Supplements

1. Revised Grading System for Recommendations

The level of evidence was rated according to the Revised Grading System for Recommendations in Evidence Based Guidelines of the Scottish Intercollegiate Guidelines Network Grading Review Group. A recommendation was rated as A when it was based on at least one meta-analysis, systematic review, or randomized clinical trial (RCT) and demonstrating overall consistency of results; B, when it was based on a body of evidence that included systematic reviews of case-control or cohort studies directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from meta-analysis, systematic review, or RCT; C, when it was based on extrapolated evidence from studies rated as systematic reviews of case-control or cohort studies; and D, when it was based on non-analytic studies (e.g. case reports, case series) or expert opinion.

2. Donor selection

Donor-recipient HLA matching, based on high resolution typing, has significantly improved the outcome of transplantation with matched unrelated donors (MUD), leading to outcomes after HSCT similar to those with HLA-matched related donors (MRD). In accordance with these data, retrospective studies from the CIBMTR evaluating outcome after HSCT from matched sibling and unrelated donors did not show significant differences between the two groups. However, MRD had superior relapse-free survival compared with recipients of only 7 of 8 HLA-A, -B, -C, DRB1 matched donors (hazard ratio [HR] 1.47, 95% CI 1.10-1.96).

Other aspects may play a role when considering the donor type for HSCT. A recent study of the EBMT in MDS patients older than 50 years showed that transplantation from younger MUDs (<30 years) was associated with a significantly improved 5-year overall survival in comparison with MRD and older MUDs (>30 years): 40% vs. 33% vs. 24% (P=0.04). The survival benefit utilizing young MUDs was not confirmed by an CIBMTR study, but this study did not analyze the impact of very young (<30 years) and young (between 30 and 50 years) MUDs separately. A recent evaluation on two large cohorts of HSCT with unrelated donors (>6,000) identified increasing donor age and increasing HLA disparity as the only donor characteristics important for survival. The expert panel recommends to consider age, gender and CMV status of donor during the donor selection process and to follow the recently formulated donor suitability criteria (recommendation level C).

Other donors, including cord blood donors, HLA haplo-identical family donors - defined as donors who share one HLA haplotype with the patient, but differ for one or more loci of the unshared HLA haplotype - or other mismatched donors are considered alternative donors. The use of HLA haplo-identical family donor transplants has gained growing acceptance recently.
by the introduction of a novel regimen, incorporating post-transplant high dose cyclophosphamide, tacrolimus and mycophenolate mofetil for prevention of GVHD.\textsuperscript{10}

A limited number of MDS patients have been transplanted from syngeneic donors.\textsuperscript{11} Both in MDS and in other diseases the low toxicity of syngeneic HSCT has compensated for a putative reduction in graft-versus-tumor effect.\textsuperscript{12} The EBMT compared the outcome of 38 MDS patients, who were transplanted from their syngeneic twins, with the outcome to patients who received transplants from their HLA-identical siblings.\textsuperscript{13} A trend for better overall survival was observed in the twin group (36\% versus 32\%, respectively)(p=0.05).

3. Factors of relevance for selection of the source of hematopoietic cells
The role of hematopoietic cell sources in HSCT for MDS has been investigated in retrospective studies.\textsuperscript{14,15} A large, retrospective study, comparing BM and mobilized PB hematopoietic cells from HLA-identical sibling donors in 234 MDS patients, showed a significantly better survival among recipients of PB cells, except for patients with either RA or high-risk cytogenetics.\textsuperscript{15} Improved survival with PB hematopoietic cells compared to BM from HLA-identical sibling donors was also noted for patients with high risk hematological malignancies, including MDS, but not for those with standard risk malignancies by a meta-analysis of nine randomized trials.\textsuperscript{16} In contrast, a prospective phase 3 trial of unrelated donor PB versus BM cells in 551 patients with hematologic neoplasms, including 93 patients with early and advanced MDS,\textsuperscript{17} showed similar rates of acute GVHD, relapse, non-relapse mortality, and overall survival in the two groups, albeit with higher risk of graft failure after BM, and higher risk of chronic GVHD after PB.\textsuperscript{17} HSCT using unrelated cord blood cells has mainly been applied in selected centers in countries with easy access to cord blood cell banks.\textsuperscript{14} The initial positive results of double cord blood cell transplants have not been confirmed in a recently published prospective study comparing single versus double cord transplants using identical transplant regimens in both arms. However, the outcome of both arms was better compared to previous studies.\textsuperscript{18}

4. Factors relevant for selecting the intensity of preparatory regimens

Myeloablative regimens
Hyper-intensive regimens containing higher than conventional doses of TBI are not considered separately in these recommendations because long-term survival was not improved compared to conventional myeloablative regimens.\textsuperscript{19} Conventional myeloablative (MA) regimens typically consist of Cy and TBI or Bu with Cy or fludarabine.\textsuperscript{20} Most studies in patients with MDS report equivocal outcome after commonly used MA regimens\textsuperscript{20,21}, but targeted intravenous BU containing regimens might be associated with better relapse-free survival, despite a higher relapse risk in patients with RAEB.\textsuperscript{22} The combination of treosulfan and fludarabine has been tested in several small phase 2 studies.\textsuperscript{23} Some regimens contain intervals of several days between the various components, such as the FLAMSA-MEL protocol, but the available information in MDS is limited.\textsuperscript{24}
**Reduced intensity regimens**

