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Allogeneic – Adult

Allogeneic Stem Cell Transplantation in Therapy-Related Myelodysplasia after Autologous Transplantation for Lymphoma: A Retrospective Study of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy

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A B S T R A C T

Therapy-related myelodysplastic syndrome (t-MDS) after autologous stem cell transplantation (ASCT) is a rare complication with no curative option. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) may be considered for eligible patients and has been understudied in t-MDS. We report 47 consecutive patients with t-MDS after an ASCT who underwent allo-HSCT with a median age of 58 years (range, 30 to 71 years) at transplantation and a median follow-up of 22 months (range, 0.7 to 107). The median overall survival (OS) was 6.9 months (95% confidence interval [CI], 0 to 19 months). OS rates were 45% (29% to 60%) and 30% (15% to 45%) at 1 and 3 years after transplantation, respectively. On univariate analysis, prior therapy for t-MDS before allo-HSCT ($P = .02$) and mismatched donors ($P = .004$) were associated with poor OS. Three-year nonrelapse mortality (NRM) and relapse rates were 44% (25% to 63%) and 41% (22% to 61%), respectively. Mismatched donors ($P < .001$) were associated with higher NRM and a high-risk MDS ($P = .008$) with a higher relapse risk. On multivariate analysis, HLA mismatch was associated with higher NRM (hazard ratio, 6.21; 95% CI, 1.63 to 23.62; $P = .007$). In conclusion, our results suggest that one third of the patients who develop t-MDS after an ASCT for lymphoma are cured after an allo-HSCT. The use of mismatched donors with standard graft-versus-host disease prophylaxis should be avoided in such an indication for allo-HSCT. It will be worthwhile to see if the implementation of cyclophosphamide post-transplantation will improve the outcome with mismatched donors.

INTRODUCTION

Treatment options for lymphoid neoplasms include autologous stem cell transplantation (ASCT). ASCT may be used for the treatment of relapsed or refractory follicular, diffuse large

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B cell, Hodgkin, or T cell lymphoma and is associated with improved remission rates and prolonged survival [1-3]. Adequate patient selection and advances in supportive care have improved outcomes of intensive chemotherapy in recent years. However, such prolongation of survival is also associated with late complications, such as the development of myeloid neoplasm consecutive to the treatment received, including the conditioning chemotherapy of ASCT [4-6].

The risk of developing therapy-related myelodysplastic syndrome (t-MDS) or therapy-related acute myeloid leukemia (t-AML) secondary to the use of both alkylating agents and topoisomerase inhibitors ranges from 5% to 7% in most series, although there are studies with variable and extreme incidences from 1% at 30 months to 11.7% at 6 years and may continue to increase until 12 to 15 years after ASCT [7,8].

t-MDS is associated with a high incidence of cytogenetic abnormalities, with frequent deletions or monosomies of chromosomes 5 and 7 [8,9]. These abnormalities have been described after the use of alkylating agents, confirming their role in the development of myelodysplasia [7,8]. Most cytogenetic alterations and acquired mutations are associated with a poor prognosis linked to a low response to chemotherapy and short duration of remission [10-12].

Although allogeneic stem cell transplantation has been widely studied in the context of t-AML, studies focusing on t-MDS are rare. Furthermore, the best time to perform allogeneic hematopoietic stem cell transplantation (allo-HSCT) in this group of patients is unknown, and predictors that might help patient selection are lacking [13,14].

We thus launched a retrospective multicentric study to evaluate the results of all consecutive allogeneic transplantations in a population with MDS secondary to autologous stem cell transplantation for lymphoma.

PATIENTS AND METHODS

Data Collection

The registry coordinated by the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) of the European Project Manager Internet Server database (ProMISe) was used as the data source. An electronic letter of authorization for the collection and use of the data for this retrospective study was sent to each center. All patients had given written consent before transplant for data collection in ProMISe for future research, in accordance with the Declaration of Helsinki. The scientific council of the SFGM-TC approved this study on February 2, 2017.

Patient Selection

For this retrospective study, we considered all consecutive adult patients who received an allogeneic transplant for the treatment of t-MDS to ASCT for lymphoid neoplasms registered from 2006 to 2016 in the ProMISe SFGM-TC database.

Patients who received an ASCT and developed secondary t-AML or those who had t-MDS that progressed to t-AML before allo-HSCT were not included. Patients who received ASCT due to neoplasms other than lymphoid neoplasms were not included.

Definitions

Lymphoid neoplasms were categorized according to the World Health Organization (WHO) 2008 classification. The types of myelodysplastic syndrome (MDS) followed the WHO 2008 criteria for MDS and were adapted to the WHO 2016 classification [15]. The cytogenetic classification was assessed according to the International Prognostic Scoring System (IPSS) score [16]. Lower-risk MDS comprised MDS with low-risk and intermediate-1 risk IPSS scores, and higher-risk MDS included those with intermediate-2 and high-risk IPSS scores. MDS with excess blasts 1 (MDS-EB-1) and MDS with excess blasts 2 (MDS-EB-2) were defined according to WHO and were analyzed together. The other categories of MDS with <5% blasts in bone marrow (MDS with single-lineage dysplasia, MDS with multilineage dysplasia, MDS with ring sideroblasts and single-lineage dysplasia, MDS with ring sideroblasts and multilineage dysplasia, MDS with isolated 5q deletion, and unclassifiable MDS) were analyzed together. The response criteria in MDS in patients who received some type of treatment after or before allo-HSCT were defined according to the International Working Group response criteria [17].

