Prognostic impact of pretransplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

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Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

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ABSTRACT

Background

Transfusion-dependency affects the natural history of myelodysplastic syndromes (MDS). Secondary iron overload may concur to this effect. The relative impact of these factors on the outcome of patients receiving allogeneic stem-cell transplantation (allo-SCT) remains to be clarified. We evaluated the prognostic effect of transfusion history and iron overload on the post-transplantation outcome of MDS patients.

Design and Methods

357 patients reported to the GITMO between 1997 and 2007 were retrospectively evaluated.

Results

Transfusion-dependency was independently associated to reduced overall survival (OS, HR=1.48, \(p=0.017\)) and increased non-relapse mortality (NRM, HR=1.68, \(p=0.024\)). The impact of transfusion-dependency was noticed only in patients receiving myeloablative conditioning (OS HR=1.76, \(p=0.003\); NRM HR=1.70 \(p=0.02\)). An inverse relationship between transfusion burden and OS after transplantation was present \(p=0.022\); the outcome was significantly worse in subjects receiving more than 20 red cell units. In multivariate analysis, transfusion-dependency was found to be a risk factor for acute GVHD \(p=0.04\). In transfusion-dependent patients receiving myeloablative allo-SCT, pre-transplantation serum ferritin level showed a significant effect on OS \(p=0.01\) and NRM \(p=0.05\). This effect was maintained after adjusting for transfusion burden and duration, suggesting that the negative effect of transfusion history on outcome might be determined at least in part by iron overload.

Conclusions

Pre-transplantation transfusion history and serum ferritin have a significant prognostic value in MDS patients undergoing myeloablative allo-SCT, inducing a significant increase of NRM. These results indicate that transfusion history should be considered in transplantation decision-making in MDS.

Key words: transfusion-dependency, myelodysplastic syndromes, secondary iron overload.


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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by peripheral cytopenia and an increasing risk of evolution into acute myeloid leukemia (AML). The natural history of MDS, ranging from indolent conditions to forms that rapidly progress to leukemia, complicates therapeutic choice and timing of intervention.

The only curative treatment in MDS patients is allogeneic stem cell transplantation (allo-SCT). However, given the considerable morbidity and mortality associated with this approach, an accurate selection of candidate patients is needed.

All patients with MDS are likely to receive red blood cell transfusions at some point of their clinical course. As consequence, many subjects with low-risk disease at diagnosis, have a long history of transfusion at the time of transplant.

The onset of transfusion requirement has been found to affect the outcome of MDS patients and is now considered an independent indicator of disease severity.

We observed, in addition, that transfusion-dependent patients may have a reduced survival after transplantation, and that the WHO classification-based Prognostic Scoring System (WPSS), which includes transfusion as a prognostic variable, improves post-transplantation outcome stratification in MDS.

Iron-related tissue damage is an important adverse prognostic factor for transfusion-dependent patients with thalassemia undergoing allo-SCT.

In MDS, hepatic iron accumulation as detected by MRI was associated with poor outcome after transplantation.

In this study we retrospactively evaluated the prognostic significance of pre-transplantation transfusion history and secondary iron overload in a cohort of MDS patients who underwent an allo-SCT between 1997 and 2007.

Design and Methods

Patients’ characteristics and transplantation procedures

We studied 357 patients undergoing allo-SCT for primary MDS between 1997 and 2007 and reported to the GITMO registry. The procedures followed were in accordance with the ethical standards of the Institutional Committee on Human Experimentation, GITMO, and with the Helsinki Declaration.

All clinical variables 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.

One hundred and ninety-five patients were male and 162 were female. The median age was 49 years (range, 18-72 years). Two hundred forty four patients were classified as having an MDS according to WHO criteria, while 113 subjects previously classified as RAEB in transformation (RAEBt) according to FAB criteria, were considered to have an AML from MDS.

Cytogenetic analysis was available for 211 of 244 patients with MDS according to WHO criteria (86%), and IPSS and WPSS were assessed in these patients. Data on extra-hematological comorbidities according to hematopoietic-cell transplantation-specific comorbidity index (HCT-CI) were obtained in 287 patients (80%).

