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Minimal Identifiable Disease and the Role of Conditioning Intensity in Hematopoietic Cell Transplantation for MDS and AML evolving from MDS

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) is the only known treatment with curative potential for myelodysplastic syndromes (MDS), but relapse is a major cause of failure. We studied results in 289 patients transplanted between June 2004 and December 2013. Minimal Identifiable Disease (MID) markers pre-HCT were determined by multiparameter flow cytometry

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(MFC) and cytogenetics on marrow aspirates. The impact of MID on outcome after low and high intensity conditioning HCT was determined. Among 287 evaluable patients, 68 (23.7%) had more than 5% marrow blasts at HCT; 219 patients were in morphologic remission but 154 (53.7%) were MID positive, while 65 (22.6%) were MID negative. The impact of MID on outcome was significantly different between patients who received low-intensity conditioning and patients who received a high-intensity regimen. The impact of conditioning intensity differed across the various MID categories. In particular, the risk of overall mortality was higher with low-intensity than with high-intensity regimens for patients who were positive for MID by cytogenetics regardless of positivity by MFC (HR=1.67 if MFC+/cytogenetics+, HR=7.23 if MFC-/cytogenetics+). On the other hand, patients who were MID-negative by both MFC and cytogenetics had similar risks of mortality with low- and high-intensity regimens (HR=0.99). The main factor responsible for mortality after low-intensity conditioning in MID positive patients was relapse. The presence of MID should be considered when deciding on conditioning intensity as it identifies subgroups of patients who may benefit from high- or low-intensity conditioning, respectively.

Keywords

MDS; minimal residual disease; minimal identifiable disease; allogeneic transplantation; conditioning regimen

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is the only treatment with proven curative potential for many patients with myelodysplastic syndrome (MDS) [1]. However, high-dose conditioning HCT may not be an option in older patients or patients with comorbidities because of potential toxicities associated with the procedure. The development of low-intensity conditioning regimens has resulted in a significant reduction in non-relapse mortality (NRM), and growing numbers of previously ineligible patients are undergoing successful HCT [2]. This is of particular importance with MDS since more than 80% of newly diagnosed patients are older than 60 years [3]. However, the advantage gained due to lower NRM may be negated by a higher incidence of relapse. Past experience has shown, indeed, that the major cause of death following HCT after low-intensity conditioning in MDS is relapse, particularly in patients with more advanced disease [4–7]. Even for patients in morphological remission at HCT, the best conditioning strategy remains controversial. A randomized trial comparing high-intensity to low-intensity conditioning for patients with MDS or AML under the auspices of the Bone Marrow Transplant Clinical Trials Network was recently closed due to a perceived benefit with high-intensity regimens. Results, published in abstract form, do show inferior overall survival among patients conditioned with reduced intensity conditioning regimens [8].

Monitoring of minimal residual disease (MRD) with multicolor flow cytometry (MFC), cytogenetics or genomic technologies, is now widely used as a guide to adjust treatment with the goal of improving outcomes, and to design new clinical trials for patients with acute leukemias [9,10]. Walter et al. reported a single center retrospective analysis of 99 AML patients in first complete remission (CR) treated with high-intensity conditioning and HCT

[9]. After adjustment for multiples variables, patients who had MRD by MFC at the time of HCT suffered a significantly higher relapse incidence than MRD negative controls (HR, 8.49; 95% CI 3.67–19.65; $p < 0.001$). Similar conclusions were recently reached by the same group in patients treated with low-intensity conditioning [11]. There is growing interest in MRD assessment as a pre-HCT prognostic predictor in acute leukemias and non-Hodgkin lymphomas [12,13]; however, no such data have been reported in patients with MDS.

We report a retrospective analysis involving 289 sequential patients with MDS transplanted at our institution between June 2004 and December 2013. Our objectives were to identify disease and treatment parameters that would predict transplant outcomes, specifically relapse of MDS.

Patients and Methods

Patients

Between June 2004 (FDA approval of Azacitidine), and December 2013, 289 consecutive patients with MDS (including patients whose disease had progressed to AML) underwent HCT at the Fred Hutchinson Cancer Research Center (FHCRC); 43% of HCT were carried out since January 2010. The median age at HCT was 57 (range, 6–77) years, 171 patients (59%) were male and 118 (41%) female. There were 207 patients (72%) with *de novo* MDS, and 82 (28%) with secondary MDS, following an antecedent hematologic disorder or cytotoxic therapy for various conditions (Supplemental Table S1).

