**ALLOGENEIC STEM CELL TRANSPLANTATION (HSCT) FOR ADULTS WITH MYELODYSPLASTIC SYNDROMES (MDS): RELEVANCE OF PRE-TRANSPLANT DISEASE STATUS.**

# Allogeneic stem cell transplant for adults with myelodysplastic syndromes: relevance of pre-transplant disease status

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**ABSTRACT**

The aim of the present study was to investigate the outcome of 94 adult patients with myelodysplasia (MDS) who received an allogeneic stem cell transplant between January 1995 and September 2010 in two Italian hematology centers. At the time of transplant, 53 patients (56%) had relapsed/refractory disease. The cumulative incidence of grades II–IV acute graft-versus-host disease (GVHD) and chronic GVHD was 33% (95% confidence interval [CI] 21–45%) and 78% (95% CI 66–90%), respectively. The cumulative incidence of transplant-related mortality (TRM) at 100 days was 13% (95% CI 6–21%). The 2-year progression free survival (PFS) and overall survival (OS) were 41% (95% CI 31–51%) and 49% (95% CI 38–59%), respectively. On multivariate analysis, advanced disease stage at transplant was the major independent variable associated with an inferior 2-year PFS (HR 3.66, 95% CI 1.98–6.76) and OS (HR 3.68, 95% CI 1.95–6.93). Use of an alternative donor was an independent variable associated with TRM (HR 3.18, 95% CI 1.31–7.72). In conclusion, our data suggest that disease status at the time of transplant is the major predictor for improved PFS and OS, and treatments required to reach this goal may have value in leading to an improved outcome.

## Introduction

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis with progressive cytopenias and a propensity for transformation to acute leukemia [1].

Allogeneic hematopoietic stem cell transplant (HSCT) is currently the only treatment with curative potential in patients with MDS. At present, patients with MDS are considered candidates for HSCT based on multiple parameters. A pivotal retrospective study showed that patients with International Prognostic Scoring System (IPSS) intermediate-2 (int-2) and high-risk MDS might benefit from early HSCT, whereas those in the IPSS intermediate-1 and low risk groups had better outcomes with delayed HSCT [2]. Despite several shortcomings of this study, the recommendation to offer HSCT to patients with int-2/ high risk MDS has been largely adopted by the majority of transplant centers. More recently, comorbidity scores have been developed and validated to select patients with MDS for HSCT [3]. In addition, advanced age, procedure morbidity and mortality and lack of a suitable donor may limit the transplant strategy to a select minority of patients. In this respect, the implementation of reduced intensity conditioning (RIC) regimens has expanded the number of patients with MDS as potential candidates for allogeneic HSCT. The availability of large worldwide registries of unrelated volunteer donors, the renewed interest in using haploidentical donors and

changes in the clinical care of transplant recipients might have a favorable impact on the outcome of patients with MDS undergoing allogeneic HSCT.
In order to explore the clinical relevance of these factors, we evaluated the results in a cohort of adult patients with MDS who received an allogeneic HSCT in two Italian hematology centers.

## Materials and methods

### Patients and disease characteristics

Between January 1995 and September 2010, 94 consecutive adult patients with MDS were referred for allogeneic HSCT at two main Piedmont hematology institutions (A.O.U. San Giovanni Battista Hospital, Turin and SC Ematologia AO SS Antonio e Biagio, Alessandria). Patients with MDS were identified through a prospective institutional bone marrow transplant database. Disease- and transplant-specific characteristics are summarized in Table I. For nine patients who received a second transplant and one patient who received a third allograft, only the first HSCT was included in the present analysis. One patient who received a syngeneic HSCT was excluded from the study. All patients in the analysis were classified according to standard French–American–British (FAB) criteria. The IPSS score was calculated for patients at diagnosis using cytogenetics data, number of cytopenias and marrow blast percentage. The patients' treatment histories were categorized as: no treatment (erythroid stimulating agents [ESAs], growth factors, transfusion support), active treatment, including hypomethylating agents (azacitidine), acute myeloid leukemia (AML)-like induction chemotherapy or miscellaneous therapy (steroid, antithymocyte globulin [ATG], hydroxyurea, thalidomide). The hematopoietic cell transplant-comorbidity index (HCT-CI) was determined retrospectively according to previous reports in patients grafted before 2008; from 2008 onward the HCT-CI was included prospectively in each institutional database. HCT-CI scores could be assigned in 73 patients.

