

# WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

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**We evaluated the impact of World Health Organization (WHO) classification and WHO classification-based Prognostic Scoring System (WPSS) on the outcome of patients with myelodysplastic syndrome (MDS) who underwent allogeneic stem cell transplantation (allo-SCT) between 1990 and 2006. Five-year overall survival (OS) was 80% in refractory anemias, 57% in refractory cytopenias, 51% in refractory anemia with excess blasts 1 (RAEB-1), 28% in RAEB-2, and 25% in acute leukemia from MDS ( $P = .001$ ). Five-**

**year probability of relapse was 9%, 22%, 24%, 56%, and 53%, respectively ( $P < .001$ ). Five-year transplant-related mortality (TRM) was 14%, 39%, 38%, 34%, and 44%, respectively ( $P = .24$ ). In multivariate analysis, WHO classification showed a significant effect on OS ( $P = .017$ ) and probability of relapse ( $P = .01$ ); transfusion dependency was associated with a reduced OS ( $P = .01$ ) and increased TRM ( $P = .037$ ), whereas WPSS showed a prognostic significance on both OS ( $P = .001$ ) and probability of**

**relapse ( $P < .001$ ). In patients without excess blasts, multilineage dysplasia and transfusion dependency affected OS ( $P = .001$  and  $P = .009$ , respectively), and were associated with an increased TRM ( $P = .013$  and  $P = .031$ , respectively). In these patients, WPSS identified 2 groups with different OS and TRM. These data suggest that WHO classification and WPSS have a relevant prognostic value in posttransplantation outcome of MDS patients. (Blood. 2008;112:895-902)**

## Introduction

Myelodysplastic syndromes (MDSs) are a heterogeneous group of disorders clinically characterized by peripheral cytopenia, and an increasing risk of evolution into acute myeloid leukemia (AML).<sup>1</sup> The natural history of MDS, ranging from indolent conditions over years to forms that rapidly progress to leukemia, complicates clinical decision-making regarding therapeutic modalities and timing of intervention.

The only curative treatment in MDS patients is allogeneic stem cell transplantation (allo-SCT). Long-term survival rates of between 25% and 70% were reported after transplantation.<sup>2-5</sup> However, despite advances in transplantation technology, there is still considerable morbidity and mortality associated with this approach.<sup>6-9</sup> Transplant-related mortality (TRM) in adult MDS ranges from 37% to 68%, whereas the relapse rate ranges from 24% to 58%.<sup>4,5,9,10</sup>

Evidence-based guidelines for the therapy of MDS emphasize the importance of basing the therapeutic strategy on the individual disease- and therapy-related risks.<sup>11,12</sup> Given the high risk associated with allo-SCT, an accurate selection of candidate patients is needed.<sup>13</sup> Several studies examined the influence of disease-related

parameters on outcome after transplantation for MDS patients. High marrow blast counts and chromosomal abnormalities were reported as unfavorable prognostic factors.<sup>4,5,10,14,15</sup> The International Prognostic Scoring System (IPSS) was shown to be effective in predicting transplantation outcome.<sup>5,10,16</sup>

In 2002, the WHO formulated a new proposal for the classification of MDS<sup>17</sup> that was shown to have a prognostic relevance in patients receiving supportive care.<sup>18,19</sup> The distinction between patients with unilineage versus multilineage dysplasia and the recognition of 2 categories of refractory anemia with excess blasts (RAEB) represent an improvement in the ability to predict survival and leukemic evolution. Interesting data have also been emerging on the ability of the WHO classification to guide clinical decision-making regarding therapeutic choice.<sup>20,21</sup> A WHO classification-based Prognostic Scoring System (WPSS) has been recently defined and validated in untreated patients.<sup>22</sup> The WPSS is based on WHO categories, karyotype abnormalities, and transfusion requirement, and is able to identify 5 risk groups of MDS patients with differences in survival and risks of leukemic progression.

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The impact of WHO classification and WPSS on the outcome of MDS patients undergoing allo-SCT remains to be clarified. In this study, we retrospectively evaluated the prognostic value of WHO classification and WPSS at the time of transplantation in a cohort of MDS patients who underwent an allo-SCT between 1990 and 2006.

## Methods

### Patient characteristics and transplantation procedures

We studied 406 patients undergoing allo-SCT for primary MDS according to the French-American-British (FAB) criteria between 1990 and 2006 and reported to the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) by 41 centers. The procedures followed were in accordance with the ethical standards of the Institutional Committee on Human Experimentation, GITMO, and with the Helsinki Declaration of 1975, as revised in 2000. Due to the retrospective nature of the study, a specific informed consent could not be submitted to patients. However, each GITMO center was asked to report the data of only those patients with a documented consent in their medical records.

All the clinical variables included in the study were analyzed at the time of transplantation in patients undergoing allo-SCT upfront and at the time of remission-induction chemotherapy in those receiving treatment before allo-SCT. Two hundred twenty-four patients were male and 182 were female. The median age was 48 years (range, 17-72 years). Patients were reclassified by each center according to the WHO classification,<sup>17</sup> as previously described.<sup>18</sup> According to WHO criteria, 27 patients were diagnosed with refractory anemia (RA) or RA with ringed sideroblasts (RARS; 7%), 3 patients with MDS associated with isolated del(5q), 57 patients with refractory cytopenia with multilineage dysplasia with or without ringed sideroblasts (RCMD/RCMD-RS; 14%), 56 patients with RA with excess blasts, type 1 (RAEB-1; 14%), and 95 patients with RAEB-2 (23%). One hundred sixty-eight patients did not meet the WHO criteria for MDS: 41 patients were classified as having chronic myelomonocytic leukemia (CMML; 10%) and 127 were considered to have an AML from MDS (AML-MDS; 31%).