Donors were human leukocyte antigen (HLA)-matched family members in 116 cases (40%), including 2 HLA-matched parents; haploidentical in 2 cases (1%); unrelated in 171 cases (59%), including 153 HLA-matched donors, 34 donors with at least 1 mismatch, and 18 cord blood units. The stem cell source was peripheral blood in 243 patients (84%), bone marrow in 28 patients (10%), and cord blood in 18 patients (6%). Fifty patients with *de novo* MDS (24%) and 16 (20%) with secondary MDS had advanced to AML before HCT. Cytogenetic risks as defined by the International Prognostic Scoring System (IPSS) criteria were comparable for patients conditioned with high intensity and those with reduced intensity regimens. Patient and disease characteristics are summarized in Table 1.

Patients or legal guardians for patients younger than 18 years gave informed consent to use medical information for the purposes of research approved by the Institutional Review Board of the FHCRC in accordance with the Declaration of Helsinki.

HCT Procedure

Patients were prepared for HCT with various conditioning regimens, categorized on the basis of treatment components and dose intensities (Table 2). Regimens considered to be of high or low intensity were administered to 195 (67.5%) and 94 patients (32.5%), respectively. The conditioning regimen was selected according to active protocols at the time of HCT and considering patient age and comorbidities. For patients receiving high-intensity regimens, prophylaxis for graft-versus-host-disease (GvHD) consisted of methotrexate (MTX) plus cyclosporine (CSP) or tacrolimus in 139 patients; mycophenolate mofetil (MMF) and CSP or tacrolimus in 38 patients; cyclophosphamide with or without CSP or

tacrolimus in 13 patients; MTX, CSP, and sirolimus in 3 patients; MMF, CSP, and sirolimus in 2 patients. Among low intensity-conditioned patients, prophylaxis for GvHD consisted of MMF and CSP or tacrolimus in 82 patients; MMF, CSP, and sirolimus in 10; MTX and CSP in 2 patients.

Graft Failure

The day of engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of $0.5 \times 10^9/L$. Primary graft failure was defined as not reaching this neutrophil count by day 28 (day 55 for cord blood recipients). Secondary graft failure was defined as a progressive decline in peripheral neutrophil counts after initial recovery. For the majority of patients the analyses were performed on days 28, 56, 84, 180 and 365, and then as clinically indicated. In addition, donor CD3+ T cells <5% on day 28 or donor T-cell decline to <5% after previous evidence of engraftment were considered evidence of primary or secondary graft failure, respectively [14].

Disease Status at HCT and Minimal Identifiable Disease (MID)-based Classification

In the entire cohort, 112 patients (38.8%) received induction chemotherapy as a frontline approach or as salvage. Among the remaining 177 patients, 86 (29.8%) were treated with hypomethylating agents, 7 (2.4%) with immunosuppression, 4 (1.4%) with lenalidomide or thalidomide, and 80 (27.7%) with supportive care only. The majority of patients (221; 76%) had less than 5% marrow blasts by morphology at the time of HCT.

We used the 2006 modified International Working Group (IWG) response criteria to assess the disease status at the time of HCT [15]. Sixty-eight patients (24%) were in CR, 75 (26%) were in marrow CR, 9 (3%) were in Partial Remission (PR), 40 (14%) had progressive disease, 29 (10%) were classified as having stable disease (following therapy), and 68 (24%) were untreated. Since the IWG criteria had been developed to classify disease response to therapy, their use in untreated patients is not appropriate, and the concept of MRD (following treatment) is not applicable. Further, patients without identifiable cytogenetic abnormalities at diagnosis generally have been considered as non-informative for cytogenetic assessment at HCT [9,16]. In order to account for those factors, we decided to use the term “Minimal *Identifiable* Disease” (MID) for pre-HCT disease stage classification of patient with less than 5% marrow blasts. Patients having 5% or more marrow blasts by morphology were defined as NO-CR. Thus, patients in PR by IWG response criteria were considered in the NO-CR group. Among the 221 patients (76%) with less than 5% marrow blasts at HCT, regardless of induction treatment received, we distinguished two groups, MID positive and MID negative. The criterion for MID positivity was the presence of an identifiable clonal cytogenetic abnormality by conventional cytogenetic studies [17] or by Fluorescence In Situ Hybridization (FISH), or, alternatively, the presence of a positive MFC test. Of note, FISH yielded a positive result only in 3 patients with normal cytogenetics. All other abnormal FISH results were observed in patients with abnormal cytogenetics. Despite the different sensitivity level of the two techniques, we decided to consider patients with isolated FISH positive results in the MID positive group. We defined as MID negative, patients with less than 5% marrow blasts and no cytogenetic, FISH, or MFC abnormalities (Table 3). We collected data on conventional cytogenetics performed at diagnosis and at the