**Table I. Patient and transplant characteristics.**

| Characteristic | | |
|---|---|---|
| Number of patients | 94 | |
| Year of transplant, *n* (%) | | |
| 1995–2000 | 23 | (24.5) |
| 2001–2003 | 20 | (21.3) |
| 2004–2007 | 22 | (23.4) |
| 2008–2010 | 29 | (30.9) |
| Age (years), median (range) | 55 | (30–70) |
| Male, *n* (%) | 45 | (47.9) |
| FAB MDS diagnosis, *n* (%) | | |
| RA | 8 | (8.5) |
| RARS | 3 | (3.2) |
| RAEB | 45 | (47.9) |
| CMML | 19 | (20.2) |
| RAEBt | 11 | (11.7) |
| Unknown | 8 | (8.5) |
| Number of cytopenias, *n* (%) | | |
| 0 | 3 | (3.2) |
| 1 | 17 | (18.1) |
| 2 | 33 | (35.1) |
| 3 | 18 | (19.1) |
| Unknown | 23 | (24.5) |
| IPSS at diagnosis, *n* (%) | | |
| Low | 6 | (6.4) |
| Int-1 | 25 | (26.6) |
| Int-2 | 30 | (31.9) |
| High | 12 | (12.8) |
| Unknown | 21 | (22.3) |
| Active therapy prior HSCT, *n* (%) | | |
| None | 18 | (19.1) |
| AML induction | 39 | (41.5) |
| Hypomethylating agents | 12 | (12.8) |
| Others | 13 | (13.8) |
| Unknown | 12 | (12.8) |
| Disease status at HSCT, *n* (%) | | |
| Complete remission | 29 | (30.9) |
| Untreated | 12 | (12.8) |
| Relapse/refractory | 53 | (56.4) |
| Time from diagnosis to HSCT (days), median (range) | 246 | (29–3439) |
| Donor, *n* (%) | | |
| HLA-identical sibling | 60 | (63.8) |
| Partially matched related donor | 3 | (3.2) |
| Unrelated volunteer donor | 31 | (33.0) |
| Myeloablative conditioning, *n* (%) | | |
| Myeloablative | 49 | (52.1) |
| Reduced intensity | 45 | (47.9) |
| GVHD prophylaxis, *n* (%) | | |
| CyA–MTX | 48 | (51.1) |
| CyA–MTX–ATG | 23 | (24.5) |
| CyA–MMF | 19 | (20.2) |
| Others | 3 | (3.2) |
| Unknown | 1 | (1.1) |
| Graft source, *n* (%) | | |
| Bone marrow | 8 | (8.5) |
| PBSCs | 85 | (90.4) |
| Umbilical cord blood | 1 | (1.1) |
| CD34 + infused $\times 10^6$/kg* | 7.41 | (0–17.20) |
| HCT-CI, *n* (%) | | |
| 0 | 28 | (29.8) |
| 1 | 12 | (12.8) |
| 2 | 8 | (8.5) |
| ≥3 | 25 | (26.6) |
| Unknown | 21 | (22.3) |

FAB, French–American–British; MDS, myelodysplastic syndromes; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess of blasts; CMML, chronic myelomonocytic leukemia; RAEBt, RAEB in transformation; IPSS, International Prognostic Scoring System; Int-1, intermediate 1; Int-2, intermediate 2; HSCT, hematopoietic stem cell transplant; AML, acute myeloid leukemia; GVHD, graft-versus-host disease; CyA, cyclosporine; MTX methotrexate; ATG, antithymocyte globulin; MMF, mycophenolate mofetil; PBSCs, peripheral blood stem cells; HCT-CI, hematopoietic cell transplant-comorbidity index.
*Data available in 46 patients only.

## Conditioning regimens and graft-versus-host disease prophylaxis

Forty-nine patients (52%) received myeloablative conditioning: in 28 cases (57%) the preparative regimen included thiotepa (15 mg/kg) and cyclophosphamide (CTX) (120–150 mg/kg); 14 patients (29%) received busulfan and CTX, and seven patients (14%) received total body irradiation (TBI) (1200 cGy over six fractions) and CTX.