Acute graft-versus-host disease (GVHD) was described according to the criteria of the International Bone Marrow Transplantation Registry [18]. For the analysis of cytomegalovirus (CMV) serostatus, the most hazardous combination, defined as a CMV-seronegative recipient and CMV-seropositive donor, was compared with the other possible combinations. Intensity of the allo-HSCT conditioning regimen was analyzed according to previously established working definitions [19]. Only 2 categories were considered in the analysis—myeloablative and reduced-intensity conditioning (RIC)—due to the multiple schemes and doses used. HLA mismatch was defined as the presence of at least 1 difference in the HLA-A, HLA-B, HLA-Cw, DR, or DQ loci. For the analysis, no mismatch HLA comprised identical-sibling donor and matched unrelated donor 10/10 (MUD), and HLA mismatched those with mismatched unrelated donor 9/10 (MMUD) and cord blood units 4/6 and 5/6.

Overall survival (OS) was defined as the period from the day of allo-HSCT until the day of death from any cause or date of the last recorded follow-up.

Nonrelapse mortality (NRM) was defined as death from any cause other than relapse of MDS, including progression to acute myeloid leukemia (AML), from the day of allo-HSCT. Relapse was defined as a relapse of MDS or progression to AML according to the WHO criteria.

Statistical Analysis

The characteristics of the patients and the factors related to lymphoma, ASCT, t-MDS, and allo-HSCT are summarized with descriptive statistics. The primary endpoint of the study was OS, which was calculated using the Kaplan-Meier method. The frequency of NRM and relapse was calculated by cumulative incidences.

The prognostic effects of the factors with respect to OS, NRM, and relapse were analyzed with a log-rank test (Mantel-Cox) by univariate analysis. The multivariate analysis was performed using the potential predicting factors that were significant by univariate analysis with Cox proportional hazards regression models. The calculations were performed with SPSS software version 23.0 (SPSS, Chicago, IL).

RESULTS

To date, the French ProMISe database includes 74,779 autologous transplant and 38,860 allogeneic transplant observations from 98 centers in France, Belgium, and Switzerland. We searched the French ProMISe database for all registered patients from January 2006 to December 2016. A total of 47 patients who met the inclusion criteria were included.

Lymphoma and ASCT

The initial neoplasm for 8 patients (17.0%) was a Hodgkin lymphoma, whereas it was a non-Hodgkin lymphoma for 37 (78.7%) (Table 1). Fourteen patients (29.8%) received more than 2 lines of chemotherapy before autologous transplantation (range, 0 to 8). Conditioning consisted of carmustine, etoposide, cytarabine, and melphalan for 80.8% of patients and other regimens for only 19.2%. Thirty-seven patients (78.7%) achieved complete remission. There were no patients with relapsed lymphoma at the time of allo-HSCT, but it is unknown whether there were patients who relapsed or progressed from lymphoma between ASCT and allo-HSCT. There were no patients who relapsed from lymphoma after allo-HSCT.

MDS

The median time from ASCT to the diagnosis of t-MDS was 74.4 months (range, 2.2 to 259 months). Eleven patients (23.5%) had MDS-EB-1, 12 (25.6%) had MDS-EB-2, and 22 (46.7%) had other types of MDS. No diagnostic information was obtained for 2 patients (4.2%).

Cytogenetic data were obtained for 41 patients: 82.9% had at least 1 cytogenetic abnormality. The most frequent cytogenetic anomalies were on chromosomes 7 (11 patients, 23.4%) and 5 (6 patients, 12.8%) or both (15 patients, 31.9%). Among the patients, 23.4% were considered at low risk and 59.6% at high risk. Sixty-eight percent of patients received at least 1 treatment line before allo-HSCT: 16 (34.1%) received hypomethylating agents and 11 (23.4%) had AML-like induction treatment. Ten patients (21.3%) achieved complete

Table 1
Patient Characteristics at Autologous Stem Cell Transplantation

Patient Characteristics	Overall Population, n (%)
Number of patients	47 (100)
Sex	
Male	37 (78.7)
Female	10 (21.3)
Lymphoid hematologic malignancy	
Follicular lymphoma	12 (25.6)
Diffuse large B cell lymphoma	12 (25.6)
Hodgkin lymphoma	8 (17.0)
Mantle cell lymphoma	5 (10.6)
Burkitt lymphoma	2 (4.3)
Nodal marginal zone lymphoma	1 (2.1)
Small lymphocytic lymphoma	1 (2.1)
Lymphoplasmacytic lymphoma	1 (2.1)
Waldenstrom macroglobulinemia	1 (2.1)
Peripheral T cell lymphoma	1 (2.1)
Angioimmunoblastic T cell lymphoma	1 (2.1)
Unknown	2 (4.3)
Previous lines of therapy	
1	9 (19.1)
2	24 (51.1)
≥3	10 (21.3)
Unknown	4 (8.5)
Conditioning ASCT	
BEAM	38 (80.8)
Chemotherapy + TBI	7 (14.9)
Unknown	2 (4.3)
Response to ASCT	
Complete remission	37 (78.7)
Not in complete remission	4 (8.5)
Unknown	6 (12.8)

BEAM indicates carmustine, etoposide, cytarabine, and melphalan.

remission before transplantation and 36 (76.6%) were not in complete remission before allo-HCST.

HSCT

The characteristics of the patients at allo-HSCT are shown in Table 2.

