Review Article

blood

Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel

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An international expert panel, active within the European Society for Blood and Marrow Transplantation, European LeukemiaNet, Blood and Marrow Transplant Clinical Trial Group, and the International Myelodysplastic Syndromes Foundation developed recommendations for allogeneic hematopoietic stem cell transplantation (HSCT) in myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). Disease risks scored according to the revised International Prognostic Scoring System (IPSS-R) and presence of comorbidity graded according to the HCT Comorbidity Index (HCT-CI) were recognized as relevant clinical variables for HSCT eligibility. Fit patients with higher-risk IPSS-R and those with lower-risk IPSS-R with poor-risk genetic features, profound cytopenias, and high transfusion burden are candidates for HSCT. Patients with a very high MDS transplantation risk score, based on combination of advanced age, high HCT-CI, very poor-risk cytogenetic and molecular features, and high IPSS-R score have a low chance of cure with standard HSCT and consideration should be given to treating these patients in investigational studies. Cytoreductive therapy prior to HSCT is advised for patients with ≥10% bone marrow myeloblasts. Evidence from prospective randomized clinical trials does not provide support for specific recommendations on the optimal high intensity conditioning regimen. For patients with contraindications to high-intensity preparative regimens, reduced intensity conditioning should be considered. Optimal timing of HSCT requires careful evaluation of the available effective nontransplant strategies. Prophylactic donor lymphocyte infusion (DLI) strategies are recommended in patients at high risk of relapse after HSCT. Immune modulation by DLI strategies or second HSCT is advised if relapse occurs beyond 6 months after HSCT. (*Blood*. 2017;129(13):1753-1762)

Introduction

Despite improved understanding of the molecular pathogenesis of myelodysplastic syndromes (MDS), currently available therapeutic agents lead to prolongation of life and no cure.[1] Therefore, allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a curative treatment option.[2] This increase in HSCT activity can be attributed largely to the introduction of reduced-intensity (RI) regimens that have extended the indication for HSCT to patients with comorbidities or reduced fitness. The ever increasing use of unrelated or mismatched family donors also contributes to the frequent use of HSCT in MDS.[3] Several factors have to be considered in the decision process of "how to select MDS patients as suitable candidates for HSCT." These can be classified into patient-related and disease-related factors.

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The online version of this article contains a data supplement.

Table 1. Prognostic risk factors relevant for HSCT eligibility and for outcome after HSCT

Prognostic risk factor	Tools to measure risk factors in patients with MDS	Outcome after	
		Nontransplant interventions, including supportive care	HSCT
Patient related			
Age (chronological)	Calendar, IPSS-R[20]	Age influences prognostic impact of disease-related factors[20]	Impact age influenced by other patient-related factors[15]
Performance status (functional ability)	Karnofsky status ≥ 80%		Better survival after HSCT[15]
Frailty (reduced physical fitness)	Specific tools have to be tested in HSCT[117]		Fit patients better outcome[12,16-18]
Comorbidities	HSCT-specific CI (HCT-CI)[14]		Low CI better outcome[13]
Disease related			
Percentage of marrow blasts	IPSS(-R), WPSS, WHO[20,21]	Related to prognosis[20,21]	Only impact if <5% marrow blasts[22]
Cytogenetic risk groups	IPSS(-R), WPSS, CPSS[20,21,44]	5 prognostic groups[19]	Only very-poor-risk[29] and monosomal karyotype[30]
Severity of cytopenias	IPSS(-R), WPSS[41,42]	IPSS-R better prediction of prognosis compared with IPSS[42]	Only very-poor-risk group of IPSS-R prognostic
Marrow fibrosis	WHO criteria[51]	Severity fibrosis prognostic[51]	Severity fibrosis prognostic[52]
Transfusions burden	WPSS[41,63]	WPSS[41]	WPSS[64]
FCM	ELN FCM score[25,27]	ELN FCM score[24]	Not validated yet[27]
Molecular mutations	No specific tools yet[34]	Mutations in RUNX1, U2AF1, ASXL1, TP53, and others: poor prognosis[34]	Mutations in TP53, EZH2, ETV6 poor prognostic[23,35]
Disease status (after nontransplant treatment interventions)			
ESA failure	High Epo levels, high transfusion intensity[6,68]	High Epo levels, high transfusion intensity[6,68]	No direct impact reported
Lenalidomide failure	Absence of $5q^{-}$[5]	Absence of $5q^{-}$[5]	No direct impact reported
HMA failure	HMA-therapy–specific risk score[71]	HMA-therapy–specific risk score,[71] complex karyotype[118] TET2 and TP53 mutations[72,73]	Best available treatment after HMA failure,[76] but response status prognostic factor
ICT	MDS-specific risk score[4]	MDS-specific risk score[4]	Best available treatment available after failure of first-line ICT,[70] but response status and remission duration prognostic factor[31]