Forty-five patients (48%) received RIC: 16 (36%) of these were given fludarabine and TBI (200 cGy single dose), 11 patients (24%) received busulfan and fludarabine and 13 patients (29%) received thiotepa (10 mg/kg) and CTX (100 mg/kg); five patients (11%) received different conditioning regimens.

Graft-versus-host disease (GVHD) prophylaxis included cyclosporine (CyA) and short course methotrexate (MTX) in the majority of patients ($n$ = 48). All unrelated-donor HSCT recipients except one received the combination of CyA–MTX and pre-transplant ATG. The patient grafted with an unrelated cord blood unit received CyA and steroids, and two patients grafted with a matched sibling donor received CyA alone.

Supportive care

Patients were nursed in a single room, ventilated with a high efficiency particulate air filtration system, and were scheduled to receive a low microbial diet without food sterilization procedures; careful washing of the hands was used in all patients. All patients had a central venous catheter inserted before conditioning. Prophylaxis with fluconazole (400 mg/day) was given to patients from the start of the conditioning regimen to day + 100 after transplant. All patients received acyclovir (500 mg i.v. every 8 h, or 400 mg po TID) from day + 1 until day + 120 post-transplant. Levofloxacin was used in all patients to prevent the onset of fever during aplasia, and it was started on day −7 and discontinued 100 days post-transplant.

Patients were monitored for cytomeglovirus (CMV) infection by PCR and/or antigenemia assay twice a week during hospitalization and at least weekly thereafter. Preemptive therapy was started with iv ganciclovir or foscarnet at the discretion of the referring physician. From 2004, oral valganciclovir (900 mg BID for 2 weeks followed by 450 mg BID for 2 additional weeks) was administered as preemptive treatment.

After obtaining sustained hematopoietic recovery, patients started prophylaxis for *Pneumocystis jirovecii* with trimethoprim–sulfamethoxazole. No growth factors were used after transplant.

Definitions and statistical analysis

Myeloid engraftment was defined as an absolute neutrophil count (ANC) greater than $0.5 \times 10^9$/L for 3 consecutive days; platelet engraftment was defined as a platelet count $> 50 \times 10^9$/L for 3 consecutive days. The incidence and the time to development of grades II–IV acute GVHD (aGVHD) were evaluated in patients surviving 21 days with evidence of engraftment. The incidence and the time to occurrence of any chronic GVHD (cGVHD) were evaluated in patients surviving 100 days or longer with evidence of engraftment. The diagnosis of aGVHD and cGVHD was based on the characteristic clinical appearance of symptoms of organ involvement. The grading of aGVHD and cGVHD followed the commonly accepted criteria [4,5]. Chimerism analysis was performed on whole bone marrow cells using the short tandem repeat (STR) technique. Full donor chimerism was defined as the presence of > 95% cells of donor origin.

Endpoints of the analysis were transplant-related mortality (TRM), relapse rate, incidence and severity of both acute and chronic GVHD, progression-free survival (PFS) and overall survival (OS). TRM was defined as death from any cause other than disease progression or relapse. Cumulative incidence of TRM and relapse was calculated with relapse and non-relapse death, respectively, as a competing event [6]. The cumulative incidence of aGVHD and cGVHD was calculated with relapse or death without relapse or GVHD, respectively, as competing events [6]. For time to onset of cGVHD, patients were censored at the time of death, donor lymphocyte infusion (DLI) or second transplant.

PFS was defined as the time from transplant to disease progression, relapse or death. OS was defined as the time from HSCT to death, and surviving patients were censored at the last follow-up. Survival curves for PFS and OS were estimated by the Kaplan–Meier method [7]. Prognostic factors potentially influencing TRM, PFS and OS that were considered in the analysis included: age at HSCT, sex, FAB MDS diagnosis, IPSS at diagnosis, disease status at transplant (complete remission [CR]/untreated versus relapsed/refractory), disease duration before HSCT, donor type (human leukocyte antigen [HLA]-identical sibling versus partially matched related donor

[PMRD]/matched unrelated donor [MUD]), year of transplant, conditioning regimen intensity (myeloablative versus RIC), HCT-CI (0 versus 1–2, versus ≥ 3). In order to take into account competing events, a Fine and Gray model was used to estimate the crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of prognostic factors for the incidence of TRM [7]. A Cox proportional hazards model was employed to estimate the crude and adjusted HRs and 95% CIs for prognostic factors of OS and PFS.

