The occurrences of engraftment, relapse, NRM, acute GVHD, and chronic GVHD were studied by using competing risk methodology. For the events 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 [28]. The individual prognostic value for each variable was assessed by the Gray's test (comparison of cumulative incidence curves: bivariate analyses). ATG and variables having a significance level of $P < .10$

in the bivariate analyses were introduced in a multivariate Fine and Gray model [29]. Adjusted hazard ratio and 95% confidence intervals were computed.

Because our study was not randomized, we used a propensity score to adjust *P* values for patients who received ATG and those who did not [30]. Thus, patients were subsequently analyzed, and *P* values were also adjusted using the propensity score method according to whether they had received ATG or not. The propensity score model included significant variables in bivariate analyses and those that might have influenced the outcome of allo-SCT. These included recipient's age, WHO category, cytogenetic features, and IPSS at diagnosis; pretransplantation progression to a more advanced disease; percentage of marrow blasts at transplantation; pretransplantation treatment; cytomegalovirus (CMV) recipient and donor serostatus; stem cell source; conditioning; and GVHD prophylaxis.

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/).

RESULTS

Patient Outcome

On the date of analysis of April 1, 2011, the median follow-up was 38.7 months (range, 15.2 to 65.6). All but 14 patients experienced neutrophil engraftment after a median time of 17 days (range, 0 to 70) (Table 2). One hundred and seven patients (44%) developed grade II to IV acute GVHD, including 55 patients (23%) with grade III to IV. Of the 200 evaluable patients who survived more than 100 days, 112 (56%) developed chronic GVHD including 78 (38%) with extensive grade. For the whole group of patients, the median 3-year OS, EFS, relapse, and NRM were 45%, 39%, 31%, and 30%, respectively.

Bivariate Analysis

As expected, among all the patient characteristics analyzed, IPSS score and cytogenetics significantly influenced OS, EFS, and relapse (Table 3). Best supportive care before transplantation, stable disease, and marrow blasts <5% at transplantation were significantly associated with improved OS and EFS and a lower rate of relapse. Patients younger than 51.7 years and those who received a graft from a donor younger than 45.5 years relapsed less often ($P = .005$ and $P = .004$, respectively) and had better EFS ($P = .031$ and $P = .037$, respectively) than the others. The cumulative incidence of relapse was also increased with reduced-intensity conditioning (RIC) regimen ($P = .003$) and graft from a CMV-seropositive donor ($P = .004$). Only 2 factors adversely influenced NRM: male patients ($P = .03$) and myeloablative conditioning (MAC) regimen ($P = .029$).

Table 2
Transplantation-Related Events

Event	Total (n = 242)	ATG (n = 93)	No-ATG (n = 149)	*P* Value*
Patients who engrafted, n (%)	228 (94)	87 (94)	141 (95)	.47
Time to ANC >500/μL, median, d	17	17	18	.95
Time to platelet >20 × 10^9/L, d	16	13	18	.002
Acute GVHD, n (%)				
0-I grades	135 (66)	68 (73)	67 (45)	
II-IV grades	107 (44)	25 (27)	82 (55)	<.0001
III-IV grades	55 (23)	13 (14)	42 (28)	.012
Chronic GVHD, n (%) (200 evaluable patients)				
None	88 (44)	40 (51)	48 (39)	
All forms (versus none)	112 (56)	38 (49)	74 (61)	.065
Extensive (versus none)	78 (38)	22 (28)	56 (46)	.057
Relapse rate at 3 years, n (%)	76 (31)	31 (33)	45 (30)	.36
Nonrelapse mortality at 3 years, n (%)	72 (30)	23 (20)	49 (33)	.11

ANC indicates absolute neutrophil count; GVHD, graft-versus-host disease.
* Comparison of the ATG and no-ATG groups.