time of HCT using standard G-banding karyotype analysis on 20 metaphases at the Seattle Cancer Care Alliance (SCCA) Cytogenetics laboratory. One patient with isolated deletion Y was not included in the MID analysis. FISH was performed at SCCA according to standard procedures [16]. MFC methods for minimal disease detection rely on the immunophenotypic deviation of malignant cells from normal hematopoietic maturation and, hence, have a variable sensitivity that, for myeloid neoplasms, ranges from 0.1% to 0.001% of leukocytes [18–20]. Data for low- and high-intensity conditioning subgroups are summarized in Table 1.

Statistical Analysis

Kaplan-Meier estimates were used to determine the unadjusted probabilities of overall survival (OS) and relapse-free survival (RFS) for the listed categories, and cumulative incidence estimates were used to summarize the probabilities of relapse and NRM, where NRM was regarded a competing risk for relapse, and relapse a competing risk for NRM. The risk of overall mortality was compared between the MID groups using Cox regression. We used a forward stepwise method to select the variables for our model. Candidate variables included patient age, gender, WHO 2008 MDS classification [21], performance status at diagnosis (ECOG), secondary MDS, IPSS-R at diagnosis, time from diagnosis to HCT, IWG 2006 disease status at HCT [15], pre-HCT evolution to AML, stem cell source, pre-HCT treatments (induction chemotherapy given as first line treatment or as salvage, hypomethylating agents only, no therapy, or other). The MID status and conditioning intensity were not included in the stepwise selection as they were to be included in the model regardless. Due to the limited number of events we restricted the final model to include only MID (4 groups), conditioning intensity, pre-HCT evolution to AML, and pre-HCT treatments, as the other factors had little or no impact on the magnitude of the effects due to MID and conditioning.

Of particular interest was the potential interaction between MID and conditioning intensity, and appropriate interaction terms were included in regression models for assessment. Given that power to detect statistically significant interactions is less than that to detect main effects (the main effect being MID status), we considered interaction p-values less than 0.15 as worthy of further investigation. No adjustments were made for multiple comparisons, and all the two-sided p values from the regression models were derived from the Wald test.

Results

Overall Outcome

Patient characteristics are summarized in Table 1. Overall, 149 patients (51.6%) had died by the time of last contact, including 93 patients (32.2%) who had relapsed. Fifty-six patients (19.4%) died from non-relapse causes. This resulted in 3-year estimates of OS (Figure 1), RFS, relapse, and NRM of 51%, 46%, 37%, and 18%, respectively. Median follow-up among the 140 survivors was 52.4 months (range, 3.5–120.6), and the median OS was 37.3 months. Among the 15 surviving patients who relapsed, 6 received a second HCT as salvage.

Grades II–IV acute GVHD occurred in 188 (68.2%) of 276 evaluable patients, and 38 patients (14%) had grades III–IV disease. Chronic GVHD occurred in 135 (54%) of 249 evaluable patients.

MID, Conditioning Intensity, and Mortality

We utilized both MFC and cytogenetics (including FISH) as indicators of MID to assess the association between MID and overall mortality and studied 4 groups: positive MFC/positive cytogenetics, positive MFC/negative cytogenetics, negative MFC/positive cytogenetics, and negative MFC/negative cytogenetics). Results that summarize the comparison of these groups after adjusting for the factors detailed above are shown in Table 4. These results suggested that both MFC and cytogenetics contributed information to the association of MID with the risk of overall mortality.

While the above results indicated an association between MID status and the risk of mortality, there was evidence that the impact of MID on overall mortality was different if patients were conditioned with a high-intensity regimen compared to low-intensity conditioning. As shown in Table 1, cytogenetic risk (by IPSS-R criteria) at diagnosis and at HCT was equally distributed between the two conditioning intensity groups. A statistical test of interaction between intensity and MID status (4 groups, as defined above) yielded $p=.02$, suggesting that the difference in mortality between MID groups was not the same across conditioning regimens, or, similarly, that the difference in mortality between high- and low-intensity conditioning was not the same across the 4 MID groups (Table 4). These results suggested that among patients who received a low-intensity conditioning regimen, the impact of a positive marker for MID by cytogenetics was more detrimental than the presence of such a marker among patients who received a high-intensity regimen. The results also suggested that patients who were MID-negative by cytogenetics had a similar risk of mortality if conditioned with low-intensity or high-intensity regimens, while patients who were MID-positive by cytogenetics and were conditioned with a low-intensity regimen had a higher risk of mortality than patients conditioned with a high-intensity regimen (Figure 2). The 3 patients with isolated FISH positivity in the MID positive group did not allow for a separate analysis. Exclusion of those 3 patients from the overall analysis did not impact results (Data not shown).