Transfusion history was defined in terms of transfusion dependency, burden and duration. Transfusion-dependency was defined according to WPSS criteria, as having at least one packed red blood cells (PRBC) transfusion every 8 weeks over a period of 4 months before intensive procedure. Data were available for 325 patients (91%). In 203 patients the total number of PRBC units received before intensive treatment was recorded. Serum ferritin assessed before intensive treatment (median time 1.9 months, range 0-5.9) was available in 228 patients (64%). In 157 patients data regarding serum albumin, serum iron and transferrin at the same time of serum ferritin assessment, were also recorded (Table 1). Seventeen patients received chelation therapy before allo-SCT and were excluded from the analyses.

Transplantation was performed with a median interval from diagnosis of 9 months (range 1-189). There were 229 HLA-matched sibling (64%) and 128 unrelated donor (36%) SCT. 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 221 patients (62%); bone marrow in 136 (38%). One hundred fifty-two patients (43%) received remission-induction chemotherapy before allo-SCT.

Two hundred seventeen patients received a myeloablative conditioning regimen (61%), whereas a reduced-intensity conditioning regimen (RIC) was administered to 140 patients (39%). Most frequent conditioning regimens included: total body irradiation (TBI) and cyclophosphamide (20% of cases), TBI and fludarabine (8%), busulphan and cyclophosphamide (28%), thiotepa and cyclophosphamide (26%), and thiotepa and fludarabine (11%). For most patients, graft-versus-host disease (GVHD) prophylaxis was with combined cyclosporine and methotrexate (Table 1).

End-points and statistical analysis

Numeric variables have been summarized by their median and range; categorical variables by count and relative frequency. Primary end points were overall survival (OS), non-relapse mortality (NRM) and probability of relapse. OS was defined as the time between transplantation and death (from any cause) or last follow-up (for censored observations). When estimating NRM, any death in the absence of disease relapse was considered an event. The probability of relapse was estimated considering treatment as a failure at the time of hematologic relapse according to standardized criteria.

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Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were also investigated. Cumulative probability of OS, NRM and relapse were estimated using the Kaplan-Meier product limit method. Comparisons between Kaplan-Meier curves were carried out by the Gehan Wilcoxon test. Probability of relapse and NRM were analysed as competing risk.

Univariate and multivariate survival analyses were performed by Cox proportional hazards regression to identify the most significant independent prognostic factors. To decide which parameterization of the covariates (categorical, with indicator variables, vs. continuous, with a single parameter) was preferable, we carried out likelihood ratio tests, all of which were not significant. Therefore, we decided to...
Results

Post-transplantation outcome according to transfusion-dependency

In the whole cohort, 5-year OS was 39%; 5-year probability of relapse was 42% and NRM was 41%. Day 100 cumulative incidence of grade I and of grade II to IV aGVHD were 23% and 39%, respectively. Five-year cumulative incidence of overall and extensive cGVHD was 64% and 34%, respectively.

A regular transfusion need before transplant was reported in 223 (68%) of 328 evaluable subjects. Median number of PRBC units received was 20 (5-151). Considering that each unit of blood contains approximately 200-250 mg of iron, the median intake of iron due to transfusions was 4 grams (1-50). Median duration of transfusion-dependency was 8 months (2-183). There was no significant difference in proportion of transfusion-dependent patients among WHO categories (p=0.31). With respect to patients who did not receive transfusion therapy, transfusion-dependent patients showed an increased time period between diagnosis and transplantation (10.7 vs. 7.6 months, p=0.004), a higher HCT-CI score (p=0.04) and an increased percentage of RIC (59% vs. 28%, p=0.024). (Table 1) An increased occurrence of aGVHD was noticed in transfusion-dependent patients (67% vs. 57%, p=0.03), while no significant difference was seen in cGVHD.

In univariate analysis, transfusion-dependency significantly affected OS (HR 1.68, p<0.001), NRM (HR 1.72, p=0.001), and probability of relapse (HR 1.61, p=0.011). We performed a multivariate Cox survival analysis with the following covariates: WHO category, cytogenetic risk (scored according to IPSS), transfusion-dependency, absolute neutrophil count (ANC), hemoglobin and platelet level, presence of extra-hematological comorbidities (according to HCT-CI), age of recipient, time between diagnosis and transplantation, year of transplantation (1997-2002 vs. 2003-2007), disease stage at transplantation (complete remission, CR or marrow blasts <5% vs. not CR or blasts ≥5%), receiving or not remission-induction chemotherapy, source of hematopoietic stem cells (peripheral blood vs. bone marrow), type of donor (HLA-identical sibling vs. matched unrelated donor) and type of conditioning (myeloablative conditioning regimen vs. RIC).