The median age at allo-HSCT was 58 years (range, 30 to 71 years), and most of the patients were male (78.7%). The median time interval from diagnosis of t-MDS to allogeneic transplantation was 7.9 months (range, 2.5 to 16.8 months).

Peripheral blood stem cells were the source used for 87.4% of patients. Nineteen patients (40.5%) underwent transplantation from an HLA-identical sibling donor and 17 (36.2%) from a matched unrelated donor. Ten patients (21.2%) had a mismatched unrelated donor, including 3 patients (6.3%) who received umbilical cord blood transplantation (1 with a double cord). None received a haploidentical donor. Myeloablative conditioning was used in 9 patients (19.1%), 4 received a combination busulfan (Bu)/cyclophosphamide (Cy) regimen (2 BuCy and 2 CyBu), with conventional doses (12.8 mg/kg Bu i.v., 120 mg/kg Cy), 3 a combination of fludarabine/Bu with anti-thymocyte globulin (ATG) (150 mg/m^2 fludarabine, 12.8 mg/kg Bu, and various doses of ATG between 2.5 and 5 mg/kg), 1 fludarabine/Bu without ATG (160 mg/m^2 fludarabine, 9.6 mg/kg Bu), and 1 fludarabine and total body irradiation (TBI) (120 mg/m^2 fludarabine, 8 Gy TBI).

Table 2
Patient Characteristics at Allogeneic Hematopoietic Stem Cell Transplantation

Patient Characteristics	Overall Population
Number of patients	47 (100)
Age at allo-HSCT, median (range), yr	58 (30-71)
Age, yr	
≥58	23 (48.9)
<58	24 (51.1)
Sex	
Male	37 (78.7)
Female	10 (21.3)
Myelodysplastic syndrome diagnosis	
MDS-SLD	5 (10.6)
MDS-MLD	12 (25.6)
MDS-RS-SLD	1 (2.1)
MDS-RS-MLD	1 (2.1)
MDS del(5q)	1 (2.1)
MDS-EB-1	11 (23.5)
MDS-EB-2	12 (25.6)
MDS-U	2 (4.2)
Unknown	2 (4.2)
Interval from ASCT to diagnosis of t-MDS, mo	
≥74	36 (76.5)
<74	11 (23.5)
Cytogenetics	
Good/favorable prognosis	3 (6.4)
Intermediate prognosis	6 (12.8)
Poor/unfavorable prognosis	32 (68.0)
Unknown	6 (12.8)
IPSS diagnosis	
Low risk/intermediate-1	11 (23.4)
Intermediate-2/high risk	28 (59.6)
Unknown	8 (17.0)
Prior therapy of MDS before allo-HSCT	
AML-like induction treatment	11 (23.4)
Hypomethylating agents	16 (34.1)
ESA	4 (8.5)
Immunosuppressants	1 (2.1)
Nothing	11 (23.4)
Unknown	4 (8.5)
Unknown	1 (2.1)
Disease status before allo-HSCT	
Complete remission	10 (21.3)
Not in complete remission	36 (76.6)
Interval from diagnosis of MDS to allo-HSCT, mo	
<6	17 (36.2)
≥6	30 (63.8)
Year of transplantation	
2006-2010	18 (38.3)
2011-2016	29 (61.7)
Conditioning regimen	
Myeloablative	9 (19.1)
Reduced intensity/nonmyeloablative	38 (80.9)
Conditioning regimen with TBI	
Yes	9 (19.1)
No	38 (80.9)
Graft type	
PBSC	41 (87.4)
BM	3 (6.3)
CB	3 (6.3)

(*continued*)

Table 2 (*Continued*)

Patient Characteristics	Overall Population
Type of donor	
HLA-identical sibling (10/10)	19 (40.5)
Matched unrelated (10/10)	17 (36.2)
Mismatched unrelated (9/10, 4/6, 5/6)	10 (21.2)
Unknown	1 (2.1)
ABO match	
Major incompatibility	15 (32.0)
Minor incompatibility	8 (17.0)
Compatible	18 (38.3)
Unknown	6 (12.7)
Sex match	
Male/male	21 (44.6)
Male/female	16 (34.0)
Female/male	4 (8.6)
Female/female	6 (12.8)
GVHD prophylaxis	
CsA-MTX	11 (23.4)
CsA-MMF	18 (38.3)
CsA	12 (25.5)
Other	6 (12.8)
CMV serostatus	
R^-/D^-	12 (25.5)
R^-/D^+	8 (17.7)
R^+/D^-	13 (27.1)
R^+/D^+	14 (29.7)
Karnofsky score	
90-100	29 (61.8)
<90	16 (34.0)
Unknown	2 (4.2)

Values are presented as n (%) unless otherwise indicated.
MDS-SLD indicates myelodysplastic syndrome with single-lineage dysplasia; MDS-MLD, myelodysplastic syndrome with multilineage dysplasia; MDS-RS-SLD, myelodysplastic syndrome with ring sideroblasts and single-lineage dysplasia; MDS-RS-MLD, myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia; MDS del(5q), myelodysplastic syndrome with isolated 5q deletion; MDS-U, myelodysplastic syndrome unclassifiable; ESA, erythropoietin stimulating agents; PBSC, peripheral blood stem cell; BM, bone marrow; CB, cord blood; MTX, methotrexate; MMF, mycophenolate mofetil; R, receptor; D, donor.