Impact of MID and Conditioning Intensity on Relapse

Results on impact of MID and conditioning intensity on relapse yielded the same qualitative conclusion as those for overall mortality (Supplemental Table S2). A test for an interaction between conditioning and MID yielded $p=.10$, where patients who were MID-positive by cytogenetics had a higher risk of relapse if they received a low-intensity regimen compared to a high-intensity regimen. However, low-intensity regimens were associated with a higher risk of relapse than high-intensity regimens for each of the MID groups, although the difference did not reach statistical significance.

Impact of MID and Conditioning Intensity on NRM

NRM did not differ across the levels of conditioning intensity, with an interaction p-value of $p=0.45$. However, with few NRM events occurring ($N=38$) the power to detect even suggestive interactions was very limited (Supplemental Table S3).

Discussion

In contrast to AML [22], data on the utility of MRD in patients with MDS as an HCT risk marker are limited [20]. In AML Chen et al. showed that the impact of unfavorable cytogenetics or the presence of *FLT3*-internal tandem duplication lost its statistical significance after adjusting for post-induction parameters as well as peripheral count recovery and MRD. However, AML and MDS are different diseases; more than 60% of MDS patients in the present analysis did not receive high-dose cytotoxic chemotherapy before HCT. Therefore, the impact of MRD, as defined for AML, may differ in patients with MDS.

A major question in our analysis was how to weigh discordant MID results by cytogenetics/FISH versus MFC. Studies in AML reported discordant results in 22% of 424 evaluable patients [16]. The rate of discordant results among the 221 evaluable patients in the current study was, similarly, 22.2%. Conventional cytogenetics have limited sensitivity, which may explain the absence/non-detection of previously present cytogenetic abnormalities in patients with positive MFC results. The reverse finding, positive cytogenetics/FISH results and negative MFC, in view of the high sensitivity of MFC, is more likely to be related to the absence of immunophenotypic markers. Further methodologic improvements are desirable.

The current results were consistent with previous reports that showed an increased risk of mortality in patients with MRD detected by either MFC or cytogenetics [16]. In addition, however, the current results showed differences in outcome between MID groups, dependent on whether patients were conditioned with low- (non-myeloablative) or high-intensity (myeloablative) regimens. We stratified conditioning regimens into low- or high-intensity groups according to the 2006 Reduced-Intensity Conditioning Regimen Workshop convened by the Center for International Blood and Marrow Transplant Research (CIBMTR) [23]. The impact of conditioning intensity varied according to MID status, where patients positive for MID as determined by cytogenetics, had a higher risk of mortality if conditioned with a low-intensity regimen as compared to a high-intensity regimen.

Most noteworthy was the observation that for patients who were negative for MID by both MFC and cytogenetics, a low-intensity conditioning regimen was as effective as a high-intensity regimen in preventing relapse, and overall survival was similar, even though patients treated with low-intensity conditioning were significantly older and had a longer interval between diagnosis and HCT than the remaining patients. This outcome suggests that a subgroup of patients usually treated with high-intensity conditioning can benefit from a less toxic low-intensity conditioning. This is important considering that the median age of MDS patients at diagnosis is 70 – 75 years, and comorbidities are prevalent [24]. Our results also support the conclusion that MID has a more profound impact on outcome among patients who receive low-intensity conditioning than among those who receive high-intensity

conditioning. This outcome is distinctly different from observations in patients with AML, where the impact of MRD positivity appeared to be independent from conditioning intensity [11]. Therefore, our data suggest that MDS patients who are MID positive by cytogenetics should be conditioned with a high-intensity regimen, while this may not be beneficial in MID negative patients, in whom the focus should be on reducing NRM.

Results of the present analysis do not invalidate previously published data on the impact of prognostic scores [25–29], particularly the IPSS-R, which gives more weight to the presence of cytogenetic abnormalities [30]. However, our analysis was adjusted for those factors and, thus, adds a refinement to risk assessment. Further, it incorporates the impact of the transplant conditioning regimen, which is not a factor in non-transplanted patients for whom IPSS and IPSS-R were originally developed.