Recipient age, WHO category, disease stage at transplantation, HCT-CI and type of donor had a significant effect on OS. WHO category with excess blasts, unfavourable cytogenetics, active/progressive disease at transplantation, RIC, and the use of HLA-identical sibling donor were associated with a higher probability of relapse. Recipient age, transplantation year before 2003, use of myeloablative conditioning, HLA-matched unrelated donor and high HCT-CI score were significant risk factors for NRM. (Table 2)

Table 2. Prognostic factors on post-transplantation outcome in the whole study population (multivariate analysis).

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>OS</th>
<th>Probability of relapse</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient sex</td>
<td>0.91</td>
<td>0.52</td>
<td>1.07</td>
</tr>
<tr>
<td>Recipient age</td>
<td>1.024</td>
<td>0.001</td>
<td>1.065</td>
</tr>
<tr>
<td>Year of transplantation (1997-2002 vs. 2003-2007)</td>
<td>0.71</td>
<td>0.09</td>
<td>1.01</td>
</tr>
<tr>
<td>Time from diagnosis to allo-SCT*</td>
<td>0.99</td>
<td>0.89</td>
<td>0.91</td>
</tr>
<tr>
<td>WHO categories*</td>
<td>1.23</td>
<td>0.001</td>
<td>1.47</td>
</tr>
<tr>
<td>Cytogenetic risk*</td>
<td>1.18</td>
<td>0.11</td>
<td>1.50</td>
</tr>
<tr>
<td>Transfusion-dependency*</td>
<td>1.48</td>
<td>0.017</td>
<td>1.21</td>
</tr>
<tr>
<td>ANC*</td>
<td>1.008</td>
<td>0.49</td>
<td>0.97</td>
</tr>
<tr>
<td>Hb level*</td>
<td>0.98</td>
<td>0.11</td>
<td>0.95</td>
</tr>
<tr>
<td>PLT level*</td>
<td>0.99</td>
<td>0.98</td>
<td>1.000</td>
</tr>
<tr>
<td>HCT-CI (low vs. intermediate vs. high)</td>
<td>1.0</td>
<td>0.014</td>
<td>0.77</td>
</tr>
<tr>
<td>Disease stage at transplant (complete remission vs. active/progressive disease)</td>
<td>1.38</td>
<td>0.033</td>
<td>1.52</td>
</tr>
<tr>
<td>Conditioning regimen, (standard conditioning vs RIC)</td>
<td>0.87</td>
<td>0.28</td>
<td>1.85</td>
</tr>
<tr>
<td>Source of HSC (peripheral blood vs. bone marrow)</td>
<td>1.15</td>
<td>0.38</td>
<td>1.20</td>
</tr>
<tr>
<td>Type of donor (HLA-identical sibling vs. MUD)</td>
<td>1.43</td>
<td>0.022</td>
<td>0.45</td>
</tr>
</tbody>
</table>

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

Transfusion-dependency had a significant effect on both OS (HR=1.48, p=0.017) and NRM (HR=1.68, p=0.024), whereas no significant effect was noticed on probability of relapse (HR=1.21, p=0.46) (Table 2, Figure 1A). The prognostic effect of transfusion-dependency was maintained when the analysis was focused on 244 patients with a diagnosis of MDS according to WHO criteria (OS HR=1.64, p=0.016; NRM HR=1.76, p=0.042).

In order to verify whether the introduction of transfusion-dependency may improve the prognostic stratification of MDS patients undergoing allo-SCT, we fitted two separate multivariate Cox analyses including the same covariates as detailed above with and without transfusion-dependency, and compared them with the
Patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation

We investigated the effect of transfusion-dependency on post-transplantation outcome. We focused on 135 transfusion-dependent subjects receiving a myeloablative conditioning, with the aim to investigate the prognostic effect of the transfusion burden in those patients.

We firstly performed a multivariate analysis including number of received PRBC units as a continuous variable, and adjusting for duration of transfusion need. WHO category, cytogenetics, ANC, hemoglobin and platelet level, age of recipient, disease stage at transplantation, source of hematopoietic stem cells and type of donor were also included as covariates. The number of PRBC units showed a significant effect on OS (HR=1.029, \( p=0.022 \)) and NRM (HR=0.67, \( p=0.031 \)).