Outcome According to ATG Use in Conditioning

As shown in Table 3 and Figure 2, patients in the ATG group developed acute grade II to IV GVHD less often (27%) than those in the no-ATG group (55%; $P < .0001$). Moreover, severe acute GVHD (grade III to IV) occurred in 14% of the patients in the ATG group versus 28% in the no-ATG group ($P = .009$). However, there was no significant difference between the 2 groups in terms of 3-year OS (50% versus 42%; $P = .25$), 3-year EFS (42% versus 36%; $P = .56$), cumulative incidence of relapse (34% versus 31%; $P = .46$) and NRM (24% versus 36%; $P = .10$). These results were similar in the subgroup of patients who progressed to a more advanced disease before transplantation (Table 4). Of note, the use of ATG tended to reduce the risk of chronic GVHD ($P = .065$ for all forms and $P = .057$ for extended forms) (Table 2).

Multivariate Analyses

As shown in Table 5, the most important factor associated with the development of grade II to IV acute GVHD was the absence of ATG in conditioning (hazard ratio [HR], 2.13; 95% CI, 1.26 to 3.61; $P = .0049$). Conversely, ATG had no impact on 3-year OS (HR, 1.25; 95% CI, .85 to 1.85; $P = .26$), EFS (HR, 1.28; 95% CI, .81 to 2.04; $P = .30$), relapse (HR, 1.36; 95% CI, .71 to 2.59; $P = .35$) and NRM (HR, 1.19; 95% CI, .68 to 2.13; $P = .54$). All these results were confirmed by propensity score analyses.

The detrimental role of a high-risk cytogenetics was confirmed for 3-year OS (HR, 2.05; 95% CI, 1.23 to 3.42; $P = .006$), EFS (HR, 2.12; 95% CI, 1.22 to 3.53; $P = .004$), and cumulative incidence of relapse (HR, 2.88; 95% CI, 1.55 to 5.37; $P = .0008$). The 3-year OS was also influenced by pretransplantation treatment; cytoreductive drugs were associated with less satisfactory OS (HR, 1.67; 95% CI, 1.11 to 2.59; $P = .013$). Finally, the other factors most closely associated with a higher risk of relapse were graft from a CMV-seropositive donor (HR, 2.32; 95% CI, 1.37 to 3.93; $P = .002$) and RIC regimen (HR, 2.49; 95% CI, 1.14 to 5.44; $P = .022$).

DISCUSSION

Findings from this study suggest that the addition of rabbit ATG to the conditioning regimen before allo-SCT can lead to a decreased incidence of acute GVHD without worsening post-transplantation outcomes in patients with MDS who are at high risk of relapse. These results were confirmed after adjustment with a propensity score that included the main patient and disease characteristics and transplantation modalities.

To the best of our knowledge, this is the largest study reporting on the role of ATG incorporated within the conditioning regimen of allo-SCT for patients with progressive MDS. Several studies have previously reported on ATG in pretransplantation setting [13-17,21]. However, the interpretation of the results of these studies is difficult because none of them restricted the inclusion criteria to a homogeneous disease setting and disease status. In addition, some of these studies included patients who received allo-SCT from

Table 3
Bivariate Analysis by Key Subsets: Three-Year Overall and Event-free Survival, Relapse, Nonrelapse Mortality, and Acute Grade 2 to 4 GVHD Rates