Cytogenetic analysis was available for 209 of the 238 patients with MDS according to WHO criteria (88%). Transfusion dependency was defined according to the WPSS criteria.<sup>22</sup> Related data were available for 231 of 238 patients with MDS according to the WHO criteria, and a regular transfusion need was reported in 115 subjects (50%).

The IPSS<sup>23</sup> could be assessed in 207 of 238 patients diagnosed with MDS according to the WHO criteria: 5 were classified as low risk (2%); 90 as intermediate-1 risk (43%); 95 as intermediate-2 risk (46%); and 17 as high risk (8%). The WPSS<sup>22</sup> was available in 181 of 238 patients diagnosed with MDS according to the WHO criteria: 3 were classified as very low risk (2%); 18 as low risk (10%); 33 as intermediate risk (18%); 103 as high risk (57%); and 24 as very high risk (13%). Clinical features of patients are summarized in Table 1.

Transplantation was performed with a median interval from diagnosis of 9 months (range, 1-189 months). There were 249 HLA-matched sibling and 116 unrelated donor SCTs. Criteria for selection of HLA-matched unrelated donors before 2002 included low-resolution typing for HLA class I (A,B) and high-resolution typing for HLA-DRB1, whereas since 2002 criteria included high-resolution typing for both HLA class I (A,B,C) and class II alleles (DRB1/3/4/5, DQA1, DPB1). The source of hematopoietic stem cells was peripheral blood in 197 patients (54%); bone marrow in 165 (45%); and cord blood in 3 (1%). One hundred seventy patients (47%) received remission-induction chemotherapy before allo-SCT, and 95 (56%) of them obtained a complete remission. Two hundred forty-five patients received a standard-dose conditioning regimen, whereas a reduced-intensity regimen (RIC) was administered to 120 patients (33%). Most frequent conditioning regimens included the following: total body irradiation (TBI) and cyclophosphamide (21% of cases), TBI and fludarabine (8%), busulphan and cyclophosphamide (29%), thiotepa and cyclophosphamide (24%), and thiotepa and fludarabine (11%). For most patients, graft-versus-host disease (GVHD) prophylaxis was combined cyclosporine

**Table 1. Clinical characteristics at the time of allo-SCT or remission-induction chemotherapy of patients classified according to WHO criteria**

Clinical variables	Diagnosis, N = 365	
	MDS	AML-MDS
No. of patients (%)	238 (65)	127 (35)
Median age, y (range)	48 (17-67)	47 (23-72)
Sex, no. male/female	132/106	69/58
<b>WHO classification (%)</b>		
RA/RARS	27 (7)	—
MDS with del5q31	3 (1)	—
RCMD/RS	57 (16)	—
RAEB-1	56 (15)	—
RAEB-2	95 (26)	—
WBC, × 10 <sup>9</sup> /L (range)	2.9 (0.2-21.3)	3.21 (0.1-27.2)
Absolute neutrophil count, × 10 <sup>9</sup> /L (range)	1.16 (0.01-11.5)	1.4 (0.2-10.7)
Hb, g/L (range)	88 (71-122)	92 (68-120)
PLT, × 10 <sup>9</sup> /L (range)	48 (3-686)	58 (3-319)
<b>Cytogenetics (%)</b>		
Good	108 (52)	49 (52)
Intermediate	62 (30)	34 (36)
Poor	39 (18)	11 (12)
Transfusion dependency (%)	115/231 (50)	73/113 (65)
<b>IPSS risk (%)</b>		
Low	5 (2)	—
Intermediate-1	90 (43)	—
Intermediate-2	95 (46)	—
High	17 (8)	—
<b>WPSS risk (%)</b>		
Very low	3 (2)	—
Low	18 (10)	—
Intermediate	33 (18)	—
High	103 (57)	—
Very high	24 (13)	—

WBC indicates white blood cell; Hb, hemoglobin; and PLT, platelet.

and methotrexate. Variables related to the transplantation procedure of patients with MDS and AML-MDS are summarized in Table 2.

### End points and statistical analysis

Numeric variables were summarized by their median and quartiles or range; categorical variables, by counts and relative frequencies. Primary end points were overall survival (OS), probability of relapse, and transplant-related mortality (TRM). Engraftment, acute GVHD (aGVHD), and chronic GVHD (cGVHD) were also investigated. Actuarial probability of OS,

**Table 2. Transplantation-related features of patients classified according to WHO criteria**

	Diagnosis, N = 365	
	MDS, n = 238	AML-MDS, n = 127
Time from diagnosis to allo-SCT, mo (range)	9.5 (1-189.3)	8.3 (1-15.2)
<b>Type of donor (%)</b>		
Sibling	9.166 (70)	83 (65)
MUD	72 (30)	44 (35)
<b>Source of hematopoietic stem cells (%)</b>		
Peripheral blood/cord blood	139 (58)	61 (48)
Bone marrow	99 (42)	66 (52)
Remission-induction chemotherapy (%)	79 (33)	91 (72)
Complete remission (%)	46 (58)	49 (54)
Standard conditioning regimen (%)	156 (66)	89 (70)
RIC (%)	82 (34)	38 (30)

MUD indicates matched unrelated donor; and RIC, reduced-intensity conditioning.

relapse, and TRM were estimated using the Kaplan-Meier product limit method. Comparisons between Kaplan-Meier curves were carried out by the Gehan Wilcoxon test. OS was defined as the time between transplantation and death (from any cause) or last follow-up (censored observations). To estimate the probability of relapse, treatment was considered a failure at the time of hematologic relapse according to standardized criteria.<sup>24</sup> Data on patients who were alive and in complete remission or dead without relapsing were censored at the end of follow-up. When estimating TRM, only deaths for causes related to transplantation were considered events. Engraftment was defined as time to achieve an absolute neutrophil count of at least  $0.5 \times 10^9/L$  sustained for 3 consecutive days. Acute GVHD was evaluated in patients who survived at least 21 days with evidence of engraftment; cGVHD was evaluated in patients who achieved engraftment and survived more than 90 days after transplantation. Univariate and multivariate analyses were performed by Cox proportional hazards regression to identify the most significant independent prognostic factors affecting posttransplantation outcome. All analyses were performed using Statistica 7.0 (Statsoft, Tulsa, OK) and Stata 9 (StataCorp, College Station, TX) software.