When focusing on MDS patients without excess blasts, transfusion-dependency significantly affected post-transplantation OS (HR=3.01, \( p=0.014 \)) and was associated with increased NRM (HR=3.49, \( p=0.02 \)). Among MDS patients with excess blasts or MDS-AML, transfusion-dependency retained a significant effect on both OS (HR=1.50, \( p=0.012 \)) and NRM (HR=1.69, \( p=0.031 \)).

We finally analysed relapse and NRM in these subgroups of patients as competing risks.

Considering patients receiving a myeloablative conditioning, cumulative incidence of relapse and NRM was 25% and 33% in transfusion-independent patients and 24% and 45% in transfusion-dependent patients, respectively. In patients receiving RIC, cumulative incidence of relapse and NRM was 64% and 21% in transfusion-independent patients and 52% and 22% in transfusion-dependent patients, respectively.

Focusing on patients with excess blasts or MDS-AML, cumulative incidence of relapse and NRM was 35% and 33% in transfusion-independent patients and 34% and 45% in transfusion-dependent patients, respectively. In patients without excess blasts, cumulative incidence of relapse and NRM was 10% and 26% in transfusion-independent patients and 17% and 33% in transfusion-dependent patients, respectively.

**Post-transplantation outcome according to transfusion burden**

We focused on 135 transfusion-dependent subjects receiving a myeloablative conditioning, with the aim to investigate the prognostic effect of the transfusion burden in those patients.

We then carried out separate multivariate analyses to investigate the prognostic effect of transfusion-dependency in selected subgroups of patients.

When stratifying according to type of conditioning, transfusion-dependency retained a significant effect in patients receiving a myeloablative conditioning (OS HR=1.76, \( p=0.003 \); NRM HR=1.70, \( p=0.02 \), probability of relapse HR=1.47, \( p=0.22 \), Table 3, Figure 1B), whereas no significant effect was noticed in patients receiving RIC (OS HR=0.84, \( p=0.60 \); NRM HR=0.67, \( p=0.28 \), probability of relapse HR=0.81, \( p=0.63 \)).

These results were confirmed when transfusion-dependent patients were grouped in three categories, as no significant effect was noticed in patients receiving RIC (OS HR=0.67, \( p=0.44 \); NRM HR=0.67, \( p=0.28 \), probability of relapse HR=0.81, \( p=0.63 \)).

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**Figure 1.** Post-transplantation outcome according to the presence of transfusion-dependency. Probability of overall survival and non-relapse mortality after allogeneic hematopoietic stem cell transplantation in the whole MDS population (A, B, respectively) and in patients receiving myeloablative conditioning (C, D, respectively). The curves were estimated from multivariable Cox regression analysis adjusted for patient age and sex, WHO, cytogenetics, disease status at transplant, presence of comorbidities, source of stem cells, type of donor and type of conditioning
With respect to transfusion-independent patients, no significant difference was noticed in patients receiving ≤20 PRBC units before allo-SCT and transfusion-independent patients (p = 0.08 and p = 0.24 for OS and NRM, respectively), while post-transplantation outcome was significantly worsened in patients receiving 21-40 PRBC units (p = 0.002 and p = 0.015 for OS and NRM, respectively) and more than 40 PRBC units (p < 0.001 and p < 0.001 for OS and NRM, respectively).

An analysis of the 96 patients with a diagnosis of MDS according to WHO criteria showed that transfusion burden has a significant effect on NRM (HR = 1.56, p = 0.023) and a borderline effect on OS (HR = 1.39, p = 0.063).

Finally, we carried out a multivariate logistic regression analyses for the presence of acute and of chronic GVHD using recipient age, presence of transfusion-dependency, source of hematopoietic stem cell and type of donor as covariates. Transfusion-dependency was found to be an independent risk factors for developing aGVHD grades II to IV (p = 0.04), while no significant effect on the occurrence of cGVHD was noticed.

**Post-transplantation outcome according to serum ferritin level**

We evaluated the impact of secondary iron overload as assessed by serum ferritin level on the outcome of transfusion-dependent MDS patients receiving myeloablative allo-SCT. Pre-transplantation serum ferritin level was available in 129 out of 135 patients (median value of 1270 ng/mL, range 547-11800). A significant correlation was seen between the number of PRBC units received before allo-SCT and serum ferritin level (r = 0.46, p < 0.001).