Factor	No. of Patients	Overall Survival		EFS		Relapse		NRM		Grade II-IV Acute GVHD	
		%	P*	%	P*	%	P†	%	P†	%	P*
Gender											
Male	151	44	.69	37	.57	32	.89	32	.03	42	.17
Female	91	46		41		32		31		49	
Patient age, yr											
<51.7	122	50	.25	47	.031	23	.005	33	.79	35	.0008
≥51.7	120	40		30		41		31		54	
IPSS					.045						
Low/int-1	139	52	.02	44		26	.03	33	.77	42	.39
Int-2/high	103	36		31		39		31		48	
Cytogenetics											
Favorable	115	52	.02	45	.015	26	.0003	32	.27	42	.74
Intermediate	65	46		42		24		39		46	
High risk	62	30		23		52		24		48	
Gender mismatch‡					.87						
No	187	45	.93	39		32	.79	33	.53	44	.91
Yes	53	43		38		34		29		43	
Pretransplantation progression§											
No	173	49	.02	43	.006	29	.05	30	.43	45	.84
Yes	67	36		28		40		35		43	
Pretransplantation treatment											
BSC	160	52	.0007	43	.003	29	.024	30	.25	46	.64
Cytoreductive	67	30		27		43		34		40	
Marrow blasts at transplantation					.022						
≤5%	87	50	.08	48		19	.0007	35	.53	41	.42
>5%	130	36		31		41		30		48	
Donor age, y											
<45.5	120	51	.15	46	.037	24	.004	32	.75	47	.31
≥45.5	117	39		31		41		30		42	
Recipient CMV serostatus											
Negative	112	48	.33	40	.34	33	.79	29	.34	50	.09
Positive	130	42		40		31		35		40	
Donor CMV serostatus											
Negative	119	49	.20	43	.13	24	.004	36	.30	50	.10
Positive	122	40		33		40		29		40	
Donor type											
Sibling	153	44	.91	37	.62	36	.09	30	.36	45	.73
HLA-matched unrelated	89	47		42		25		35		44	
Stem cell source											
Marrow	90	45	.84	38	.93	27	.14	37	.16	55	.009
PBSC	152	45		38		35		29		38	
Conditioning											
MAC	109	47	.97	41	.68	22	.003	39	.029	56	.0002
RIC	133	43		36		40		26		35	
Antithymocyte globulin											
No	149	42	.25	36	.56	31	.46	36	.10	55	<.0001
Yes	93	50		42		34		24		27	
Total body irradiation											
No	146	47	.21	41	.22	31	.60	29	.32	44	.85
Yes	96	41		34		34		36		46	
GVHD prophylaxis											
Cs-A and MTX	119	47	.35	43	.093	27	.09	33	.83	51	.04
Cs-A and other drugs	120	43		35		36		31		38	

EFS indicates event-free survival; NRM, nonrelapse mortality; GVHD, graft-versus-host disease; IPSS, International Prognostic Scoring System; int, intermediate; BSC, best supportive care; CMV, cytomegalovirus; BSC, peripheral blood stem cells; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; Cs-A, Cysclosporine-A; MTX, short course of methotrexate.

* Log-Rank.

† Gray (cumulative incidence).

‡ Gender mismatch is defined as male recipient who received graft from female donor.

§ Encompasses patients who progressed to a more advanced disease before transplantation.

HLA-matched and mismatched donors, adding other confounding factors [13,14,21].

Bacigalupo et al. [15] showed in the early 2000s that pretransplantation rabbit ATG (Thymoglobuline) administration decreased the risk of acute and chronic GVHD. However, these study reported only small series (75 patients included in 2 different trials), which precluded authors from drawing firm conclusions. In 2009, Finke et al. [14] analyzed the addition of a different brand of rabbit ATG (ATG Fresenius, Fresenius Biotech, Waltham, MA) to standard GVHD prophylaxis in 201 patients enrolled in a prospective, randomized, multicenter trial. Patients with various hematologic malignancies (acute and chronic leukemia, MDS, and osteomyelofibrosis) received MAC before allo-SCT from matched unrelated donors. Donors and recipients were only required to be HLA-A, -B, -DRB1 and -DQB1 identical (8 out of 8 alleles), and HLA-C mismatch was present in 35 cases. The addition of ATG Fresenius resulted in a decreased incidence of acute and chronic GVHD without