## Results

### Posttransplantation outcome of MDS patients classified according to WHO criteria

In patients diagnosed with MDS according to WHO criteria ( $n = 238$ ), 5-year OS was 42%, whereas 5-year probability of relapse was 33% and TRM was 36%. Cumulative incidence of neutrophil recovery at 100 days was 94%. Day-100 cumulative incidence of grades 0, I, and II to IV aGVHD were 36%, 21%, and 43%, respectively. Five-year incidences of overall and extensive cGVHD were 61% and 29%, respectively.

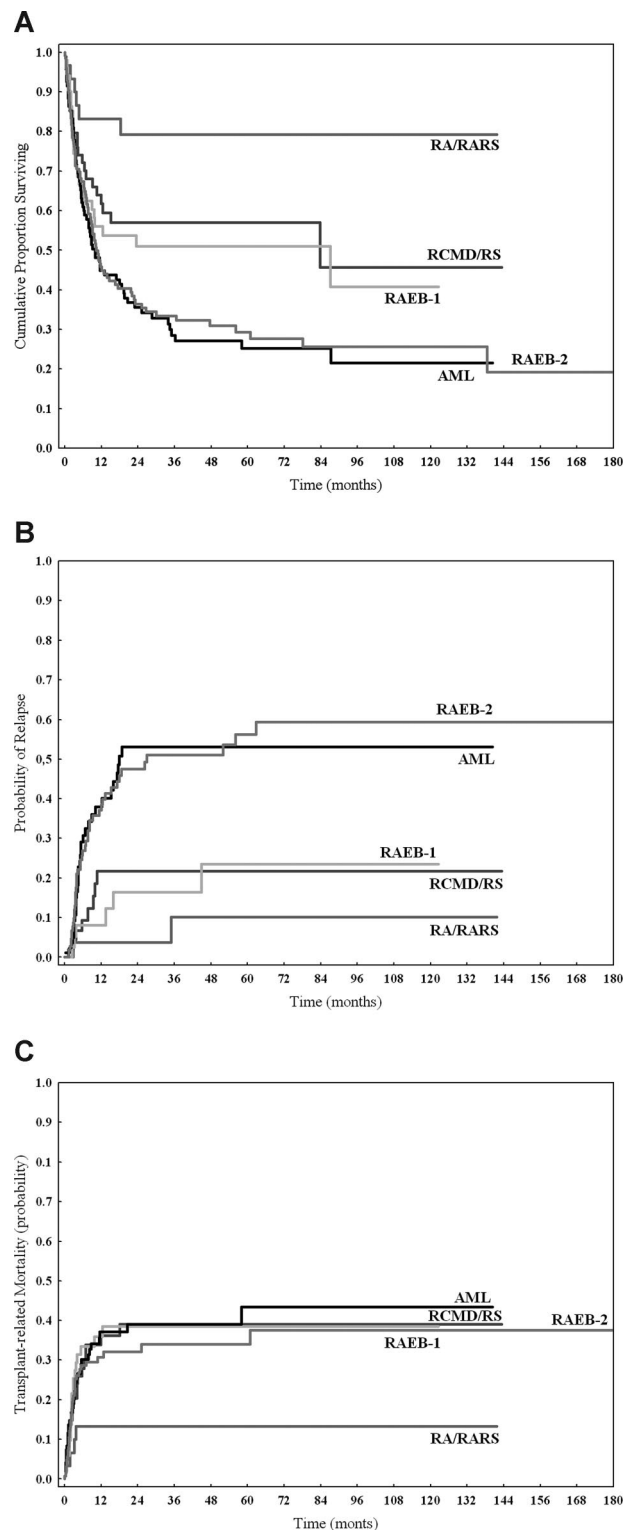
Considering WHO categories at the time of transplantation in patients undergoing allo-SCT upfront and at the time of remission-induction chemotherapy in those treated before transplantation, 5-year OS was 80% in RA/RARS, 57% in RCMD/RCMD-RS, 51% in RAEB-1, 28% in RAEB-2, and 25% in AML-MDS ( $P = .001$ ), whereas 5-year probability of relapse was 9%, 22%, 24%, 56%, and 53%, respectively ( $P < .001$ ). Five-year TRM was 14% in RA/RARS, 39% in RCMD/RCMD-RS, 38% in RAEB-1, 34% in RAEB-2, and 44% in AML-MDS ( $P = .24$ ; Figure 1).

There was a significant difference in posttransplantation OS between patients with RA/RARS and those with RCMD/RCMD-RS ( $P = .009$ ; Figure 1). Patients with RA/RARS also showed a significantly lower probability of TRM ( $P = .031$ , Figure 1).

A nonsignificant difference in OS, probability of relapse, and TRM was seen between patients with RCMD and those with RAEB-1 ( $P = .80$ ,  $P = .60$ , and  $P = .88$ , respectively; Figure 1). Significant differences in both OS and probability of relapse were seen between patients with RAEB-1 and RAEB-2 ( $P = .04$  and  $P = .001$ , respectively; Figure 1), whereas no significant difference in TRM was seen ( $P = .95$ ; Figure 2). Finally, a nonsignificant difference in OS, probability of relapse, and TRM was seen between patients with RAEB-2 and those with AML-MDS ( $P = .73$ ,  $P = .98$ , and  $P = .67$ , respectively; Figure 1).