In order to verify whether increased ferritin level was expression of iron overload in transfusion-dependent patients, we analysed the percentage of transferrin saturation that had a median value of 86% (range 58-100). Transfusion-dependent patients were grouped on the basis of serum ferritin concentration as follow: serum ferritin <1000 ng/mL (47 patients, 36%), 1000-1999 ng/ml (55 patients, 43%), 2000-3000 ng/mL (17 patients, 13%) and >3000 ng/mL (10 patients, 8%).

Pre-transplantation ferritin level showed a significant effect on OS (HR = 1.40, p = 0.01) and NRM (HR = 1.42 p = 0.03) in a multivariate analysis including WHO category, cytogenetics, ANC, hemoglobin and platelet level, age of recipient, disease stage at transplantation, source of hematopoietic stem cells and type of donor as covariates (Figure 3). No significant effect on probability of relapse was found.

After adding transfusion burden (number of PRBC units) and transfusion duration to the model, the effect of serum ferritin was maintained on both OS and NRM (HR = 1.47 p = 0.038 and HR = 1.54 p = 0.04, respectively). A trend toward significance of transfusion burden on post-transplantation outcome was also detected (OS HR = 1.34 p = 0.10 and NRM HR = 1.48, p = 0.09).

Limiting the analysis on transfusion-dependent patients with a diagnosis of MDS according to WHO criteria serum ferritin level showed a negative effect on NRM (HR = 1.44, p = 0.04), while a borderline significance on OS was seen (HR = 1.39, p = 0.07).

In order to account for the possible role of ferritin as
an acute-phase reactant, we included pre-transplantation serum albumin in the model, and we found that the impact of ferritin on outcome was unchanged (data not shown). Finally, by applying the same multivariate analysis to transfusion-dependent patients receiving RIC, no significant effect of pre-transplantation serum ferritin on OS (HR = 1.03, p = 0.61) and NRM (HR = 1.11, p = 0.28) was observed.

**Discussion**

We previously showed that transfusion-dependent MDS patients may have a reduced survival after transplantation, and that WPSS, which includes transfusion as a prognostic variable, is able to stratify post-transplantation outcome in MDS. The present study had a wider scope. The analysis was focused on a more recent and restricted period, in which transplant procedures have been more homogeneous and data registration more complete and accurate. Moreover, the clinical effect of additional parameters such as pre-transplantation transfusion burden, duration and serum ferritin level was assessed. We clarified that the negative impact of transfusion-dependency is associated with an increased risk of NRM, while no significant effect was seen on the probability of relapse. The effect of transfusion-dependency was restricted to MDS patients receiving a myeloablative conditioning regimen that are at higher risk of developing transplant-related toxicity, whereas no significant effect was noticed in patients receiving RIC. An inverse relationship was seen between transfusion burden and probability of surviving after transplantation: post-transplantation outcome was comparable between patients receiving <=20 PRBC units and transfusion-independent patients, but was significantly worse in subjects with a long history of transfusion-dependency. We also found that the negative effect of transfusion history on post-transplantation outcome might be related at least in part to secondary iron overload.
In MDS, the presence of transfusion-dependency has already been shown to have negative prognostic value due to the concomitant effect of more severe anemia, more aggressive disease and secondary iron overload.\textsuperscript{23,24} Recently, an elevated pre-transplantation serum ferritin level was found to be associated with reduced survival in patients with MDS.\textsuperscript{25-27} Nevertheless, these studies are potentially biased by the fact that they did not take into account transfusion history before transplantation. It is very important to clarify whether high ferritin levels at the time of transplant were due to transfusions or inflammation: in fact, these two clinical conditions are quite different in terms of biological characteristics and, more importantly, of iron metabolism.\textsuperscript{28}

The prognostic effect of transfusion-dependency, the relationship between transfusion burden and TRM but not relapse rate, the selective effect in patients receiving myeloablative conditioning, the escalating effect of transfusion burden, the relationship between serum ferritin and transplantation outcome, the fact that there is no difference between non-transfused and lightly transfused patients, all consistently indicate a direct effect of secondary iron overload on post-transplantation outcome.