Thirty-eight patients (80.9%) received RIC. Twenty-two patients received a combination of fludarabine-Bu-based RIC with ATG or antilymphocyte globulin (100 to 150 mg/m^2 fludarabine, 3.2 to 6.4 mg/kg Bu, 2.5 to 5 mg/kg ATG, or 5 to 20 mg/kg antilymphocyte globulin). Four patients received fludarabine-Bu-based RIC without ATG. Eight patients received fludarabine-TBI-based RIC (2 to 8 Gy) and 4 patients received sequential Fludarabine - Amsacrine - Cytarabine chemotherapy-RIC

Eighteen patients (38.3%) received prophylaxis with cyclosporine (CsA) and mycophenolate mofetil and 11 (23.4%) CsA and methotrexate. Twelve patients (25.5%) received only CsA, and 6 (12.8%) received other regimens. The most frequent serologic status for CMV was 29.7% R^+/D^+. Thirteen transplants (27.1%) were performed with the combination R^+/D^-.

Performance status was assessed using the Karnofsky Performance Score: 29 patients (61.8%) had a score of 90 to 100 before transplantation.

Response to Allo-HSCT and Complications

The median duration of post-transplant follow-up was 22 months (range, 0.7 to 107 months), with a median survival of 6.9 months (95% confidence interval [CI], 0 to 19 months).

Table 3
Causes of Death According to the Response at Allo-HSCT

Cause of Death	Total, n (%)	CR, n	Not in CR, n	Unknown, n
Relapse/ progression	12 (44.4)	4	8	
NRM causes	14 (51.9)	11		3
Sepsis/MODS	8			
GVHD	3			
Pulmonary toxicity	1			
Hemorrhage	2			
Graft rejection	0	1		
VOD	0			
Unknown	1 (3.7)			
Total deaths, n (%)	27 (100)	16 (59.3)	8 (29.6)	3 (11.1)

CR indicates complete remission; MODS, multiple-organ dysfunction syndrome; VOD, veno-occlusive disease.

Thirty-four patients (72.3%) were in complete response after allo-HSCT, and 9 patients (19.1%) had a relapse/progression post-transplantation. The response was not evaluated for 4 patients (8.6%) because of the early death of 3 and loss to follow-up for 1.

Acute GVHD occurred in 20 patients (42.5%): 7 (14.8%) had grade I, and 13 (27.7%) had a grade requiring treatment (grades II to IV). Ten patients (21.3%) developed chronic GVHD, of whom 4 (8.6%) had extensive and 6 (12.7%) had limited involvement. At the time of the analysis in August 2017, of the 15 patients who had relapses or progressions, 13 died: 12 related to relapse and 1 could not be determined. Eleven patients in complete remission died of transplant complications, mainly infectious. Three patients had early death due to transplant complications without knowing the response obtained to the transplant. No deaths due to veno-occlusive disease or graft rejection were reported. The causes of death are listed in Table 3.

Univariate and Multivariate Analysis of Patients

OS for all patients was 45% (95% CI, 29% to 60%) in the first year, 39% (95% CI, 24% to 55%) at 2 years, and 30% (95% CI, 15% to 45%) at 3 years (Table 4 and Figure 1). Univariate analysis found that prior therapy of t-MDS with hypomethylating agents before allo-HSCT ($P = .02$) and the presence of an HLA mismatch ($P = .004$) were associated with poorer OS (Table 5). Multivariate analysis showed only a nonstatistically significant association with poorer OS for patients receiving a treatment based on hypomethylating agents (hazard ratio [HR], 3.55; 95% CI, 0.97 to 12.97; $P = .06$) and no other clinically significant factors (Table 6).

NRM was 35% (95% CI, 18% to 51%) in the first year, 39% (95% CI, 21% to 56%) at 2 years, and 44% (95% CI, 25% to 63%) at 3 years (Table 4 and Figure 1). Univariate analysis identified sex ($P = .02$), graft type ($P = .02$), mismatched unrelated donor type ($P < .001$), and the presence of an HLA mismatch ($P = .001$) as significant risk factors (Figure 2). Multivariate analysis showed an

Table 4
Outcome of Patients Treated with Allo-HSCT for t-MDS to ASCT for Lymphoid Neoplasms

Characteristic	NRM	Relapse	OS
At 1 year	35 (18-51)	35 (18-53)	45 (29-60)
At 2 years	39 (21-56)	41 (22-61)	39 (24-55)
At 3 years	44 (25-63)	41 (22-61)	30 (15– 45)

All values are represented as % (95% CI).

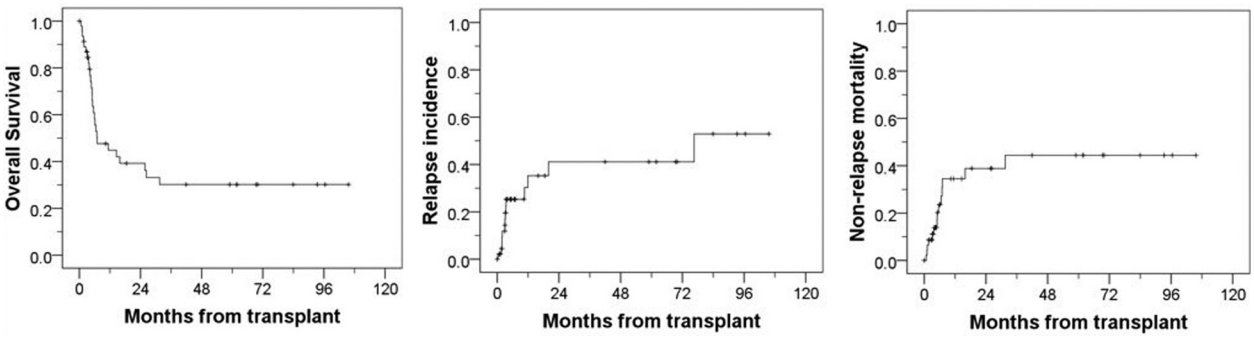

Figure 1. OS, NRM, and relapse incidence of all patients who underwent allo-HSCT for a t-MDS to ASCT for lymphoid neoplasms.

association between the use of an MMUD and shorter survival after transplantation, relative to identical siblings or MUDs (HR, 6.21; 95% CI, 1.63 to 23.62; $P = .007$).