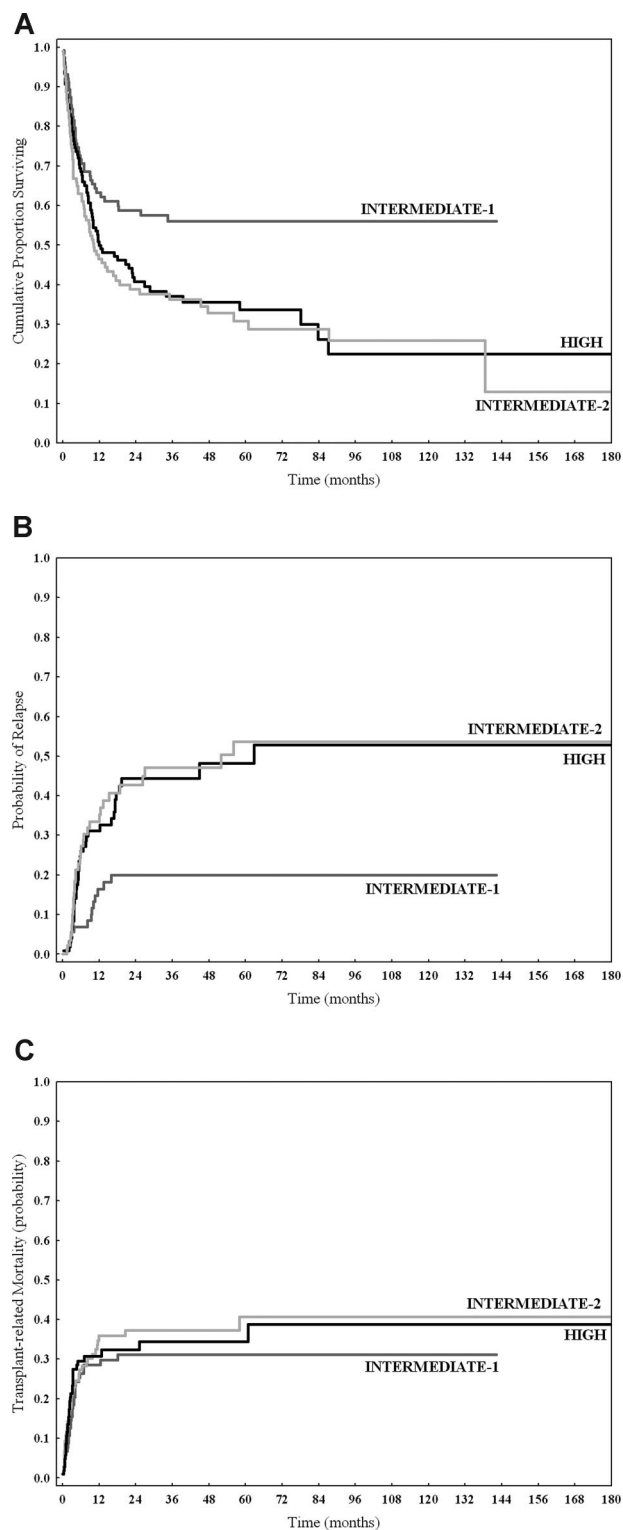
### Prognostic factors on posttransplantation outcome in MDS patients classified according to WHO criteria

We performed a multivariate Cox survival analysis considering as covariates WHO categories, cytogenetic risk (scored into 3 groups according to IPSS), transfusion dependency, absolute neutrophil count (ANC), hemoglobin and platelet level, age and sex of recipient, time



**Figure 1. Posttransplantation outcome according to WHO category.** Overall survival (A), probability of relapse (B), and transplant-related mortality (C) after allogeneic hematopoietic stem cell transplantation in MDS patients classified into WHO categories evaluated at the time of transplantation in patients undergoing allo-SCT upfront and before remission-induction chemotherapy in those receiving treatment before transplantation.

between diagnosis and transplantation (months), year of transplantation (1990-1995; 1996-2000; 2001-2006), disease stage at transplantation (active/progressive disease vs complete remission), source of hematopoietic stem cells (peripheral blood vs bone marrow), type of donor



**Figure 2. Posttransplantation outcome according to IPSS.** Overall survival (A), probability of relapse (B), and transplant-related mortality (C) after allogeneic hematopoietic stem cell transplantation in patients diagnosed with MDS according to WHO criteria and classified according to IPSS. Risk categories were evaluated at the time of transplantation in patients undergoing allo-SCT upfront and before remission-induction chemotherapy in those receiving treatment before transplantation.

(HLA-identical sibling vs matched unrelated donor), and type of conditioning (standard conditioning regimen vs RIC; Table 3). The analysis was carried out considering clinical and demographic variables at the time of transplantation in patients undergoing allo-SCT upfront

and at the time of remission-induction chemotherapy in those treated before transplantation.

WHO classification had a significant effect on both OS (HR = 1.21,  $P = .017$ ) and probability of relapse (HR = 1.23,  $P = .01$ ), whereas no significant effect was noticed on TRM (HR = 1.01,  $P = .82$ ).

Cytogenetic risk significantly affected the probability of relapse (HR = 1.87,  $P = .04$ ) and had a borderline effect on OS (HR = 1.21,  $P = .09$ ). Five-year probability of relapse was 39%, 44%, and 56% in good-, intermediate-, and poor-risk cytogenetic groups, respectively. Patients with poor-risk karyotype showed a significantly higher probability of relapse compared with good- and intermediate-risk patients ( $P = .01$  and  $P = .02$ , respectively), whereas no significant difference was noticed between the 2 latter groups. The presence of a transfusion dependency was associated with a reduced OS (HR = 1.59,  $P = .01$ ) and an increased TRM (HR = 1.56,  $P = .037$ ), whereas no significant effect on the probability of relapse was noticed (HR = 1.28,  $P = .54$ ; Table 3).