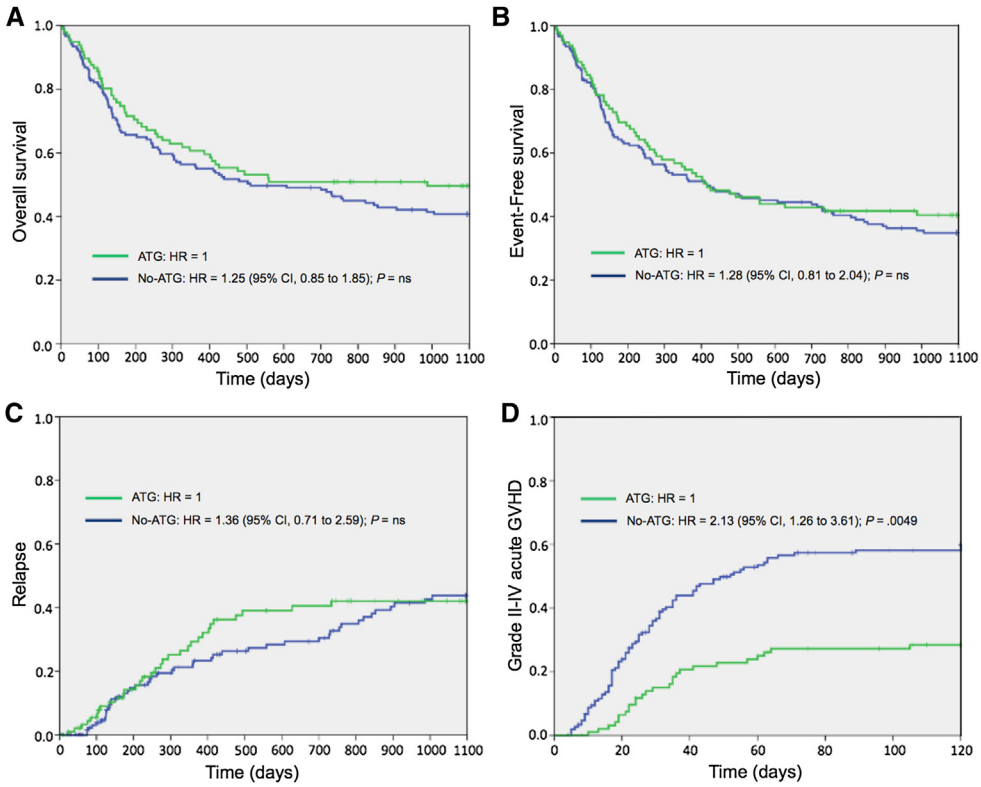

Figure 2. Kaplan-Meier estimates of (A) 3-year overall survival, (B) 3-year event-free survival, (C) cumulative incidence of 3-year relapse, and (D) grade II to IV acute graft-versus-host disease (GVHD) in 242 patients, according to the administration of antithymocyte globulin (ATG) in the conditioning. HR indicates hazard ratio; CI, confidence interval; ns, not significant.

increasing relapse and NRM, and without compromising OS. Data from Mohty et al. [13] confirmed these results with ATG Thymoglobuline in a retrospective report on 120 patients with acute leukemia and MDS undergoing allo-SCT from matched unrelated donors after MAC.

The impact of rabbit ATG was also analyzed with RIC in a retrospective multicenter study on 1676 adults undergoing transplantation for hematologic malignancies. Soiffer et al. [21] reported a higher risk of relapse with ATG compared to T cell–replete regimens (51% and 38%, respectively; $P < .001$). Although these data are supported by a large series, their interpretation may be confounded by the lack of homogeneity of the underlying diseases (acute and chronic leukemia, MDS, osteomyelofibrosis, and lymphoma) and the conditioning regimens. Conversely, in a recent phase 2 prospective study [16], patients with hematologic malignancies underwent allo-SCT from HLA-identical sibling and were randomized between 2 different strategies of conditioning: fludarabine was associated with either busulfan and ATG (n = 69) or total body irradiation alone (n = 70). After 5-year follow-up, the busulfan-ATG regimen was associated with greater disease control. However, because of higher NRM rate, this did not translate into better OS. Recently, de Masson et al. [22] assessed the outcomes of 37 cases of advanced-stage primary cutaneous T cell lymphomas treated with allo-SCT in a multicenter retrospective analysis. In multivariate analysis, the use of rabbit ATG was the only factor associated with an increased incidence of relapse (HR, 4.8; 95% CI, 1.8 to 12.9; $P = .002$) and a reduced progression-free survival (HR, 2.9; 95% CI, 1.3 to 6.2; $P = .04$). This demonstrates that ATG may have a different impact on relapse depending on the disease treated with allo-SCT.