These factors may determine response to treatment modalities, including intensive chemotherapy (ICT),[4] hypomethylating agents (HMAs), immunomodulatory agents, such as lenalidomide,[5] and hematopoietic growth factors.[6]

The Chronic Malignancies Working Party (CMWP) of the European Blood and Marrow Transplant Society (EBMT) has developed an initiative to refine and update the general international guidelines[7,8] for patients with MDS who are potential candidates for HSCT. Using the information from the general MDS guidelines,[7,8] an expert task force developed HSCT scenarios for patients with MDS, which were evaluated and discussed by a panel of experts during several consensus meetings. This international expert panel, consisting of members of the European Society for Blood and Marrow Transplantation, European LeukemiaNet, the Blood and Marrow Transplant Clinical Trial Group, and the International Myelodysplastic Syndromes Foundation, developed the recommendations presented in this article.

Design and methods

The task force has followed the procedures used for the development of the current European Leukemia Net (ELN) MDS guidelines.[7] Consensus development for the recommendations of the guidelines was based on a systematic literature review and scenario analysis by 32 transplant and nontransplant MDS experts from Europe and the United States. The first round of scenarios was based on the issues raised in the general ELN MDS guidelines; the second round was based on the outcome of expert suggestions raised during the consensus meetings. The scenarios were considered to have yielded a consensus when more than two-thirds of the experts agreed and the remaining experts accepted the proposed scenario. 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 (supplemental Data Section 1, see supplemental Data available at the *Blood* Web site).[9] Patients in certain scenarios might have a dismal outcome either with or without HSCT. These patients might be recommended for HSCT in clinical trials.

General structure of the recommendations

The expert panel assumed that the diagnostic approaches and the nontransplant strategies in individual patients followed the recommendations of the general diagnostic guidelines.[7,8] The expert panel agreed to avoid topics dealing with general issues around HSCT, pertaining to all indications including MDS. We analyzed the impact of the individual components of the current risk-scoring systems because these variables might have different impact on outcomes after ICT, HMA, and HSCT (summarized in Table 1). Several HSCT approaches are available: HSCT immediately after diagnosis or delayed transplantation after progression of disease or after failure of nontransplant strategies. HSCT may be performed without reduction of disease burden prior to conditioning or after cytoreduction. The general transplantation risk index defined by Armand et al[10] and the EBMT transplantation risk score,[11] might not be sufficiently specific for MDS because specific risk categories, including percentage of marrow blasts, cytogenetic risk groups, and severity of cytopenias are lacking. The ELN and the National Comprehensive Cancer Network (NCCN) formulated the general recommendation for HSCT at diagnosis based on the International Prognostic Scoring System (IPSS).[7,8] The panel recognized the disease risk scored according to the revised IPSS (IPSS-R) and Comorbidity Index (CI), graded according to the Hematopoietic Cell