Recipient age, disease stage at transplantation, and type of donor had a significant effect on OS (HR = 1.03,  $P = .001$ ; HR = 0.64,  $P = .036$ ; and HR = 1.67,  $P = .006$ , respectively). Active/progressive disease, RIC, and the use of HLA-identical sibling donor were associated with a higher probability of relapse (HR = 0.34,  $P = .017$ ; HR = 2.5,  $P = .005$ ; and HR = 0.32,  $P = .01$ , respectively). Recipient age, use of myeloablative conditioning, and HLA-matched unrelated donor were significant risk factors for TRM (HR = 1.02,  $P = .018$ ; HR = 0.53,  $P = .032$ ; and HR = 1.97,  $P = .001$ , respectively).

Year of transplantation showed a significant effect on TRM (HR = 0.50,  $P = .009$ ) and a borderline on OS (HR = 0.62,  $P = .06$ ), whereas probability of relapse was not significantly affected (Table 3). To clarify whether the effect of year of transplantation on TRM may be solely due to the introduction of RIC, we restricted the analysis to patients receiving a standard conditioning regimen. In this model, year of transplantation retained a significant effect (HR = 0.51,  $P = .001$ ).

The presence of aGVHD grades II to IV had a significant effect on both OS (HR = 1.22,  $P = .01$ ) and TRM (HR = 1.28,  $P = .005$ ). Extensive cGVHD was associated with a decreased OS (HR = 1.98,  $P = .001$ ) and increased probability of TRM (HR = 2.1,  $P = .001$ ).

We fitted separate multivariate models to investigate the prognostic effect of WHO classification in selected subgroups of patients.

According to type of conditioning (either standard conditioning regimen or RIC), WHO classification retained a significant effect on posttransplantation OS (HR = 1.13,  $P = .04$  and HR = 1.66,  $P = .001$ , respectively) and probability of relapse (HR = 1.46,  $P = .02$  and HR = 1.74,  $P = .006$ , respectively), whereas no significant effect on TRM was noticed.

Considering the proportion of patients aged 50 years or older ( $n = 168$ ), a significant effect of WHO categories was confirmed for both OS (HR = 1.21,  $P = .04$ ) and probability of relapse (HR = 1.41,  $P = .02$ ).

When focusing on 87 MDS patients without excess blasts, multilineage dysplasia and transfusion dependency significantly affected posttransplantation OS (HR = 3.31,  $P = .001$  and HR = 2.77,  $P = .009$ , respectively) and were associated with increased TRM (HR = 3.37,  $P = .013$  and HR = 3.59,  $P = .031$ , respectively). Among 151 MDS patients with excess blasts, WHO category significantly affected the probability of relapse (HR = 1.56,  $P = .031$ ) and had a borderline effect on OS (HR = 1.29,  $P = .06$ ), whereas no significant effect on TRM was noticed. Transfusion



**Table 3. Prognostic factors on posttransplantation outcome in multivariate analysis**

Clinical variables	OS		Probability of relapse		TRM	
	HR	P	HR	P	HR	P
Recipient sex	1.16	.7	1.10	.68	0.45	.12
Recipient age*	1.03	.001	1.007	.72	1.029	.018
Time from diagnosis to allo-SCT*	0.99	.36	0.98	.21	0.91	.66
Year of transplantation, 1990-1995 versus 1996-2000 versus 2001-2006	0.62	.06	0.81	.14	0.50	.009
WHO categories*	1.21	.017	1.23	.01	1.01	.82
Cytogenetic risk*	1.21	.09	1.87	.04	1.07	.74
Transfusion dependency*	1.59	.01	1.28	.54	1.56	.037
ANC*	0.99	.93	1.01	.77	0.98	.36
Hb level*	1.01	.09	0.94	.61	1.01	.24
PLT level*	0.99	.23	0.99	.17	0.92	.37
Disease stage at transplantation, active/progressive disease vs complete remission	0.64	.036	0.34	.017	0.81	.44
Source of HSCs, peripheral blood vs bone marrow	1.07	.72	1.2	.55	1.52	.09
Type of donor, HLA-identical sibling vs MUD	1.67	.006	0.32	.01	1.97	.001
Conditioning regimen, standard conditioning vs RIC	0.70	.10	2.5	.005	0.53	.032

PLT indicates platelet; and HSCs, hematopoietic stem cells.

\*Clinical and demographic variables were evaluated at the time of transplantation in patients undergoing allo-SCT upfront, and before remission-induction chemotherapy in patients receiving treatment before transplantation.

dependency had a borderline effect on OS (HR = 1.41,  $P = .07$ ) and TRM (HR = 1.48,  $P = .08$ ), whereas no significant effect on the probability of relapse was seen.

We studied the effect of remission-induction chemotherapy on MDS patients undergoing allo-SCT. To evaluate whether achieving a complete remission (CR) before allo-SCT may improve transplantation outcome, we carried out a multivariate analysis focused on patients with excess blasts, adding disease status at transplantation (CR vs not CR) as covariate: in this model we observed a significant effect of disease status at transplantation on both OS (HR = 0.64,  $P = .02$ ) and probability of relapse (HR = 0.55,  $P = .03$ ). When stratifying for WHO category, no significant effect of disease status at transplantation on OS, probability of relapse, and TRM was noticed among RAEB-1 and RAEB-2 patients, whereas a significant effect of disease status at transplantation was present in patients affected with AML from MDS on both OS (HR = 0.50,  $P = .007$ ) and probability of relapse (HR = 0.31,  $P = .001$ ).

To investigate the effect of the disease status at transplantation according to the type of conditioning regimen, we fitted separate Cox models for patients receiving standard conditioning or RIC. In patients affected with AML from MDS, a significant advantage of undergoing transplantation in CR was found in both standard and RIC groups (OS: HR = 0.51,  $P = .038$  and HR = 0.32,  $P = .043$ , respectively; probability of relapse: HR = 0.32,  $P = .026$  and HR = 0.11,  $P = .01$ , respectively). Considering patients affected with RAEB-1 and RAEB-2, a borderline effect on the probability of relapse was noticed in patients receiving RIC (HR = 0.42,  $P = .07$ ).