We, therefore, chose to restrict our study to only 1 disease and focused on progressive patients, hypothesizing that ATG before transplantation could have a significant impact on outcome in this setting. Because the outcome of allo-SCT depends on the degree of donor-recipient HLA matching [31], we only included patients who received allo-SCT from

Table 4
Bivariate Analysis by Key Subsets in the Sub-Group of Patients Who Progressed to a More Advanced Disease before Transplantation: Three-Year Overall Survival, Event-Free Survival, Relapse, and Nonrelapse Mortality Rates

	No. of Patients	Overall Survival		EFS		Relapse		NRM	
		%	P*	%	P*	%	P†	%	P†
Antithymocyte globulin									
No	43	33	.42	26	.68	37	.65	37	.22
Yes	25	46		33		46		21	

EFS indicates event-free survival; NRM, nonrelapse mortality.
* Log-rank.
† Gray (cumulative incidence).

Table 5
Multivariate Analyses

Characteristics	3-Year Overall Survival			3-Year Event-Free Survival			3-Year Relapse			Grade II-IV Acute GVHD		
	HR	95% CI	P*	HR	95% CI	P*	HR	95% CI	P*	HR	95% CI	P*
Recipient age, yr												
<57.6	-†			1			1			1		
≥57.6				1.23	.78-1.91	.37	1.38	.71-2.68	.34	.68	.43-1.09	.11
Donor age, yr												
<44.9	-			1			1			-		
≥44.9				1.10	.73-1.64	.65	1.09	.64-1.88	.74			
Cytogenetics										-		
Low	1			1			1					
Intermediate	1.63	1.04-2.57	**.033**	1.52	.97-2.39	.066	1.02	.52-1.98	.96			
High risk	2.05	1.23-3.42	**.006**	2.12	1.22-3.53	**.004**	2.88	1.55-5.37	**.0008**			
IPSS at diagnosis										-		
Low/int-1	1			1			1					
Int-2/high	1.33	.83-2.13	.24	1.26	.80-1.99	.31	1.01	.56-1.83	.97			
Pretransplantation progression‡												
No	1			1			1			-		
Yes	1.33	.85-2.09	.21	1.33	.85-2.07	.21	1.45	.80-2.62	.21			
Pretransplantation treatment												
BSC	1			1			-					
Cytoreductive	1.67	1.11-2.59	**.013**	1.34	.88-2.04	.18						
Marrow blasts at transplantation												
<5%	1			1			1					
≥5%	.90	.55-1.46	.66	1.01	.63-1.62	.97	1.73	.88-3.41	.11			
CMV recipient serostatus												
Negative	-			-			-			1		
Positive										.84	.57-1.25	.39
CMV donor serostatus												
Negative	-			-			1			1		
Positive							2.32	1.37-3.93	**.002**	.86	.58-1.28	.45
Donor type												
Sibling	-			-			-			-		
HLA-matched unrelated												
Stem cell source												
Marrow	-			-			-			1		
PBSC										.86	.54-1.38	.54
Conditioning												
MAC	-			-			-	1.14-5.44	**.022**	1		
RIC										.86	.47-1.55	.61
ATG§												
ATG group	1			1			1			1		
No-ATG group	1.25	.85-1.85	.26	1.28	.81-2.04	.30	1.36	.71-2.59	.35	2.13	1.26-3.61	**.0049**
GVHD prophylaxis	-											
Cs-A and MTX				1			1			1		
Cs-A and other drugs				1.15	.72-1.85	.57	1.67	.88-3.16	.11	1.2	.71-2.02	.49