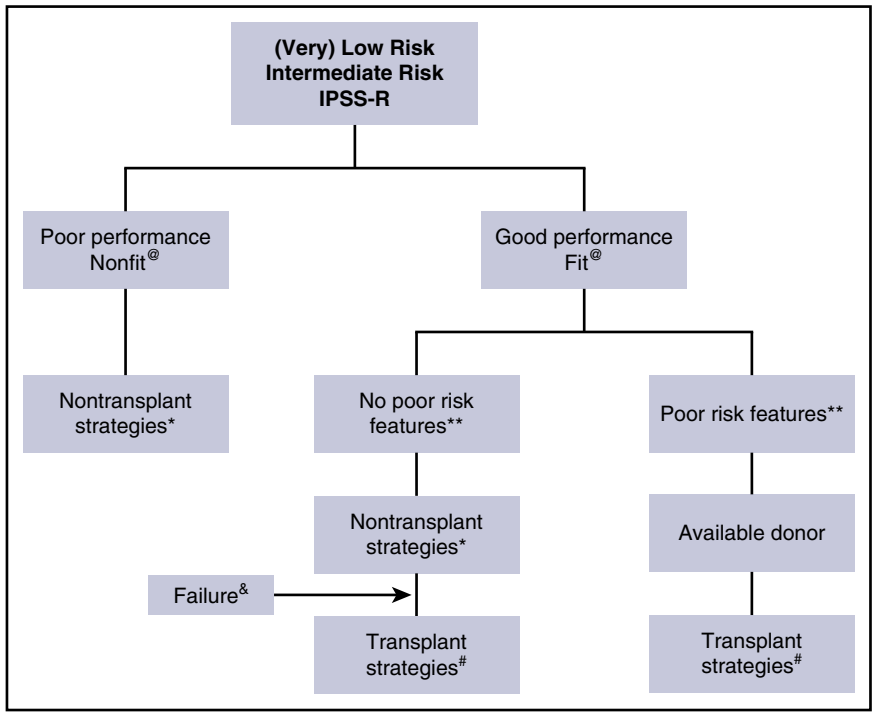

Figure 1. Therapeutic algorithm for adult patients with MDS and (very) low-risk or intermediate IPSS-R risk scores. @ indicates nonfit (patients with multiple comorbidities and/or poor performance) or fit (patients with no comorbidities and good performance status). * indicates nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN. & indicates failure of nontransplant strategies (for details of various nontransplant interventions [transfusions, ESAs, lenalidomide, and cytoreductive therapy], see "Timing of transplantation." Nontransplant interventions may include >1 line of nontransplant intervention, eg, treatment with ESAs, followed by lenalidomide in patients with 5q−). ** indicates poor-risk features (defined as poor-risk cytogenetic characteristics, persistent blast increase [>50% or with >15% BM blasts], life-threatening cytopenias [neutrophil counts, $<0.3 \times 10^9$/L; platelet counts, $<30 \times 10^9$/L], high transfusion intensity ≥2 units per months for 6 months; molecular testing should be seriously considered, in case of absence of poor-risk cytogenetic characteristics or persistent blast increase). # indicates transplant strategies (all forms of HSCT, for details of donor selection, type of conditioning and posttransplant strategies, see text; no upper age limit if patients are fit, without serious comorbidity and good Karnofsky status). @ indicates donor availability (the improved outcome of HSCT with haploidentical donors utilizing posttransplant cyclophosphamide increases the donor availability).

Transplantation–Comorbidity Index (HCT-CI), as the most relevant clinical variables for patients for HSCT eligibility. In the following sections, we will discuss factors that need to be considered for HSCT recommendations.

Specific recommendations

Risk factors

Patient characteristics. Age,[12] performance status (functional ability), frailty (reduced physical fitness or physical reserve), and comorbidities[13] are important patient-related factors which determine outcome after HSCT. Prognostic tools, including performance status (eg, Karnofsky score) and HSCT-specific CI (HSCT-CI),[14] show a strong prognostic impact on outcome, independently of disease characteristics. The impact of age per se is less evident, if other factors, including HSCT-CI are considered appropriately.[15] A recent study[16] showed that higher-risk patients, aged 60 to 70 years, benefit from transplantation after RI regimens. All fit patients without comorbidities should be considered for HSCT, provided that disease-related factors allow the recommendation for HSCT (Figures 1 and 2)[12,16-18] (recommendation level C). Nonfit higher-risk MDS patients with multiple comorbidities and/or reduced performance status are generally not candidates for HSCT, but these patients may be considered for HSCT in clinical trials (recommendation level D).