Finally, we performed multivariate analyses considering as covariate "receiving or not remission-induction chemotherapy," with the aim to evaluate whether the strategy of treating patients with chemotherapy before transplantation could result in a better outcome. We found that receiving remission-induction chemotherapy did not affect posttransplantation OS, probability of relapse, and TRM.

#### Posttransplantation outcome of MDS patients classified according to IPSS and WPSS

The IPSS and WPSS at the time of transplantation or of remission-induction chemotherapy were available in 207 and 181 of

238 MDS patients diagnosed according to the WHO criteria, respectively (Table 1). Due to the low number of patients in the lowest risk categories, patients with low IPSS and very low WPSS risks were excluded from the analysis.

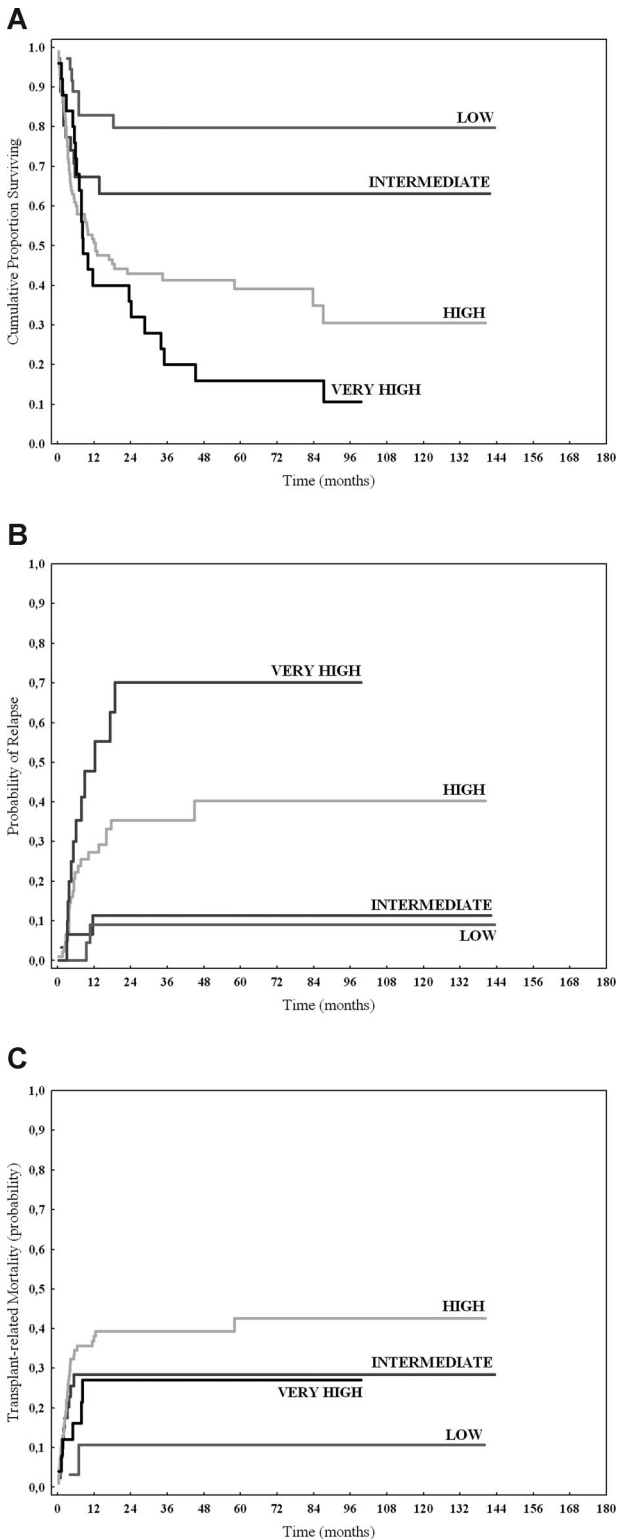
Considering IPSS categories, 5-year OS was 57% in the intermediate-1-risk, 28% in the intermediate-2-risk, and 32% in the high-risk ( $P = .017$ ) groups, whereas 5-year probability of relapse was 20%, 54%, and 48%, respectively ( $P = .002$ ). Five-year TRM was 31% in the intermediate-1-risk, 41% in the intermediate-2-risk, and 34% in the high-risk ( $P = .67$ ) groups (Figure 2).

There was a significant difference in posttransplantation OS between patients with intermediate-1 and either those with intermediate-2 or high risk ( $P = .006$  and  $P = .029$ , respectively), whereas there was no statistical difference in OS between intermediate-2- and high-risk patients ( $P = .38$ ). Patients with intermediate-1 risk also showed a significantly lower probability of relapse with respect to the intermediate-2- and high-risk groups ( $P = .001$  and  $P = .002$ , respectively), whereas no significant difference was seen between the 2 latter groups ( $P = .42$ ).

Considering WPSS categories, the 5-year OS was 80% in patients with low risk, 63% in those with intermediate, 40% in patients with high, and 16% in patients with very high risk ( $P < .001$ ), whereas 5-year probability of relapse was 9%, 11%, 40%, and 70%, respectively ( $P < .001$ ). Five-year TRM was 11%, 28%, 40%, and 26% in patients with low, intermediate, high, and very high risk, respectively ( $P = .005$ ; Figure 3).

There was a significant difference in OS between patients with low and with intermediate risk ( $P = .005$ ) and between patients with intermediate and with high risk ( $P = .03$ ), whereas there was no statistical difference in OS between high- and very high-risk patients ( $P = .98$ ).