In order to obtain robust estimates, we included in the multivariable models only a few known prognostic factors (age, disease status at HSCT and donor); then, in order to estimate effects of all remaining prognostic factors, we defined different models that included a set of common confounders (age, disease status at HSCT and donor type) and only one at a time the other prognostic factors (sex, FAB MDS diagnosis, IPSS at diagnosis, disease duration before HSCT, year of transplant, conditioning regimen intensity, HCT-CI). Statistical analysis was performed using Stata 9.2 (StataCorp LP, College Station, TX) and R (version 2.12.1).

## Results

**Table II shows the main clinical results of transplant.**

| Parameter | |
|---|---|
| No. of patients | 94 |
| Neutrophil engraftment, *n* | 86 (91%) |
| Median days (range) | 15 (6–30) |
| Platelet engraftment, *n* | 62 (66%) |
| Median days (range) | 14 (5–146) |
| Acute GVHD grades II–IV, *n* | 25 (29%) |
| Chronic GVHD, *n* | 48 (86%) |
| Relapse rate, *n* | 34 (36%) |
| No. of patients who died | 52 (55%) |
| Relapse/progression | 30 (58%) |
| TRM | 21 (40%) |
| Secondary neoplasm | 1 (2%) |
| No. of patients alive | 42 (45%) |
| No. of patients alive and disease free | 39 (41%) |

GVHD, graft-versus-host disease; TRM, transplant related mortality.

### Engraftment

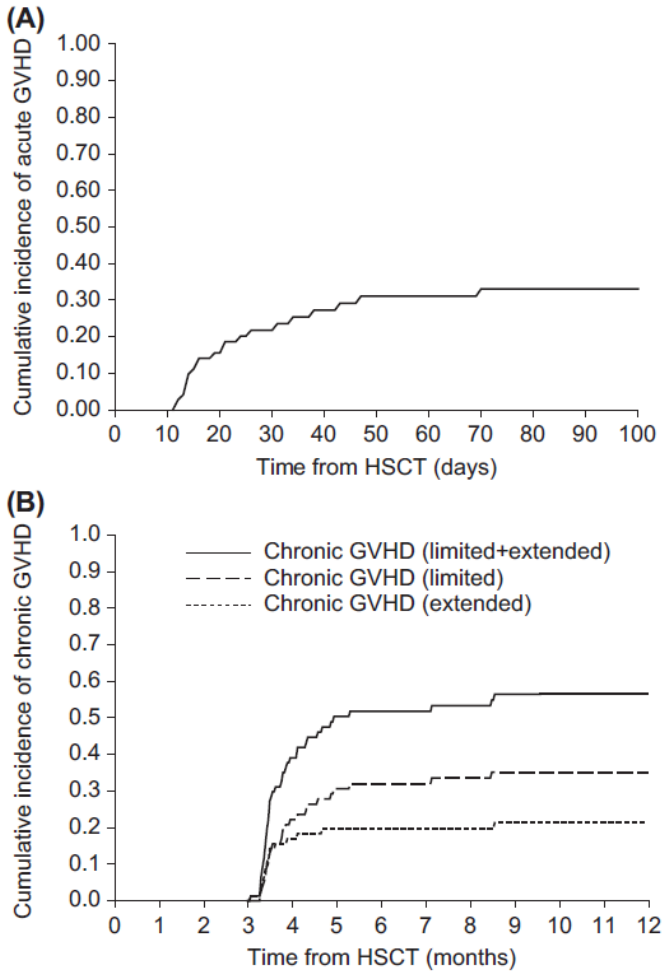
Primary neutrophil engraftment was achieved in 86 of the 94 patients (91%) at a median of 15 days (range 6–30 days) after transplant. Four patients who died early (before day + 14), and two patients who experienced an early disease progression after transplant, failed to reach a sustained neutrophil engraftment. Two patients never became granulocytopenic. Two patients (2%) experienced secondary graft failure: full donor chimerism was achieved after DLI in one case and after a second

peripheral blood stem cell (PBSC) infusion in the second case. Rates of complete donor-cell chimerism at days + 30 and + 100 were 69% and 70%, respectively. There was no significant difference in time to neutrophil engraftment between myeloablative (median 16 days) or RIC (median 15 days) ($p$ = 0.4). Sixty-two patients (66%) achieved platelet engraftment at a median time of 14 days (range 5–146 days) after transplant.