Intermediate intensity or reduced intensity conditioning (RIC) and non-myeloablative (NMA) regimens are not considered separately, since the number of patients with MDS, transplanted with the NMA regimens, is too limited to allow adequate analysis. However, in the larger CIBMTR study, which included also AML patients, NMA (396 patients) regimens were associated with decreased OS and DFS when compared to 3,659 patients transplanted, utilizing MA regimens (HR: 1.28, 95% CI, 1.12–1.45; P <0.001). A retrospective analysis in patients aged 60 to 70 years showed that performing HSCT after RI regimens appeared beneficial (longer survival and better quality of life) in de novo higher risk MDS when compared to treatment with HMA. Many retrospective studies have assessed the value of RIC compared with MA regimens in patients with MDS. These studies showed significantly increased relapse rates after RIC when compared to patients transplanted after MA regimens, but decreased non-relapse mortality in the RI cohorts, resulting in a comparable overall survival of both groups.

Some retrospective studies comparing MA with RIC did not observe a difference in survival when patients were transplanted in CR1, while none of the patients transplanted with active disease survived after RIC. Additionally, the MRD level of patients in morphological remission before HSCT, may influence the outcome after HSCT depending on the intensity of conditioning. MRD was determined by FCM and cytogenetics in 219 patients in morphologic remission pre-HSCT, but 154 (54%) were MRD positive, whereas 65 (23%) were MRD negative. The impact of MRD on outcome was significantly different between patients who received RI regimens and patients who received a MA regimen. The impact of a positive marker for MRD by cytogenetics was more detrimental after RIC than the presence of such a marker among patients who received a MA regimen.

Table: Overview of transplant preparatory regimens

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<th>Type of regimen</th>
<th>Description</th>
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<tr>
<td>Conventional myeloablative (high) intensity (MA) regimen</td>
<td>Standard dose total body irradiation (TBI) (&gt;500 cGy, single dose or &gt;800 cGy fractionated dose) with or without standard dose cyclophosphamide (Cy) or fludarabine (Flu); busulphan (Bu) and Cy/Flu in standard doses (Bu: ≥9 mg/kg orally or equivalent intravenous dose); melphalan &gt;150 mg/m² ± other agents. new regimens, including treosulfan (42 g/m²) and fludarabine (Flu: 150 mg/m²)</td>
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<tr>
<td>Intermediate, reduced intensity conditioning (RIC)</td>
<td>Reduced TBI dose &gt;200 cGy and &lt;500cGY single dose or fractionated TBI dose &lt;800cGY ± other reduced Cy/Flu; reduced dose of Bu ≤8 mg/kg oral dose or equivalent intravenous dose combined with reduced dose of Cy/Flu; melphalan: ≤150 mg/m² total dose combined with reduced dose Cy/Flu</td>
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Non myeloablative (low) intensity (NMA) regimen

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<th>Preparative regimens in special situations (other)</th>
<th>ATG or alemtuzimab containing regimens for HSCT with cord blood cells or unrelated donors; T-cell depleted HSCT or high dose cyclophosphamide after HSCT for transplants with HLA haplo-identical family donors.</th>
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### 5. Monitoring and prevention/treatment of iron overload

Assessment of serum ferritin is the most convenient and frequently performed test for iron overload in this setting. Serum ferritin levels may be unreliable because of various concomitant inflammatory conditions. Magnetic resonance imaging (MRI) technology is becoming increasingly available as a diagnostic tool in this setting. New MRI techniques, such as FerriScan®, might be appropriate for liver iron determination. Myocardial T2* (mT2*) is now the most commonly used method to detect myocardial iron. A strong association was observed between pre-transplantation serum ferritin levels and lower overall survival, especially in patients with MDS and acute leukemia. In a prospective study of 45 MDS and acute leukemia patients, who received HSCT after myeloablative conditioning, serial measurements of liver and heart iron by MRI did not show significant relation between pre-transplant liver iron and outcome and no significant increases of liver and cardiac iron after HSCT, in contrast to several other studies. Alessandrino et al showed an inferior survival probability and increased TRM in patients who were transfusion dependent prior to HSCT. The same group confirmed in a more recent study the negative prognostic impact of a transfusion history and an even worse outcome in subjects having received more than 20 RBC units prior to their myeloablative HSCT. The expert panel could not recommend a specific method to evaluate iron overload in the transplant setting. Ferritin levels may be predictive for survival, but confounding variables may obscure the impact of ferritin levels in determining the level of iron overload.

Phlebotomies in a single center cohort of 61 transplant recipients were well tolerated and resulted in a negative iron balance and a rise in hemoglobin levels in the majority of patients. Phlebotomy treatment was initiated relatively early after HSCT. Iron chelation after HSCT with deferasirox in relatively low dosages appeared feasible in a prospective efficacy and safety study of 76 patients confirming the results of a smaller study in 30 patients. Several retrospective studies in patients treated after HSCT with deferoxamine, the classical parenteral iron chelator, showed a reduction of relapse after HSCT and a better survival. Another study evaluated the role of deferasirox in the treatment of iron overload in 43 patients, selected from a larger group of 80 patients, who served as controls. The treated group was too highly selected for interval between treatment and AHCT and for other variables, to allow objective evaluation.