There was no significant difference in the probability of relapse between patients with low and with intermediate risk ( $P = .42$ ), whereas the probability of relapse was statistically different between intermediate and high risk ( $P = .005$ ). Moreover, a borderline difference was found in the probability of relapse between high- and very high-risk patients ( $P = .07$ ). Patients with low risk also showed a significantly lower TRM compared with the intermediate- and high-risk groups ( $P = .02$  and  $P = .001$ , respectively), whereas no significant



**Figure 3.** Posttransplantation outcome according to WPSS. Overall survival (A), probability of relapse (B), and transplant-related mortality (C) after allogeneic hematopoietic stem cell transplantation in patients diagnosed with MDS according to WHO criteria and classified according to WPSS. Risk categories were evaluated at the time of transplantation in patients undergoing allo-SCT upfront and before remission-induction chemotherapy in those receiving treatment before transplantation.

difference was seen between the intermediate-, high-, and very high-risk groups.

We then investigated in multivariate models the prognostic value of IPSS and WPSS scores on posttransplantation outcome

of MDS patients classified according to WHO criteria. We first performed a multivariate Cox survival analysis including IPSS, transfusion dependency, age and sex of recipient, time between diagnosis and allo-SCT, year of transplantation, disease stage at transplantation, source of stem cells, type of donor, and type of conditioning as covariates. In this model, IPSS showed a prognostic significance on both OS (HR = 1.25,  $P = .028$ ) and probability of relapse (HR = 1.82,  $P < .001$ ), but not on TRM (HR = 0.97,  $P = .85$ ).

Then we introduced WHO categories as covariate in the model. Because both WHO and IPSS are based on similar criteria with regard to the ranking of bone marrow blasts, we performed a multivariate Cox analysis considering unilineage versus multilineage dysplasia, percentage of marrow blasts, peripheral blood cytopenias, and cytogenetics as single covariates, to clarify which WHO- and IPSS-related variables have an independent prognostic effect on posttransplantation outcome.

In this model, multilineage dysplasia was significantly associated with a reduced OS and increased TRM (HR = 3.36,  $P = .01$  and HR = 2.28,  $P = .03$ , respectively), marrow blasts and cytogenetics retained a prognostic significance on probability of relapse (HR = 1.79,  $P = .03$  and HR = 1.67,  $P = .04$ , respectively), whereas the number of peripheral blood cytopenias did not affect posttransplantation outcome.

We then tested the effect of WPSS categories on posttransplantation outcome in a multivariate Cox survival analysis also including age and sex of recipient, time between diagnosis and allo-SCT, year of transplantation, disease stage at transplantation, source of stem cells, type of donor, and type of conditioning. In this model, WPSS showed an independent prognostic significance on both OS (HR = 1.50,  $P = .001$ ) and probability of relapse (HR = 2.22,  $P < .001$ ) but not on TRM (HR = 1.2,  $P = .45$ ). Focusing the analysis on 87 MDS patients without excess blasts, WPSS identified 2 groups (low vs intermediate risk) with significant differences in OS and TRM ( $P = .013$  and  $P = .039$ , respectively), whereas IPSS did not produce significant prognostic stratification.

Finally, we carried out additional analyses to investigate the prognostic effect of WPSS in selected group of patients. Focusing the analysis on 123 patients receiving standard conditioning regimen and on 58 patients receiving RIC, WPSS maintained its prognostic effect on posttransplantation outcome on both groups (OS: HR = 1.46,  $P = .07$  and HR = 2.17,  $P = .001$ , respectively; probability of relapse: HR = 1.96,  $P = .03$  and HR = 1.98,  $P = .01$ , respectively). Considering 81 patients aged 50 years or older, the results of multivariate analysis showed that WPSS independently affected the probability of relapse (HR = 1.84,  $P = .02$ ) and had a borderline effect on OS (HR = 1.43,  $P = .06$ ).

## Discussion

In this study, we tested the impact on posttransplantation outcome of WHO classification and WPSS in MDS patients undergoing an allo-SCT. The WHO classification and the WPSS have already been shown to have prognostic relevance in untreated MDS patients.<sup>18,22</sup> These patients, however, differ from those undergoing transplantation in many ways. First, a significant proportion of untreated MDS patients are older than 65 years, the usual age limit for intensive procedures.<sup>11</sup> Furthermore, transplantation series include a high proportion of patients with adverse karyotype and

with transfusion need, leading to a shift to higher IPSS and WPSS risk scores.<sup>4,5,10,15,16</sup>

We showed that WHO classification has an independent predictive effect on posttransplantation outcome in a large cohort of patients. In patients without excess blasts, the presence of marrow multilineage dysplasia was significantly associated with a reduced OS and an increased TRM, which were not significantly different from those observed in patients with RAEB-1. Considering WHO categories with excess blasts, RAEB-1 and RAEB-2 patients showed a significant difference in OS and probability of relapse.

Karyotype has been shown to be prognostically significant after allo-SCT.<sup>15</sup> The availability of cytogenetic data for a large proportion of patients in this study allowed us to confirm that cytogenetic risk is an independent predictor of the probability of relapse. The main negative effect on posttransplantation outcome was associated with the presence of chromosome 7 abnormalities or complex karyotype, whereas no significant difference was seen between good and intermediate cytogenetic risk groups defined by IPSS criteria.

In this series of WHO-classified MDS patients, IPSS calculated at the time of intensive treatment identifies 2 groups of patients with significantly different OS and probability of relapse: intermediate-1 versus intermediate-2 or high risk. However, IPSS failed to retain an independent prognostic significance in a multivariate analysis with WHO category as covariate. This may be partly related to the fact that both systems are based on similar criteria with regard to the ranking of bone marrow blasts, but the effect of multilineage dysplasia on posttransplantation outcome might also play a role.