Acute and chronic GVHD

Eighty-five patients (90%) were evaluable for acute GVHD. Forty-six patients (54%) developed aGVHD: grade I aGVHD was observed in 21 cases, grade II in 20 cases, grade III in four cases and grade IV in one case. The median time to onset of aGVHD was 19 days (range 12–70 days). The cumulative incidence of grades II–IV aGVHD was 33.1% (95% CI 21.1–45.1%) [Figure 1(A)].

**Figure 1. Cumulative incidence estimate of grades II–IV acute (A) and chronic (B) GVHD.**



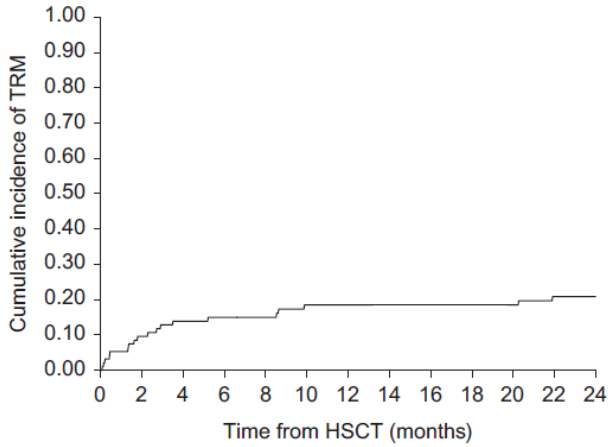

Among the 56 evaluable patients, 48 (86%) developed cGVHD, which was limited in 26 and extensive in 22 cases. The median time to onset of cGVHD was 107 days (range 93–206 days). The 1-year cumulative incidence of cGVHD was 77.8% (95% CI 66.0–89.6) [Figure 1(B)].

Relapse rate and transplant-related mortality

Overall, 34 patients (36%) relapsed after transplant: 18 relapsed after myeloablative HSCT and 16 after RIC HSCT. Thirty patients (58%) died as a consequence of post-transplant relapse after a median observation time of 5 months (range 1–41) following HSCT. Twenty-one patients (40%) died from transplant-related complications, including infections ($n$ = 9), multiorgan failure ($n$ = 4), GVHD ($n$ = 2), encephalitis ($n$ = 1), microangiopathy ($n$ = 3) and hemorrhage ($n$ = 1), and one

patient died of a secondary cancer. The cumulative incidence of TRM at 100 days and 1 year was 12.8% (95% CI 6.0–19.6) and 18.5% (95% CI 10.5–26.5), respectively (Figure 2). Three out of 28 patients (11%) with HCT-CI = 0 and eight out of 25 patients (32%) with HCT-CI ≥ 3 died of transplant-related complications. The use of a donor other than an HLA-identical sibling increased the hazard of TRM (HR 3.18, 95% CI 1.31–7.72) (Table III).

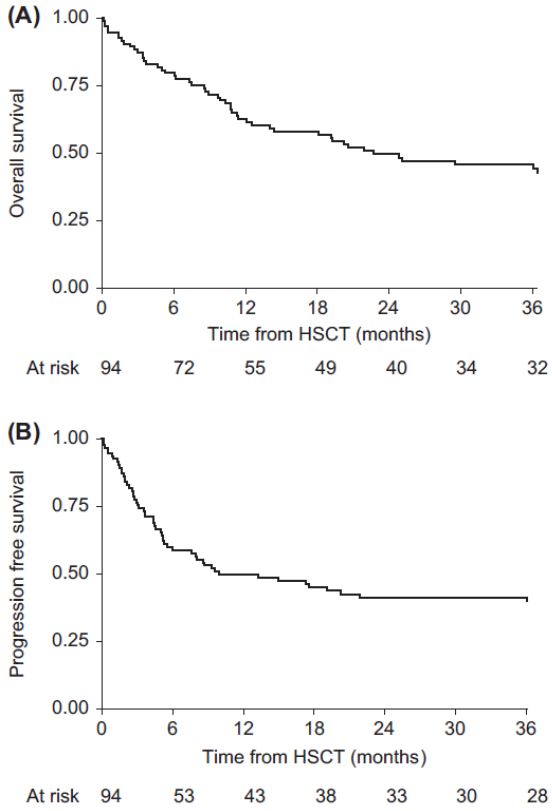
**Figure 2. Cumulative incidence estimate of transplant–related mortality.**