Our study has some limitations. First, as in all retrospective studies, patients were not assigned to the conditioning intensity group in a randomized fashion, and a selection bias cannot be excluded. Second, the numbers of patients in some subgroups, based on MID status and conditioning intensity, were small, making it difficult to draw more definitive conclusions. Third, our data do not allow to draw conclusions regarding the impact of isolated FISH positivity (normal cytogenetics) at pre-HCT evaluation.

In summary, MID by cytogenetics appears to be a powerful predictor of post-HCT outcome after low-intensity conditioning HCT. High-intensity conditioning was able to overcome the profound prognostic impact of MID. We propose to include MID in the risk classification of patients with MDS who are being considered for HCT. Finally, the recent identification with genomic technologies of molecular abnormalities such as mutations in *TET2*, *DNMT3A*, *RUNX1*, *ASXL1*, *EHZ2*, *ETV6* and *TP53* [31,32], which influence survival in non-transplanted patients and, presumably, after HCT, will likely increase our ability of MID and MRD detection and monitoring, once available in clinical practice. Together with the refinement of cytogenetic classification, the HCT-CI, and the newly identified somatic mutations, the MID classification will affect the decision on transplant procedures and, as a result, should improve HCT outcomes in MDS patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Minimal Identifiable Disease (MID) was assessed by cytogenetics and flow cytometry
- MID status at transplant had significant impact on post-transplant outcome
- MID-positive patients by cytogenetics had inferior outcome with low intensity conditioning
- MID-negative patients had similar outcome with high intensity and low intensity conditioning

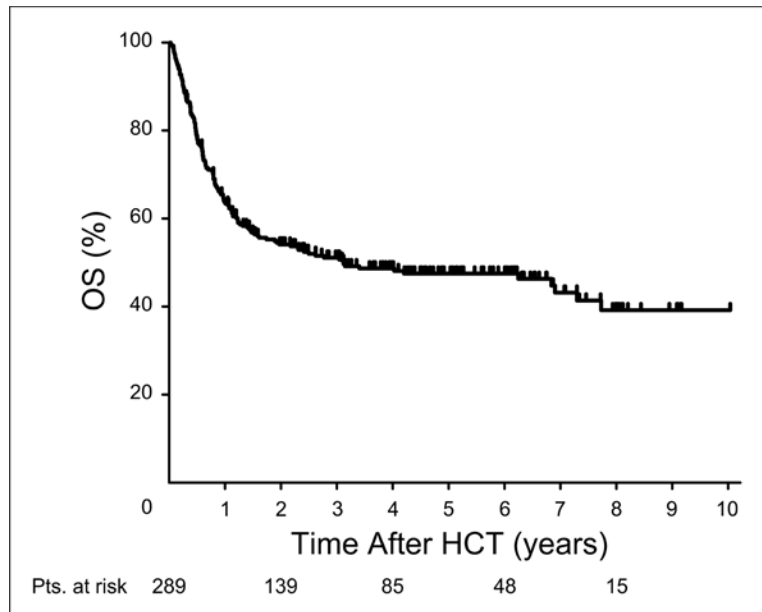


Figure 1. Overall survival of all patients

Abbreviations: OS = overall survival; HCT = hematopoietic cell transplantation.