Transfusion dependency was shown to be an independent prognostic factor in untreated MDS patients due to the concurrent effect of more severe anemia, more aggressive disease, and secondary iron overload.<sup>13,18</sup> Transfusion-dependent iron overload is an important adverse prognostic factor for patients with thalassemia undergoing allo-SCT.<sup>25</sup> In a recent study, an elevated pretransplantation serum ferritin level in patients with MDS was strongly associated with lower OS due to a significant increase in TRM.<sup>26</sup> We found that the presence of a transfusion dependency in MDS patients who underwent allo-SCT was associated with a reduced OS and increased TRM.

The recently defined WPSS was able to identify 5 risk groups of untreated MDS patients with different survival and risk of leukemic progression, compared with the 4 groups defined by IPSS.<sup>22</sup> We observed in addition that WPSS has an independent prognostic significance on both OS and probability of relapse in MDS patients undergoing allo-SCT. This score appeared to improve posttransplantation prognostic stratification with respect to IPSS. Considering MDS patients without excess blasts, WPSS identified 2 groups of patients (low vs intermediate risk) with a significant difference in OS and TRM, whereas in the same group of patients IPSS failed to stratify the prognosis.

Interestingly, both WHO and WPSS maintained their prognostic effect on posttransplantation outcome also in specific subsets of patients, such as subjects older than 50 years as well as patients receiving RIC. This observation might be relevant in the light of the increased number of RICs performed in MDS in most recent years, after the demonstration of their efficacy in allowing engraftment and in decreasing TRM in patients ineligible for standard conditioning allo-SCT.<sup>27</sup>

Whether there is any advantage in administering chemotherapy to achieve remission before transplantation for MDS is the subject of debate.<sup>4</sup> Our data suggest that in patients with high-risk MDS according to WHO criteria (ie, RAEB-1, RAEB-2), achieving a complete remission before a standard allo-SCT seems not to be associated with a better posttransplantation outcome. In patients

receiving RIC, complete remission is associated with a trend to a reduced relapse rate. As expected, a significant impact of disease status at transplantation is present in patients affected with AML from MDS (formerly classified as RAEB-t according to FAB criteria). We are aware that our dataset is partly inadequate to address the effect of the strategy of treating patients with chemotherapy before transplantation. In fact, our study is based on transplantation registry, and a proportion of patients who received chemotherapy with the intent to proceed to transplantation but lost the eligibility to allo-SCT due to chemotherapy-related mortality and morbidity were probably underreported. With these limitations, we found that receiving AML-like chemotherapy did not affect posttransplantation OS, probability of relapse, and TRM.

There are potential sources of bias in our analysis that are inherent to the retrospective nature of a study based on a national transplantation registry. Factors to consider include patient selection, missing data in a proportion of patients, long period of recruitment, and different types of transplantation and of pretransplantation treatment. However, WHO and WPSS-related data were available in the great majority of the original patient population. Moreover, the analyses were adjusted for all known potential confounding factors. Although we are aware that a prospective validation of these results is needed, we are confident that the findings of this study are reliable and can be useful to the clinical management of MDS patients. In particular, WHO classification and WPSS show a relevant prognostic value in posttransplantation outcome of MDS patients and might help decision making in transplantation.

## Appendix

The following institutions (GITMO centers) in Italy contributed to the trial: Division of Hematology, Ospedale "S. S. Antonio e Biagio" Alessandria (A. Levis); Division of Hematology, Ospedali Riuniti, Bergamo (A. Rambaldi); Institute of Hematology and Clinical Oncology "L. A. Seragnoli," Ospedale "S. Orsola-Malpighi," University of Bologna, Bologna (G. Bandini); Department of Hematology, Ospedale Regionale, Bolzano (M. Casini); Division of Hematology, Spedali Civili, Brescia (G. Rossi); Division of Hematology and Bone Marrow Transplant Center, Ospedale Oncologico "A. Businco," Cagliari (E. Angelucci, D. Baronciani); Bone Marrow Transplantation Unit, Ospedale "R. Binagli," University of Cagliari, Cagliari (G. La Nasa); Division of Hematology and Bone Marrow Transplantation, Ospedale "Ferrarotto," Catania (G. Milone); Division of Hematology, Ospedale "S. Croce e Carlo," Cuneo (N. Mordini); Department of Hematology, Ospedale "Careggi," University of Florence, Firenze (S. Guidi, A. Bosi); Division of Hematology, Ospedale "S. Martino," Genova (A. Bacigalupo, M. T. Van Lint), Hematology–Bone Marrow Transplantation Unit, Istituto Nazionale dei Tumori, University of Milano, Milano (P. Corradini, R. Milani), Division of Hematology Ospedale "Cà Granda" Niguarda, Milano (E. Morra, P. Marengo); Department of Hematology, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milano (G. Lambretenghi Deliliers, F. Onida); Hematology and Bone Marrow Transplantation Unit, S. Raffaele Scientific Institute, Milano (F. Ciceri, M. Bernardi); Transplantation Unit Department of Oncology–Hematology, IRCCS Clinica Humanitas, Rozzano (L. Castagna); Department of Oncology and Hematology University of Modena and Reggio Emilia, Modena (F. Nami); Division of Hematology and Transplant Unit, Ospedale "S. Gerardo," University of Milano-Bicocca, Monza (P. Pioltelli), Division of Hematology, University of Napoli "Federico II" Medical School, Napoli (C. Selleri); Division of



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## Authorship

Contribution: E.P.A., M.G.D.P., A. Bacigalupo, and A. Bosi designed the research; E.P.A., M.G.D.P., A. Bacigalupo, M.T.V.L., M.F., F.O., M.B., A.P.I., A.R., R.C., P.M., P.P., L.M., R.F., and A. Bosi collected data; E.P.A., M.G.D.P., L.M., and C.P. analyzed and interpreted data; C.P. and R.O. performed statistical analysis; and E.P.A., M.G.D.P., and A. Bacigalupo wrote the paper.

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