Our results also suggest that the presence of pre-transplantation transfusion-dependency might be a risk factor for acute GVHD. It is possible to speculate that the presence of parenchymal iron overload, through a free iron radical-mediated injury, may increase the susceptibility of the organs (in particular in the liver) to GVHD. Available data on the role of iron in organ damage in MDS are limited.\textsuperscript{29} Serum ferritin is the most commonly used indirect estimate of iron overload,\textsuperscript{30,31} and a direct correlation between serum ferritin and the number of transfusion received has been observed.\textsuperscript{32} On average, each PRBC unit adds about 200-250 mg of iron to the total iron pool in the body, and an iron overload can occur after about 20 transfusions.\textsuperscript{33} The presence of hepatic iron accumulation as detected by MRI was recently described in all MDS patients receiving 20 or more red cell units,\textsuperscript{33} and serum ferritin was found to have a significant impact on survival of patients with refractory anemia.\textsuperscript{34}

In this study we observed a significant effect of serum ferritin in transfusion-dependent MDS who underwent a myeloablative allo-SCT. The effect was maintained after adjusting for both transfusion burden and duration. The negative effect of increased serum ferritin levels was mainly noticeable in terms of increased NRM, while no effect on the probability of relapse was seen. The prognostic effect of secondary iron overload was not noticeable in patients receiving RIC, being less exposed to risk of NRM with respect to those receiving a standard conditioning regimen.

Single determination of serum ferritin as a marker of iron overload should be considered with some caution due to its concomitant role as acute-phase reactant.\textsuperscript{35,36} However, we found that the prognostic effect of serum ferritin is unlikely to depend substantially on acute-phase issues. Moreover, when considering transferrin saturation for defining the site of iron accumulation\textsuperscript{37} we observed very high values, suggesting the presence of parenchymal iron loading in transfusion-dependent patients.

There are potential sources of bias in our analysis, inherent to the retrospective nature of a study based on a transplantation registry. However, data about transfusion history and pre-transplantation serum ferritin were available in the great majority of the original patient population, and the analyses were adjusted for all known potential confounding factors by adopting multivariate techniques and/or performing stratified and subgroup analyses.

In spite of these limitations, the findings of this study might have relevant clinical implications.

Our results suggest that transfusion history should be considered in MDS transplantation decision-making, as also indicated by the significant impact of WFSS on post-transplantation outcome.\textsuperscript{15}

For patients candidate to allo-SCT, it is very important to avoid complications related to the presence of transfusion-dependent anemia (such as secondary iron overload), and this might be particularly relevant for younger patients, that usually receive a myeloablative conditioning. A decision analysis from the International Bone Marrow Transplant Registry demonstrated that life expectancy of patients with low-risk MDS was longer when transplantation was delayed by some period.\textsuperscript{39} However, the additional risk of disease complications that might increase transplant toxicity or preclude these patients from transplantation are to be considered when implementing delayed treatment strategies in the clinical practice.

On the other hand, patients with a long history of transfusion and evidence of iron overload at the time of transplant might benefit for a reduced-intensity conditioning regimen, in order to reduce the probability of NRM.

Finally, the results of the present study sustained the rationale to implement a direct evaluation of iron overload and of iron-mediated tissue damage in MDS patients candidate to allo-SCT and to clarify the possible role of chelation therapy in reducing transfusion-related complication on post-transplantation outcome in these patients.

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. Seragno,” 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. Binaghi,” University of Cagliari, Cagliari (G. La Nasa); Division of Hematology and Bone Marrow Transplantation,
Patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation

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Authorship and Disclosures

EPA, MGDP, ABA and ABo designed the research; EPA, MGDP, ABA, LM, EA, MTVL, MF, FO, MB, SG, BL, AR, RC, PM, FP, LP, RF and ABo collected data; EPA, MG DP, AB, LM and CP analyzed and interpreted data; CP and RO performed statistical analysis; EPA, MGDP, ABA, LM and AA wrote the manuscript. The authors indicated no potential conflicts of interest.

This study is a major extension of the work published in Blood 2008;112:895-902. The present analysis is focused on a more recent and restricted period, in which transplant procedures have been more homogeneous and data registration more complete and accurate. The novel data - not reported in the Blood paper - include the clinical effect of pre-transplantation transfusion burden, duration and serum ferritin level on post-transplantation outcome of MDS patients. The results of the present study show that pre-transplantation transfusion history and serum ferritin have a significant prognostic value in MDS patients undergoing myeloablative allo-SCT, inducing a significant increase of NRM, and indicate that these parameters should be considered in transplantation decision-making.


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