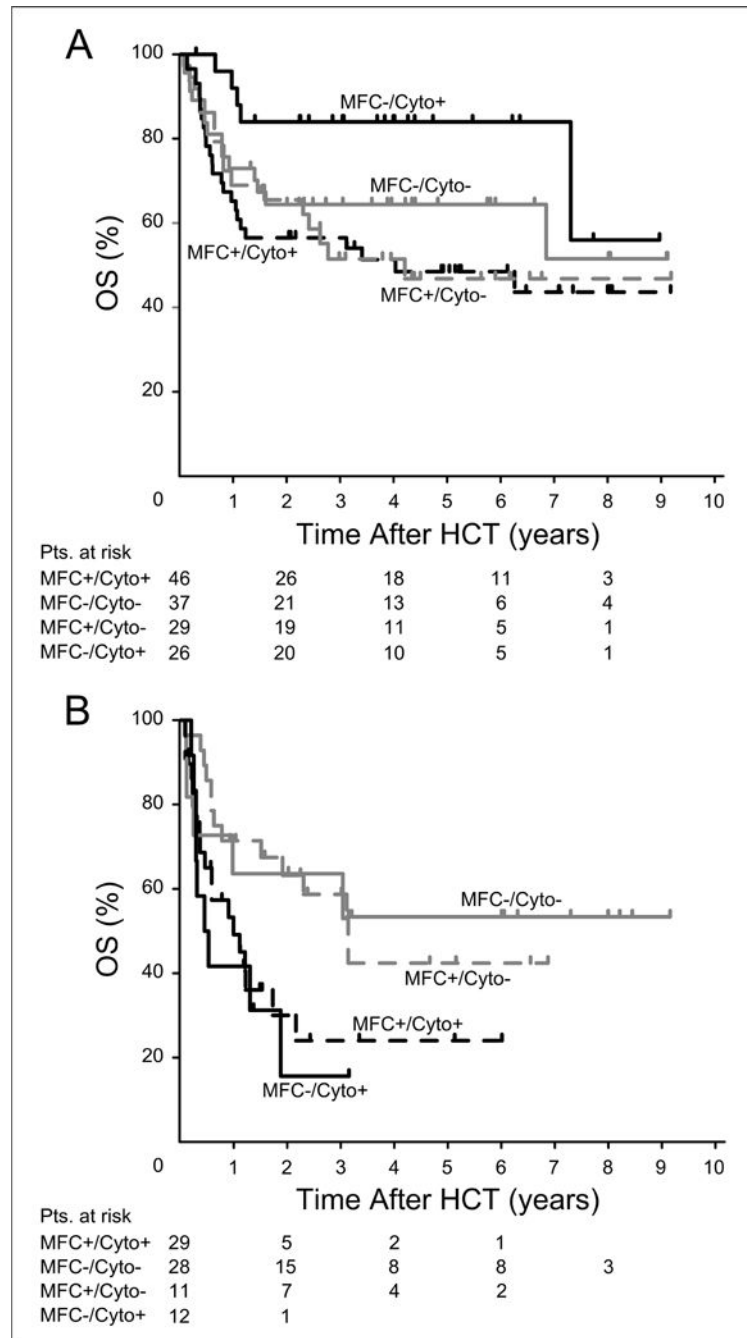


Figure 2. Overall survival by MID subgroups

A. High intensity conditioning patients. **B.** Low intensity conditioning patients.

Abbreviations: OS = overall survival; HCT = hematopoietic cell transplantation; MID = minimal identifiable disease; MFC = multiparameter flow cytometry; Cyto = cytogenetics.

Table 1

Patient and disease characteristics

Characteristics	Overall	Low intensity	High intensity	p-value
Patients, no.	289	94	195	
Male/female, no. (%)	171 (59)/118 (41)	62 (66)/32 (34)	109 (56)/86 (44)	0.13
Median age at diagnosis, years (range)	56 (5 – 76)	64 (24 – 76)	52 (5 – 74)	<0.001
Median age at HCT, years (range)	57 (6 – 77)	66 (25 – 77)	53 (6 – 76)	<0.001
Diagnosis – WHO 2008 criteria				
RCMD, no. (%)	97 (34)	34 (36)	63 (32)	0.6
RARS, no. (%)	6 (2)	3 (3)	3 (2)	0.39
Del 5q, no. (%)	3 (1)	2 (2)	1 (1)	0.25
MDS-U, no. (%)	21 (7)	6 (6)	15 (8)	0.81
RCUD, no. (%)	17 (6)	5 (5)	12 (6)	1
RAEB-1, no. (%)	55 (19)	18 (19)	37 (19)	1
RAEB-2, no. (%)	86 (30)	23 (24)	63 (32)	0.22
CMML, no. (%)	4 (1)	3 (3)	1 (1)	0.1
Etiology				
Primary, no. (%)	207 (72)	62 (66)	145 (74)	
Secondary, no. (%)	82 (28)	32 (34)	50 (26)	0.16
Disease duration				
Median time between diagnosis and HCT, months (range)	7 (1 – 82)	10 (1 – 82)	6 (1 – 82)	<0.001
IPSS risk at diagnosis				
Low, no. (%)	18 (6)	6 (6)	12 (6)	1
Intermediate-1, no. (%)	123 (43)	41 (44)	82 (42)	0.8
Intermediate-2, no. (%)	110 (38)	35 (37)	75 (38)	1
High, no. (%)	33 (11)	10 (11)	23 (12)	1
Not evaluable, no. (%)	5* (2)	2 (2)	3 (2)	0.66
IPSS-R risk at diagnosis				
Very low, no. (%)	10 (3)	4 (4)	6 (3)	0.73
Low, no. (%)	52 (18)	19 (20)	33 (17)	0.52
Intermediate, no. (%)	79 (27)	24 (26)	55 (28)	0.67