The risk of relapse was 35% (95% CI, 18% to 53%) in the first year, 41% (95% CI, 22% to 61%) at 2 years, and 41% (95% CI, 22% to 61%) at 3 years (Table 4 and Figure 1). The type of MDS and presence of marrow blasts ($P = .008$) were the most significant predictive factors of relapse in univariate analysis, but multivariate analysis did not identify the presence of marrow blasts as a significant factor of relapse.

DISCUSSION

This retrospective study of the SFGM-TC, which examined the experience of allo-HSCT in patients, with t-MDS after an ASCT for lymphoid neoplasm, over 10 years, showed donor mismatch to adversely affect OS. To our knowledge, this is the first series published in this specific population. In other studies, such patients account for 7% to 32% of the sample [13,14,20-27]. Most of the survival data of these studies show results for a mix of patients, including those with t-AML and t-MDS exposed to multiple treatments (chemotherapy and/or radiotherapy and not necessarily previous ASCT) and various primary diseases (solid organ neoplasms, lymphoid neoplasms, myeloid neoplasms, and congenital anomalies).

Although allo-HSCT has been used as a curative therapeutic modality for eligible patients, data published by several groups have shown poor long-term survival [13,14,20-22]. In our series, the median OS was 6.9 months, with OS in the first and third years of 45% and 30%, respectively. The high NRM and relapse rates at 3 years (44% and 41%, respectively) were similar to those previously reported by other studies, consistent with the poor prognosis of these patients.

Relapse or progression of t-MDS was the main cause of mortality (44.4%) in our study. Patients with MDS-EB-1 and MDS-EB-2 had a higher risk of relapse by univariate analysis. The association of these aggressive variants of myelodysplasia with higher relapse rates has been described in other studies on patients with various primary diseases. It is not known whether treating t-MDS before transplantation can decrease the risk of relapse or whether maintenance treatment should be started after transplant to prevent relapse. In our study, the only type of pretransplant treatment associated with improved survival was AML-like therapy, even if they had not achieved complete remission before transplantation, in univariate analysis ($P = .02$). The multivariate analysis shows a nonstatistically significant association of hypomethylating agents before transplantation with a poorer OS (HR, 3.55; 95% CI, 0.97 to 12.97; $P = .06$) regardless of the response they obtained with this treatment before transplantation, in contrast to patients with de novo MDS and poor risk cytogenetics, who normally benefit from this approach [28]. Our results are not valued for the sample size and the retrospective analysis. Prospective studies are necessary to determine the benefit of a type of treatment before transplantation. A retrospective analysis that included more patients with t-AML than t-MDS reports relapse rates of 42% and 44% at 5 and 10 years with OS of 38% and 24%, respectively, when AML-like chemotherapy is used before transplantation [26].

No patient in our study received post-transplant maintenance therapy. The use of maintenance therapy, with low doses of azacytidine after allo-HSCT [29] and azacytidine [30] or decitabine with infusion of donor lymphocytes [31], has been published recently and may be worth considering. Targeted therapies, directed against mutated oncogenes, such as IDH-1, IDH-2, or FLT-3 genomic alterations, may improve the outcome of specific subsets of patients in the future.

Infections and GVHD were the main cause of NRM.

In our series there were 27 deaths: 12 were due to relapse, 8 due to infections, and 3 due to GVHD. The cause of death could not be established in 4 patients. The few deaths due to GVHD show the intensity of the immunosuppressive prophylaxis used, limiting the graft-versus-tumor effect and increasing the possibility of relapse and the appearance of infections. Multiple schemes and doses used in conditioning and immunosuppressive prophylaxis, testing the usual drugs, have not allowed us to identify whether one scheme is superior to another. A significant factor to improve survival was the absence of a mismatch by using either HLA identical-sibling or matched unrelated donors, as previously reported [14]. A prospective study of the SFGM-TC reported better OS (37% versus 15%, $P = .02$) of patients with high-risk MDS who had identical HLA donors versus those who did not [32]. In our series, there was a lower frequency of NRM in patients with 10/10 donors than 9/10 donors (HR, 6.21; 95% CI, 1.63 to 23.62; $P = .007$), although this was not significative in OS by multivariate analysis. NRM associated with mismatched HLA donors could be improved with new prophylactic strategies to counter GVHD, such as post-transplant Cy (PT-Cy). Reports over the past years on a small number of patients with de novo MDS/AML and Therapy-related myeloid neoplasms who underwent allo-HSCT show similar results for HLA identical-sibling, MUD, or haploidentical donors [33]. A recent retrospective series of European Society for Blood and Marrow Transplantation(EBMT) in patients with MDS who underwent haploidentical transplants reported better OS for patients treated with PT-Cy than those who were not (OS at 3 years of 38% versus 28%) but with high NRM (41% versus 55%) [34]. This modality may be an acceptable option, although the risk of relapse remains high, and variations in the dose of PT-Cy have even been tested in high-risk patients with refractory MDS/AML [35]. Indeed, older patients were recently reported to have an OS of 42% and a relapse rate of 24% at 2 years [36]. Strategies to improve progression-free survival