**Survival and progression-free survival**

Median follow-up of surviving patients after HSCT was 61.4 months (range 1.8–184.6 months). Forty-two patients were alive at the last follow-up, 39 in continuous CR, three after relapse. Twenty-two (45%) of 49 patients who received myeloablative conditioning and 20 (44%) of the 45 patients who received RIC were alive. Seventeen patients (61%) with HCT-CI = 0 and 10 patients (40%) with HCT-CI ≥ 3 survived. The 1-year and 2-year OS rates were 62.6% (95% CI 51.8–71.7) and 49.6 (95% CI 38.7–59.5) and the 1-year and 2-year PFS rates were 49.7% (95% CI 40.0–59.4) and 41.3 (95% CI 31.0–51.3) (Figure 3).
Advanced disease status was the strongest prognostic factor of OS (HR 3.68, 95% CI 1.95–6.93) and PFS (HR 3.66, 95% CI 1.98–6.76) (Table III).

**Figure 3. Kaplan–Meier curves of (A) overall survival and (B) progression-free survival.**




## Discussion

The present study evaluated the results of allogeneic HSCT in a large cohort of patients with MDS. The majority of patients had high risk characteristics including advanced age at transplant (median age 55 years), active disease in more than half of the patients and the use of alternative donors in one-third of cases. Bearing in mind these considerations some conclusions should be drawn.

The results of our study showed a low TRM, leading to a 2-year OS and PFS of 49.6% and 41.3%, respectively. These results compare favorably to those reported in the literature, in particular if we consider that over 50% of our patients were refractory or in relapse at the time of transplant, although differences in the sample size of studies, patient characteristics and follow-up must be considered as potential confounding factors. Nevill and co-workers [8] analyzed retrospectively 156 patients with MDS and secondary AML who received HSCT from related and unrelated donors; 15% of patients had relapsed/refractory disease at the time of transplant. The estimated 7-year event-free survival (EFS) was 36%, and IPSS poor-risk karyotype was strongly associated with an unfavorable outcome, although high-risk patients appeared to benefit from the use of PBSCs. Warlick *et al*. [9] reviewed the outcome of 84 patients with MDS (median age 50 years) undergoing allogeneic HSCT between 1995 and 2007; one-third of the patients had marrow blasts > 5% at the time of transplant. One-year TRM, disease-free survival (DFS) and OS were 39%, 38% and 48%, and pre-transplant disease burden was the major predictor for improved outcome: patients with < 5% blasts at the time of transplant had an OS at 1 year of 53% compared to 35% in those with 5–20% blasts.

A recent review [10], including 24 studies on the use of myeloablative regimens and 30 publications combining reduced-intensity and non-myeloablative conditioning in patients with MDS, reported an OS and DFS ranging from 25% and 16% at 2 years to 52% and 50% at 4 years, respectively, in patients receiving myeloablative regimens; similarly, OS and DFS varied from 22% and 20% at 2 years to 79% at 4 years in patients who received reduced-intensity or non-myeloablative regimens. The impact of conditioning intensity on disease control remains a matter of debate: if we assume that providing optimixed cytoreduction contributes to improved long-term disease control [11,12],

patients might benefit from myeloablative regimens but often at the expense of increased toxicity [13,14]. Very recently, Weisdorf and colleagues [15] showed in a large cohort of patients with AML ($n$ = 4224) and MDS ($n$ = 1517) that the graft-versus-leukemia (GVL) effect is stronger and less harmful with RIC regimens, while after myeloablative conditioning, GVHD has a detrimental effect on TRM and survival. In our experience both myeloablative and reduced intensity preparative regimens were able to ensure myeloid engraftment; however, the intensity of the preparative regimen did not have a significant influence on post-transplant outcomes. In particular we did not find a significant difference in terms of relapse rate and survival between patients who received either myeloablative or reduced intensity conditioning.