Disease-related factors. The IPSS-R is an age-adjusted risk score and is based on 3 parameters: percentage of marrow blasts, modified cytogenetic risk groups,[19] and the severity of cytopenias.[20] The IPSS-R can be simplified into 3 risk groups when considering HSCT as a treatment option: lower risk (low and very-low IPSS-R risk), intermediate risk, and higher risk (high and very-high IPSS-R risk).

Percentage of BM myeloblasts and flow cytometric characteristics. The percentage of bone marrow (BM) myeloblasts is incorporated into all current prognostic scoring systems in MDS.[20,21] However, the overall survival of MDS patients, primarily treated with HSCT, is not significantly influenced by the percentage of myeloblasts, except for patients with <5% myeloblasts who showed a better outcome.[22] No consensus was reached as to whether intermediate-risk patients with myeloblasts between 5% and 10% should be considered for HSCT immediately after diagnosis or after development of additional risk factors.[23] General consensus was obtained concerning the indication for HSCT early after diagnosis in fit, higher-risk patients if myeloblasts exceed 10% (recommendation level C).

Flow cytometry (FCM) may be used in addition to general risk assessment, choice of therapy, and monitoring of disease activity in adult patients with MDS.[24,25] The severity of pretransplantation flow cytometric aberrancies on marrow cells correlated with posttransplantation relapse in 1 study.[26] Widespread clinical implementation of FCM is still lacking, despite published standardization protocols.[27]

Cytogenetic characteristics. The new cytogenetic risk classification[19,28] has prognostic significance following HSCT. The very-poor-risk category predicts for increased mortality and relapse following HSCT.[29] The presence of complex karyotype abnormalities, monosomal karyotype or both predicted inferior survival after HSCT in MDS patients.[30] A recent study in 903 MDS patients showed poor survival in the IPSS-R cytogenetic poor-risk group in combination with monosomal karyotype.[31] The cytogenetic classification in IPSS-R has changed the prognostic impact of some cytogenetic subcategories. For example, del (7q) as a single abnormality is classified as intermediate cytogenetic risk, which implies that such a patient may qualify as a low-risk patient. No consensus was reached as to whether this patient should be proposed for HSCT immediately after diagnosis.

Molecular characteristics. Molecular characteristics significantly impact on the prognosis of MDS.[23,32,33] MDS associated with SF3B1 mutations[34] form a distinct entity with a favorable prognosis. DNMT3A, TET2, IDH1, and IDH2 are associated with multilineage dysplasia.[34] SRSF2, RUNX1, U2AF1, ASXL1, and TP53 mutations are associated with poor prognosis.[34] Bejar et al[23] reported prognostic significance for EZH2 and ETV6 mutations in a study of 87 allograft recipients.[35] TP53 mutations and especially the combination of complex karyotype and TP53 mutations resulted in very-poor outcome