Table 5
Univariate Analysis for Probabilities of Outcomes of NRM, Relapse, and OS at 3 Years after HSCT

	NRM		Relapse		OS	
All Probabilities Estimated at 3 yr	Cumulative Incidence (95% CI)	*P* Value	Cumulative Incidence (95% CI)	*P* Value	Cumulative Incidence (95% CI)	*P* Value
Age at HSCT, yr		.23		.21		.69
≥58	0.43 (0.20-0.66)		0.37 (0.05-0.68)		0.33 (0.09-0.57)	
<58	0.45 (0.18-0.73)		0.44 (0.20-0.68)		0.29 (0.09-0.48)	
Sex		**.02**		.19		**.002**
Male	0.38 (0.17-0.59)		0.38 (0.16-0.59)		0.37 (0.18-0.55)	
Female	0.74 (0.34-1.14)		0.50 (0.15-0.85)		0.10 (0-0.29)	
Hematologic malignancy		.24		.65		.98
NHL	0.50 (0.29-0.71)		0.53 (0.22-0.85)		0.30 (0.13-0.47)	
HL	0.25 (0-0.68)		0.63 (0.08-1.17)		0.21 (0-0.56)	
Previous lines of therapy		.75		.40		.34
1-2	0.52 (0.29-0.75)		0.41 (0.18-0.65)		0.27 (0.10-0.44)	
>2	0.37 (0.03-0.70)		0.11 (0-0.31)		0.48 (0.11-0.84)	
Conditioning ASCT		.45		.44		.85
BEAM	0.44 (0.23-0.66)		0.39 (0.17-0.60)		0.31 (0.14-0.48)	
Others	0.57 (0.13-1.01)		0.20 (0-0.55)		0.34 (0-0.73)	
Conditioning ASCT		.34		.76		.91
TBI	0.65 (0.26-1.03)		0.44 (0-0.93)		0.29 (0-0.63)	
Non-TBI	0.39 (0.19-0.59)		0.33 (0.13-0.52)		0.33 (0.15-0.51)	
Interval from ASCT to diagnosis of MDS, mo		.52		.80		.27
≥74	0.41 (0.16-0.65)		0.55 (0.20-0.89)		0.20 (0-0.39)	
<74	0.43 (0.17-0.68)		0.36 (0.12-0.59)		0.39 (0.17-0.60)	
MDS diagnosis		.49		**.008**		.08
MDS-EB-1/EB-2	0.55 (0.24-0.87)		0.65 (0.37-0.93)		0.17 (0-0.34)	
Other MDS	0.40 (0.14-0.65)		0.10 (0-0.23)		0.45 (0.20-0.70)	
IPSS diagnosis		.25		.94		.64
Lower	0.21 (0-0.47)		0.45 (0.06-0.85)		0.34 (0.03-0.65)	
Higher	0.62 (0.37-0.87)		0.41 (0.11-0.70)		0.25 (0.06-0.44)	
Cytogenetics		.40		.27		.40
Good prognosis	0 (0-0)		0 (0-0)		0.67	
Intermediate prognosis	0.5 (0.01-0.1)		0.6 (0.02-1.18)		0.20	
Poor prognosis	0.57 (0.31-0.83)		0.48 (0.21-0.75)		0.21	
Prior therapy for MDS before HSCT		.12		.21		**.02**
AML-like therapy	0.1 (0-0.29)		0.38 (0.04-0.71)		0.56 (0.24-0.89)	
Hypomethylating agents	0.52 (0.21-0.83)		0 (0-0)		0 (0-0)	
No chemotherapy	0.51 (0.20-0.82)		0.42 (0.08-0.76)		0.35 (0.09-0.61)	
Year of transplantation		.72		.95		.61
2006-2010	0.39 (0.14-0.63)		0.43 (0.15-0.70)		0.33 (0.12-0.55)	
2011-2016	0.52 (0.22-0.81)		0.41 (0.12-0.71)		0.28 (0.07-0.49)	
Duration of MDS from diagnosis to HSCT, mo		.37		.31		.13
<6	0.36 (0.06-0.65)		0.22 (0-0.43)		0.47 (0.20-0.74)	
>6	0.50 (0.25-0.75)		0.55 (0.28-0.81)		0.22 (0.05-0.39)	
Disease status before HSCT		.67		.64		.70
Complete remission	0.25 (0-0.55)		0.61 (0.20-1.01)		0.25 (0-0.55)	
Partial remission	0.53 (0.10-0.96)		0.30 (0.01-0.59)		0.25 (0-0.53)	
Active/progression	0.48 (0.23-0.74)		0.33 (0.07-0.58)		0.38 (0.15-0.60)	
MDS before HSCT		.10		.37		.07
MDS-EB-1/EB-2	0.64 (0.30-0.98)		0.44 (0.19-0.68)		0.14 (0-0.32)	
Other MDS	0.22 (0-0.45)		0.30 (0.03-0.56)		0.44 (0.17-0.71)	
IPSS before HSCT		.50		.47		.70
Lower	0.31 (0.01-0.60)		0.40 (0.10-0.70)		0.27 (0.01-0.54)	
Higher	0.58 (0.25-0.91)		0.37 (0-0.75)		0.34 (0.12-0.58)	
Conditioning regimen		.49		.45		.54
Myeloablative (MAC)	0.61 (0.21-1.01)		0.58 (0.18-0.98)		0.22 (0-0.49)	