Characteristics	Overall	Low intensity	High intensity	p-value
High, no (%)	77 (27)	28 (30)	49 (25)	0.4
Very high, no (%)	66 (23)	17 (18)	49 (25)	0.23
Not evaluable, no (%)	5 (2)	2 (2)	3 (2)	0.66
IPSS-R cytogenetics risk at diagnosis				
Very good/good, no (%)	124 (43)	41 (44)	83 (43)	0.9
Intermediate, no (%)	58 (20)	21 (22)	37 (19)	0.53
Poor/very poor, no (%)	103 (36)	31 (33)	72 (37)	0.6
Not evaluable, no (%)	3 (1)	1 (1)	2 (1)	–
Preceding therapies				
Induction chemotherapy as a first treatment, no. (%)	81 (28)	18 (19)	63 (32)	0.025
Hypomethylating agents as a first treatment, no. (%)	117 (40)	54 (57)	63 (32)	<0.001
No therapy, no. (%)	80 (28)	19 (20)	61 (31)	0.05
Other, no. (%)	11 (4)	3 (3)	8 (4)	1
Disease status at HCT – IWG 2006 criteria				
Complete remission, no. (%)	68 (24)	29 (31)	39 (20)	0.05
Marrow CR, no. (%)	75 (26)	27 (29)	48 (25)	0.48
Partial remission, no. (%)	9 (3)	2 (2)	7 (4)	0.72
Stable disease/untreated, no. (%)	97 (34)	28 (30)	69 (35)	0.59
Disease progression or relapse, no. (%)	40 (14)	8 (9)	32 (16)	0.07
Donors				
HLA-matched family members, no. (%)	116 ^{**} (40)	33 (35)	83 [*] (43)	0.3
Haploidentical, no. (%)	2 (1)	0	2 (1)	1
Matched unrelated, no. (%)	119 (41)	41 (44)	78 (40)	0.61
Mismatched unrelated, no. (%)	34 (12)	9 (10)	25 (13)	0.56
Cord, no. (%)	18 (6)	10 (11)	8 (4)	0.04
Source of stem cells				
Peripheral blood, no. (%)	243 (84)	84 (89)	159 (82)	0.12
Marrow, no. (%)	28 (10)	0	28 (14)	<0.001
Cord, no. (%)	18 (6)	10 (11)	8 (4)	0.04
IPSS risk at HCT				
Low, no. (%)	61 (21)	25 (27)	36 (18)	0.13

Characteristics	Overall	Low intensity	High intensity	p-value
Intermediate-1, no. (%)	136 (47)	40 (43)	96 (49)	0.32
Intermediate-2, no. (%)	68 (24)	25 (27)	43 (22)	0.46
High, no (%)	22 (8)	3 (3)	19 (10)	0.06
Not evaluable, no (%)	2 (1)	1 (1)	1 (1)	0.54
IPSS-R risk at HCT				
Very low, no. (%)	40 (14)	21 (22)	19 (10)	0.006
Low, no. (%)	77 (27)	22 (23)	55 (28)	0.48
Intermediate, no. (%)	69 (24)	23 (24)	46 (24)	1
High, no (%)	61 (21)	19 (20)	42 (22)	0.88
Very high, no (%)	40 (14)	8 (9)	32 (16)	0.10
Not evaluable, no (%)	2 (1)	1 (1)	1 (1)	0.54
IPSS-R cytogenetics risk at HCT				
Very good/good, no (%)	135 (47)	47 (50)	88 (45)	0.45
Intermediate, no (%)	59 (20)	18 (19)	41 (21)	0.76
Poor/very poor, no (%)	94 (33)	29 (31)	65 (33)	0.69
Not evaluable, no (%)	1 (0)	0 (0)	1 (1)	–
AML evolution before HCT				
Yes, no. (%)	66 (23)	23 (25)	43 (22)	
No, no. (%)	223 (77)	71 (76)	152 (78)	0.66

* 3 missing cytogenetics, 2 missing peripheral blood counts;

** 2 HLA matched parents. Abbreviations: WHO = World Health Organization; RCMD = refractory cytopenia with multilineage dysplasia; RARS = refractory anemia with ring sideroblasts; Del 5q = myelodysplastic syndrome associated with isolated deletion 5q; MDS-U = myelodysplastic syndrome unclassified; RCUD = refractory cytopenia with unilineage dysplasia; RAEB = refractory anemia with excess blasts; CMML = chronic myelomonocytic leukemia; HCT = allogeneic hematopoietic cell transplantation; IWG = International Working Group; IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System; CR = complete remission; HLA = human leukocyte antigen; AML = acute myeloid leukemia.