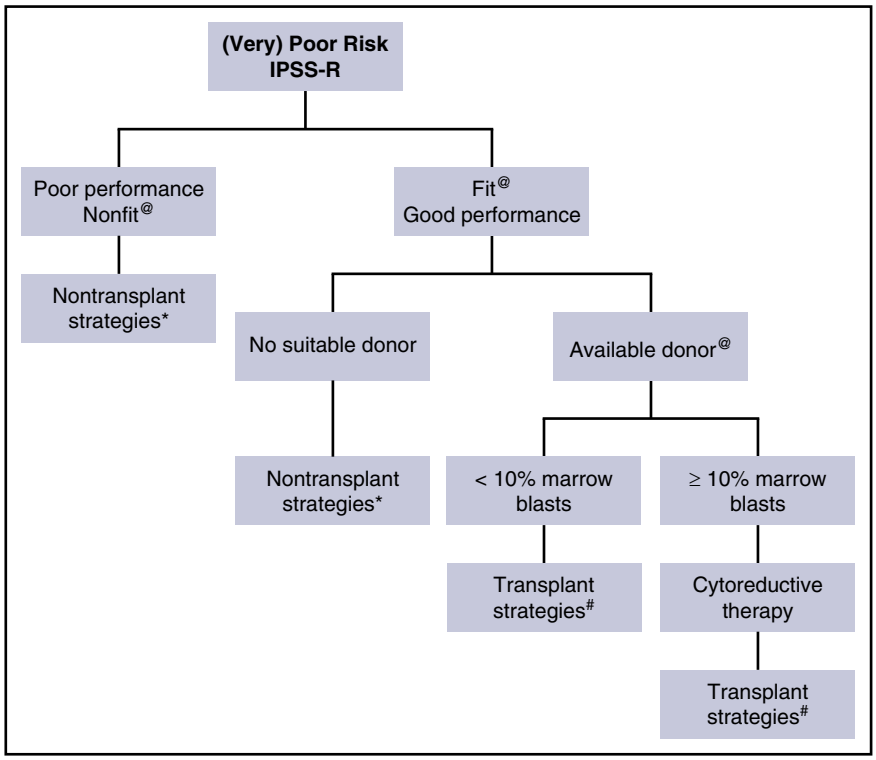

Figure 2. Therapeutic algorithm for adult patients with MDS and poor IPSS-R scores. @ indicates nonfit (patients with multiple comorbidities and/or poor performance) or fit (patients with no comorbidities and good performance status). * indicates nontransplant strategies according to most recent versions published by international MDS expert groups, including ELN and NCCN. & indicates failure of nontransplant strategies (for details of various nontransplant interventions [transfusions, ESAs, lenalidomide and cytoreductive therapy], see "Timing of transplantation." Nontransplant interventions may include >1 line of nontransplant intervention, eg, treatment with ESAs, followed by lenalidomide in patients with 5q−). ** indicates poor-risk features (defined as poor-risk cytogenetic characteristics, persistent blast increase [>50% or with >15% BM blasts], life-threatening cytopenias [neutrophil counts, $<0.3 \times 10^9$/L; platelet counts, $<30 \times 10^9$/L], high transfusion intensity ≥2 units per months for 6 months; molecular testing should be seriously considered, in case of absence of poor-risk cytogenetic characteristics or persistent blast increase). # indicates transplant strategies (all forms of HSCT, for details of donor selection, type of conditioning and posttransplant strategies, see text; no upper age limit if patients are fit, without serious comorbidity and good Karnofsky status). @ indicates donor availability (the improved outcome of HSCT with haploidentical donors utilizing posttransplant cyclophosphamide increases the donor availability).

after HSCT.[35] A recent study in 401 patients who received HSCT for MDS or MDS/acute myeloid leukemia (AML) showed that somatic mutations in ASXL1, RUNX1, or TP53 were independently associated with unfavorable outcomes and shorter survival after allogeneic HSCT for patients with MDS and MDS/AML.[36] A high prevalence of SRSF2 mutations has been reported in patients with chronic myelomonocytic leukemia (CMML) with concurrent TET2 or ZRSR2 mutations, but only ASXL1 mutations retained their prognostic significance in a multivariate prognostic score.[37,38] A large Center for International Blood and Marrow Transplant Research (CIBMTR) study (in total 1514 patients) presented at the 2016 American Society of Hematology (ASH) annual meeting reported relevant new findings. RAS pathway mutations and JAK2 mutations were associated with a poor outcome after allogeneic HSCT, independently of TP53 mutations in patients older than 40 years.[39] HSCT in clinical trials may be considered for patients with ASXL1, RUNX1, RAS pathway and JAK2, and especially TP53 mutations. The relatively poor survival after HSCT suggests that new transplantation strategies must be developed for these patients, including posttransplant strategies to prevent relapse (Recommendation level D).

Cytopenias, including RBC transfusion dependence. The presence and the degree of cytopenias contribute to the IPSS-R classification risk score.[20] Symptomatic, severe cytopenias refractory to growth factors or requiring intensive red blood cell (RBC) transfusion support may be independent indications for HSCT. Usually, this indication requires observation time (see "Timing of transplantation").

WHO classification, WPSS, IPSS, and IPSS-R. The World Health Organization (WHO) classification has been updated recently,[40] but its contribution to the outcome in relation to HSCT recommendations has not been evaluated yet. The WHO classification-based prognostic system (WPSS) uses a previous version of the WHO classification.[41] A recent study showed that IPSS-R provided better prediction of survival after HSCT compared with IPSS.[42] The IPSS-R changed the risk groups in about 65% of patients.[42] Patients with a very-high-risk score (>4 points) based on age, CI, monosomal karyotype, and IPSS-R[42] appear to have a low cure rate by HSCT and should be considered for investigational studies (recommendation level C).