(*continued*)

Table 5 (*Continued*)

	NRM		Relapse		OS	
All Probabilities Estimated at 3 yr	Cumulative Incidence (95% CI)	*P* Value	Cumulative Incidence (95% CI)	*P* Value	Cumulative Incidence (95% CI)	*P* Value
Nonmyeloablative/RIC	0.37 (0.18-0.56)		0.36 (0.15-0.57)		0.33 (0.15-0.50)	
Graft type		**.02**		.32		.18
PBSC	0.31 (0.13-0.49)		0.37 (0.19-0.56)		0.36 (0.19-0.53)	
BM	0 (0-0)		0 (0-0)		0 (0-0)	
CB	0 (0-0)		0 (0-0)		0 (0-0)	
GVHD prophylaxis		0.95		0.24		0.55
CsA-MTX	0.49 (0.15-0.84)		0.35 (0.01-0.70)		0.40 (0.10-0.71)	
CsA-MMF	0.47 (0.19-0.75)		0.49 (0.15-0.82)		0.18 (0-0.39)	
CsA	0.17 (0-0.38)		0.58 (0.17-0.98)		0.25 (0-0.54)	
Other	0.33 (0-0.71)		0 (0-0)		0.67 (0.29-1.04)	
Type of donor		**<.001**		.90		.58
HLA-identical sibling	0.30 (0.04-0.56)		0.46 (0.19-0.71)		0.35 (0.12-0.58)	
Matched unrelated	0.36 (0.05-0.66)		0.33 (0.04-0.62)		0.40 (0.13-0.66)	
Mismatched unrelated	0.83 (0.53-1.13)		0.25 (0-0.55)		0.12 (0-0.34)	
Mismatch HLA		**.001**		.86		**.004**
No (10/10)	0.34 (0.13-0.54)		0.41 (0.21-0.61)		0.37 (0.19-0.54)	
Yes (no 10/10)	0.83 (0.53-1.13)		0.25 (0-0.55)		0.12 (0-0.34)	
ABO match		.58		.72		.59
Compatible	0.49 (0.19-0.78)		0.46 (0.11-0.81)		0.19 (0-0.41)	
Major incompatibility	0.59 (0.21-0.96)		0.66 (0.30-1.02)		0.16 (0-0.36)	
Minor incompatibility	0.33 (0-0.87)		0.29 (0-0.62)		0.40 (0-0.83)	
Sex match		.50		.66		.40
Yes	0.37 (0.13-0.61)		0.35 (0.11-0.58)		0.36 (0.14-0.58)	
No	0.15 (0-0.44)		0.50 (0.19-0.81)		0.25 (0.05-0.45)	
CMV serostatus		.31		.16		.07
R^+/D^-	0.60 (0.19-1.01)		0.64 (0.14-1.16)		0.12 (0-0.34)	
Others	0.41 (0.20-0.62)		0.37 (0.16-0.57)		0.36 (0.18-0.53)	
Karnofsky score		.50		.65		.92
90-100	0.47 (0.24-0.69)		0.44 (0.20-0.68)		0.30 (0.12-0.48)	
<90	0.27 (0-0.57)		0.35 (0.05-0.64)		0.34 (0.05-0.63)	
Acute GVHD		.29		.61		.81
Yes	0.63 (0.34-0.93)		0.43 (0.08-0.79)		0.24 (0.02-0.47)	
No	0.29 (0.08-0.49)		0.42 (0.17-0.66)		0.35 (0.15-0.54)	

P values in bold represent statistically significant P values <0.05 in the univariate and multivariate analysis.
NHL indicates non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MAC, myeloablative conditioning.

and decrease NRM using PT-Cy have been implemented. The (Haploidentical and Mismatched Unrelated Donors Hematopoietic Stem Cell Transplant) trial (NCT03250546), currently in the inclusion phase, will evaluate the effect of PT-Cy for the prevention of GVHD in haploidentical and HLA-9/10 mismatched unrelated donor transplants.

The proportion of patients with high-risk cytogenetics has been previously reported to be 17% to 49% [13,14,24,25]. In our study, 68% (32 patients) had adverse cytogenetic alterations, especially abnormalities in chromosomes 5 and 7. However, the results were probably not significant for the few patients in the other risk categories.

The best time to perform the transplant is unknown. It is possible that rapid transplantation could reduce the risk of t-MDS/t-AML-related deterioration [26]. Although a higher frequency of NRM is possible if the transplant is performed beyond 6 months (50% versus 12.5%, $P = .03$), caused by toxicity and infections due to multiple chemotherapy cycles [24], we found no difference in OS or NRM. Although the median age of 58 years is higher than for other large related series and 60% of patients had a Karnofsky Performance Score ≥90, these factors did not play a significant role in survival, as in other series [12-14,21,24,26].

Our data also do not support that factors related to the primary disease and its treatment can influence survival. Interestingly, no veno-occlusive disease was observed in this population having received a previous autologous transplantation.

A retrospective report of EBMT found better results between 1998 and 2006 than for transplants performed before 1998 (40% versus 29%, $P = .02$) [13]. We found no differences between 2006 to 2010 and 2011 to 2016, probably because support care has not changed as much in the past 10 years as during the transition from the 1980s to 1990s.

Treatment options are still limited for patients who are not candidates for allo-HSCT. Other therapeutic strategies have been tested using azacitidine or clofarabine associated with chemotherapy with encouraging results [37,38].