Table 2

Transplant conditioning regimens

High intensity regimens (N=195)		Low intensity regimens (N=94)	
BU ₁₆ /CY, no. (%)	90 (46)	FLU/TBI ₂₀₀₋₃₀₀ , no. (%)	60 (64)
BU ₁₆ /FLU, no. (%)	27 (14)	FLU/TBI ₄₀₀₋₄₅₀ , no. (%)	20 (21)
TREO ₄₂ /FLU/TBI ₂₀₀ , no. (%)	31 (16)	CY/FLU/TBI ₂₀₀₋₃₀₀ , no. (%)	9 (10)
RAB/FLU/TBI ₂₀₀ , no. (%)	17 (9)	CLOFA/TBI ₂₀₀ , no. (%)	3 (3)
TREO ₄₂ /FLU, no. (%)	12 (6)	CY/FLU/TBI ₄₀₀ , no. (%)	1 (1)
TBI ₁₂₀₀₋₁₃₂₀ /CY, no. (%)	7 (4)	BU ₈ /FLU, no. (%)	1 (1)
RDB/BC8SA/FLU/TBI ₂₀₀ , no. (%)	5 (3)		
RAB/FLU/TBI ₂₀₀ /CY, no. (%)	2 (1)		
TBI ₁₃₂₀ /THIO/FLU, no. (%)	2 (1)		
TBI ₁₃₂₀ /CY/FLU, no. (%)	1 (1)		
RAB/FLU/TBI/LI ₁₄₀₀ , no. (%)	1 (1)		

Abbreviations: BU = busulfan; CY = cyclophosphamide; FLU = fludarabine; TREO = treosulfan; TBI = total body irradiation; RAB = radiolabeled antibodies; RDB = radiolabeled dota-biotin; BC8SA = streptavidin-conjugated antiCD45 antibodies; THIO = thiotepa; LI = localized irradiation; CLOFA = clofarabine.

Table 3

MID classification at HCT

Disease status	Definition	Patients (%)
NO-CR	5% or more marrow blasts by morphology on marrow aspirate smear	68 (23.5)
MID negative	Less than 5% marrow blasts and no cytogenetics, FISH, or MFC abnormalities	65 (22.5)
MID positive	Less than 5% marrow blasts and cytogenetics, FISH, or MFC abnormalities	154 (53.3)
Unknown	Less than 5% marrow blasts and cytogenetics, FISH, or MFC results not available	2 (0.7)

Abbreviations: MID = minimal identifiable disease; HCT = hematopoietic cell transplantation; CR = complete remission; FISH = Fluorescence In Situ Hybridization; MFC = multicolor flow cytometry.

Table 4

Multivariable regression model for Overall Survival considering MID and conditioning regimens

Group	Covariate	HR	95% CI	p-value
MID MFC+/Cyto+ N 75; events 43	Conditioning Intensity			
	<i>Low</i>	1.67	0.89 – 3.13	0.11
	<i>High (Baseline)</i>			
MID MFC+/Cyto– N 40; events 21	Conditioning Intensity			
	<i>Low</i>	1.00	0.39 – 2.60	0.99
	<i>High (Baseline)</i>			
MID MFC–/Cyto+ N 38; events 14	Conditioning Intensity			
	<i>Low</i>	7.23	2.38 – 22.00	<0.001
	<i>High (Baseline)</i>			
MID MFC–/Cyto– N 65; events 26	Conditioning Intensity			
	<i>Low</i>	0.99	0.45 – 2.16	0.98
	<i>High (Baseline)</i>			
	MID			
	<i>MFC–/Cyto– (Baseline)</i>			
HIGH intensity N 138; events 58	MFC+/Cyto+	1.98	1.00 – 3.92	0.05
	MFC+/Cyto–	1.44	0.69 – 2.99	0.33
	MFC–/Cyto+	0.67	0.24 – 1.92	0.46
	MID			
	<i>MFC–/Cyto– (Baseline)</i>			
LOW intensity N 80; events 46	MFC+/Cyto+	3.33	1.58 – 7.03	<0.01
	MFC+/Cyto–	1.61	0.60 – 4.36	0.34
	MFC–/Cyto+	4.90	1.98 – 12.09	<0.001

* The model is adjusted for pre-HCT evolution to AML, pre-HCT treatments (induction chemotherapy given as first line treatment or as salvage, hypomethylating agents only, no therapy, or other), MID, and conditioning intensity.

Abbreviations: HR = hazard ratio; CI = confidence intervals; MID = minimal identifiable disease; MFC = multiparameter flow cytometry; Cyto = cytogenetics; HCT = hematopoietic cell transplant.