HR indicates hazard ratio; CI, confidence interval; GVHD, graft-versus-host disease; IPSS, international prognostic scoring system; int, intermediate; BSC, best supportive care; CMV, cytomegalovirus; PBSC, peripheral blood stem cells; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; ATG, antithymocyte globulin; Cs-A, Cysclosporine A; MTX, short course of methotrexate.
Antithymocyte globulin and variables having a significance level of $P < .10$ in the bivariate analyses were introduced in a multivariate model.

* $P \leq 0.05$ was considered statistically significant.

† Variables having a significance level of $P > .10$ in the bivariate analyses.

‡ Encompasses patients who progressed to a more advanced disease before transplantation.

§ Propensity score analyses: the absence of ATG was significantly associated with acute grade II to IV GVHD (HR, 2.13; 95% CI, 1.35 to 3.37; $P = .0012$). However, there was no impact of ATG on 3-year OS ($P = .11$), EFS ($P = .10$), and relapse ($P = .30$).
Bold indicates significant *P* values.

HLA-identical siblings or 10/10 matched unrelated donors. Donor-recipient HLA-matching was verified in the database of the French National Donor Registry as previously described [32]. In addition, data were cross checked meticulously using different methods of verification (matching of several sources of data, on-site verification, and computerized search for discrepancy errors).

Given the retrospective nature of our study, we used a propensity score adjustment in multivariate analyses to accurately identify the impact of ATG on patient outcome, by balancing the covariates in the 2 groups and reducing bias when treatment assignment was not random [30].

In line with previous reports [13-21], we found that the absence of ATG had a detrimental impact on acute GVHD development. However, one may question the reasons why such a beneficial effect of ATG in reducing acute GVHD does not have an effect on survival. Indeed, measuring the outcome of allo-SCT therapy is difficult because the net outcome is affected by several complex variables that all might have a role in determining the final outcome. However, better GVHD prevention, even if it does not significantly improve survival, may still be a desirable approach, especially given the overall burden of GVHD for patients. Of note, patients in the ATG group were older and received more often an allo-SCT after a RIC regimen than patients in the no-ATG group. Although the recipient's age is known to adversely influence survival [5], RIC is known to increase the risk of relapse [33]. On the other hand, this study did not observe a significant impact of ATG on chronic GVHD development. Although the difference did not reach statistical significance, there was a

clear trend towards less chronic GVHD in the ATG group ($P = .065$). Also, one should bear in mind that peripheral blood stem cells (PBSC) were more often used in the ATG group (82%) than in the no-ATG group (51%) ($P = .0001$), and PBSC use is known to be associated with an increased incidence of chronic GVHD [34,35]. Therefore, the addition of rabbit ATG as part of the conditioning regimen might have played a role in the reduction of the expected incidence of chronic GVHD in the ATG group.

With respect to the ATG dose impact, the majority of patients received ATG at the total dose of 5 mg/kg. Thus, this study did not have sufficient statistical power to assess the impact of ATG dose on patient outcome. In addition, based on our experience and different other reports, it is likely that the use of low to moderate doses (5 to 7 mg/kg) of ATG before allo-SCT can decrease the risk of GVHD without increasing the risk of relapse [36,37].

In conclusion, this study demonstrates that the addition of ATG to conditioning regimens results in a decreased incidence of acute GVHD without increasing the risk of relapse or compromising survival of patients undergoing allo-SCT for progressive MDS. Although prospective studies are still needed to assess the optimal ATG dose and administration schedule and determine whether ATG affects immune reconstitution, such a protective effect of ATG against acute GVHD is of benefit to patients undergoing allo-SCT. With the ever-growing use of PBSC, ATG should be incorporated within the conditioning regimen of patients with MDS, even if the disease is progressive.

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