Recent data suggest that the HSCT-specific comorbidity index may be an important prognostic factor in patients with MDS who are candidate for HSCT [3,16,17]. According to these findings, patients included in our study with an HCT-CI score of zero had a superior outcome compared to patients with higher scores. Unfortunately, the HCT-CI was not available in a consistent proportion of our patients, thereby limiting the statistical power of the study, and multivariate analysis failed to demonstrate any significant influence on survival and TRM.

Ninety percent of the patients included in our analysis received PBSCs, leading to a significant rate of chronic GVHD (78% cumulative incidence), although additional factors including advanced age and use of an unrelated donor should be taken into account. Even if we did not have the opportunity to document the detrimental effect on morbidity, it should be emphasized that the high rate of chronic GVHD did not have an impact on TRM, as demonstrated by the fact that GVHD was the primary cause of death in two patients only, although the short follow-up might be considered a limiting factor to detect the potential effect of cGVHD on survival. The preference for PBSCs is based on the observation that the use of blood cells rather than bone marrow has been associated in some studies with better outcomes [18,19], due to a more rapid engraftment and a lower relapse rate secondary to a higher incidence of chronic GVHD leading to a GVL effect.

It has been shown by several studies that the leukemic burden at the time of transplant is one of the major prognostic factors for patients with MDS, in particular for those receiving dose-reduced conditioning regimens [9,20,21]. In line with these results, our study showed that pre-transplant disease status was an independent variable associated with inferior OS and PFS. By contrast, other investigators did not find any beneficial effect of induction therapy before allogeneic HSCT [22,23]. In view of these observations, whether and how cytoreductive pre-transplant therapy should be performed in order to reduce the number of blasts is still controversial. An intriguing strategy has been investigated by a German group, with use of sequential conditioning therapy with FLAMSA (fludarabine, amsacrine and ara-C) followed after 2 or 3 days of rest by high-dose melphalan. Thirty patients with high-risk MDS and secondary AML were treated, and in spite of a relatively short median follow-up of 28 months, OS and EFS at 2 years were 70% and 63%, respectively, supporting the evidence that high-dose sequential therapy is well tolerated and may be an effective treatment modality.

Demethylating agents, including azacitidine and decitabine, have emerged as new active therapeutic drugs in patients with MDS, and may potentially achieve cytoreduction with limited toxicity. Preliminary results suggest that the post-HSCT outcome in patients who received hypomethylating agents before transplant is comparable to that of patients treated with induction chemotherapy, although azacitidine and decitabine may offer benefits with regard to reduced toxicity [24,25]. Another promising agent that has been tested in induction therapy before HSCT is lenalidomide [26,27]. A different approach that has been investigated is the prevention of relapse with the administration of maintenance therapy after transplant. The M. D. Anderson Cancer Center evaluated the administration of azacitidine as maintenance therapy after transplant in patients with AML and MDS: no severe side effects and no impact on GVHD and chimerism were reported [28]. Ten patients with del(5q) cytogenetic abnormality and MDS or AML were treated with lenalidomide maintenance at a median of 2.5 months from HSCT; however, the trial was stopped prematurely due to the induction of acute GVHD [29]. In our analysis, transplants from an

alternative donor, in particular unrelated volunteer donors, were associated with a risk of TRM three-fold higher than with grafts from matched sibling donors. This was not expected if we assume that innovations have been made in HLA typing and matching, and also more effective approaches in GVHD prevention and infectious complication control have been introduced in recent years [30,31]. According to these observations, comparable outcomes between unrelated and related donor HSCT have recently been reported [32]. Nevertheless, it should be stressed that in our study, one-third of MUD recipients had HCT-CI $\geq 3$ and 55% were in relapse at the time of transplant: these factors together most likely contributed to the high rate of transplant related complications. Even if our data are clearly in line with the available literature, they should be interpreted with caution. In fact, our study has some limitations mainly because of its retrospective nature and considerable heterogeneity of the patients included in the analysis. In addition, transplants were performed over a wide period of time, precluding a complete and detailed data collection.
In summary, the results of our study suggest that allogeneic HSCT is a curative treatment approach for patients with MDS. Disease status at HSCT has been found to have a significant impact on the overall and progression free survival of patients with MDS. Whether the availability of active drugs offers a new option to reduce the tumor burden prior to HSCT needs to be investigated in prospective clinical studies.

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