Other subtypes of MDS

Chronic myelomonocytic leukemia. The 2008 WHO classification distinguishes 2 different types of CMML based on percentage of blasts and promonocytes in peripheral blood (PB) and BM.[43] The panel agreed to use the CMML-specific scoring system (CPSS)[44] for the recommendation of HSCT for CMML patients, but IPSS-R may also be used for patients with the dysplastic type of CMML. From a recent large retrospective analysis on 513 CMML patients, treated with HSCT, it appears that achievement of a better remission state before HSCT is the most important prognostic factor for a favorable outcome.[45] The experts agreed to recommend upfront HSCT in cases of CPSS intermediate-2 or high risk (recommendation level D). Many experts would consider pretreatment with HMA in cases of CMML-2 and an indication for HSCT, preferably early after diagnosis, but evidence from prospective clinical trials and retrospective analyses is lacking.

Treatment-related MDS. The prognosis of treatment-related MDS (t-MDS) is generally worse compared with de novo MDS.[46] The CIBMTR analyzed a series of 323 t-MDS patients treated with HSCT.[47] Age >35 years, poor-risk cytogenetics, advanced t-MDS, and alternative donors were negative prognostic factors for post-HSCT outcome. The major cause of failure after HSCT was nonrelapse mortality (NRM).[48] The 5-year relapse-free survival in this group of 257 patients with t-MDS/transformed AML was 29%. Multivariate analyses failed to show significant differences in outcome, when the t-MDS cohort was compared with a cohort of 339 patients who received HSCT for de novo MDS/transformed AML.[49] Overall survival rates improved significantly ($P < .001$) per calendar year in a large cohort (461 patients) due to a marked reduction in NRM.[50] The expert panel agreed that recommendations for HSCT in patients with t-MDS should

follow the recommendations developed for de novo MDS/transformed AML (recommendation level D).

MDS with BM fibrosis. MDS patients with marrow fibrosis usually have pancytopenia. The IPSS-R classification can be used to assess prognosis, but the severity of BM fibrosis should also be considered.[51] The outcome of HSCT was analyzed among 721 patients with known BM histology at time of HSCT.[52] The degree of fibrosis did not correlate with disease status nor abnormal cytogenetics. The 3-year survival in this study was 49%, 40%, and 21% in patients with no, mild/moderate, or severe BM fibrosis, respectively.[52] Patients with MDS and marrow fibrosis should be considered for HSCT before development of severe marrow fibrosis (recommendation level D).

Hypoplastic MDS. Hypoplastic MDS has distinct features when compared with other MDS types with low blast infiltration in the marrow, but the distinction between severe aplastic anemia and severe hypoplastic MDS might be difficult, especially in the absence of specific cytogenetic abnormalities or molecular genetic markers.[53] In general, the IPSS risk score does predict survival well in hypoplastic MDS patients.[54] A minority of patients with hypoplastic MDS may respond to immunosuppression.[55] The timing of HSCT depends on the severity of cytopenias, the intensity of RBC transfusions, and the probability of response to immunosuppression (for details, see "Timing of transplantation").

MDS originating from inherited germ line mutations. These forms of MDS should be considered in young patients (<40-50 years) with a (family) history of dyskeratosis congenita, Fanconi anemia (FA), Shwachman-Diamond Syndrome, Diamond-Blackfan anemia,[56] and GATA2 mutations.[57,58] Specific germ line mutations and mutations in the genes of the telomerase complex may occur more frequently in these disorders.[56,57] These patients may be candidates for HSCT at an early stage and should be referred to specialist centers in view of the specific sensitivity to conditioning in some of these syndromes (eg, FA) and the selection of family donors who may carry the involved mutation (recommendation level C).