The limitations of our study include the collection of retrospective data and the absence of a historical group for comparisons. Patient selection may have varied between centers. The small number of patients and the low incidence of secondary myelodysplasia make it difficult to perform a prospective study.

In summary, although the number of patients in this study was small, the results suggest that patients receiving an ASCT for

Table 6
Multivariate Analysis of Outcomes of NRM, Relapse, and OS after HSCT

	OS		NRM		Relapse	
Characteristic	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Prior therapy for MDS before HSCT						
AML-like induction	1.0	.13				
Hypomethylating agents	3.55 (0.97-12.97)	.06				
No chemotherapy	1.79 (0.52-6.15)	.35				
HLA mismatch		.13		**.007**		
No (10/10)	1.0		1.0			
Yes (9/10, 4/6, 5/6)	2.04 (0.80-5.22)		6.21 (1.63-23.62)			
MDS diagnosis						.21
Other MDS					1.0	
MDS-EB-1/EB-2					2.63 (0.57-12.03)	

P values in bold represent statistically significant P values <0.05 in the univariate and multivariate analysis.

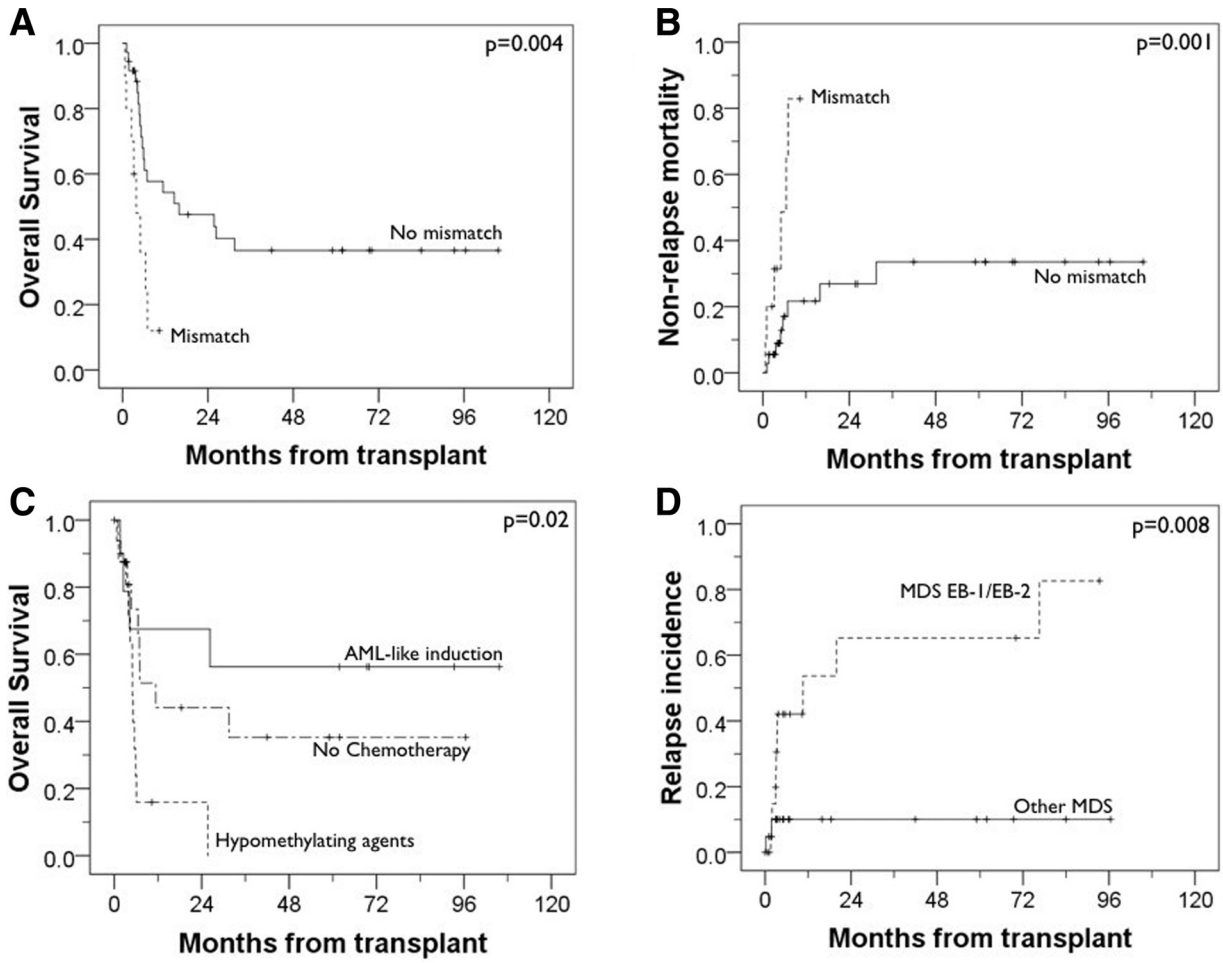

Figure 2. OS and NRM of patients with or without HLA mismatch donor (A, B). OS in regard to prior therapy of MDS before allo-HSCT (C). Relapse rate by type of MDS at diagnosis (D).

a lymphoid neoplasm who develop t-MDS have short OS after allo-HSCT, with few long-time survivors. The use of MMUD donors with standard GVHD prophylaxis should be avoided in such indications for allo-HSCT. Studies that attempt to determine whether the implementation of Cy post-transplantation would improve these outcomes with mismatched donors are still ongoing. It remains necessary to explore more alternatives and transplant strategies in this critical population.

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