MDS with multilineage dysplasia defined by WHO2008. Refractory cytopenia with multilineage dysplasia (RCMD) is an accepted subtype according to the 2008 WHO classification.[43] The prognosis of patients with RCMD is similar to the prognosis of other MDS patients with <5% marrow blasts, bearing in mind the prognostic impact of individual cytogenetic[59] and molecular characteristics.[34] The expert panel agreed that the recommendations for HSCT in RCMD should follow the recommendations for MDS without MD, taking into account the established risk factors, including genetic risk factors (recommendation level D).

Donor selection

Potential stem cell donors include standard donors, such as HLA-matched siblings, syngeneic donors and matched (8 of 8) unrelated donors, and alternative stem cell donors, including umbilical cord blood donors. Selection of stem cell donors for patients with MDS has improved markedly during the last 2 decades similar to other indications for HSCT (supplemental Data Section 2). The expert panel agreed to accept as standard donors: HLA-identical siblings (including 1 class I[A/B] mismatch), syngeneic donors and 8 of 8 (or 10 of 10) matched unrelated donors (MUDs; recommendation level D). In addition, the expert panel recommends considering age, sex, and cytomegalovirus (CMV) status of donors during the donor selection process and to follow the recently formulated donor suitability criteria (recommendation level C; supplemental Data Section 2).[60]

Alternative donor transplants may be considered for higher-risk and fit patients, for whom no matched sibling donor or MUD can be identified within a reasonable search period (recommendation level D).

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,[61,62] similar to other indications for HSCT (supplemental Data Section 3). The source of hematopoietic cells should not influence the preferred preparation for MDS patients with an accepted indication for HSCT (recommendation level C).

Timing of transplantation

Poor-risk factors incorporated in prognostic scores. Usually, lower-risk patients at diagnosis according to IPSS-R remain lower risk over time, whereas the prognosis in higher-risk patients showed a decreasing risk.[63] The timing of HSCT has been studied using Markov models in several retrospective studies.[64-66] Delay of HSCT in lower-risk MDS patients is associated with the best achievable life expectancy, whereas conflicting findings were reported for intermediate-1 risk (IPSS) patients. Superior survival was observed when HSCT was delayed for intermediate-1 IPSS patients,[65] whereas another study[64] showed better survival in intermediate-1 risk patients when HSCT was performed at diagnosis. In patients with lower-risk disease, HSCT may be best carried out when progression occurs to intermediate-1 risk (by IPSS) or intermediate risk by WPSS.[64] Several poor-risk factors, including frequent RBC transfusions (≥2 units per month), life-threatening cytopenias (neutrophil counts, $<0.3 \times 10^9$/L or platelet counts, $<30 \times 10^9$/L) and very-poor prognostic cytogenetic markers might be identified both in lower-risk and in intermediate-risk patients and justify HSCT early after diagnosis (Figure 1). In the remaining patients, HSCT may be proposed after a change in prognosis. However, in a study of 374 patients with refractory anemia (RA) and no progression, survival was improved in patients transplanted <1 year from diagnosis.[67] The panel agreed that deterioration of cytopenias, which does not affect the IPSS-R classification, should not necessarily imply a recommendation to proceed to HSCT (recommendation level D). If an increase of myeloblasts leads to a more advanced-risk group by IPSS-R, the expert panel recommended proceeding to HSCT (recommendation level C) (Figure 2). Patients become candidates for HSCT if additional cytogenetic aberrations lead to more advanced-risk classification (recommendation level C).[64]

Poor-risk factors not included in IPSS-R. Transfusion dependence has been recognized as a prognostic factor in the original WPSS.[41] The gain in life expectancy was 4 years when HSCT was performed in MDS patients with intermediate risk according to WPSS, in contrast to patients considered intermediate-1 risk according to IPSS.[64] The difference between the 2 risk classifications is mainly based on the consideration of multilineage dysplasia and transfusion dependency. These differences may not play a role when using IPSS-R because of the weighting of severe anemia (hemoglobin levels <8 g/dL), which is usually associated with transfusion dependency.[20] Progression of anemia, leading to heavy transfusion burden and lack of response to erythropoietin-stimulating agent (ESA) treatment in lower-risk patients should be considered an indication for HSCT. Increase of transfusion frequency, and a cumulative number of transfusions >20 units are frequently considered as an appropriate time point for HSCT, but the expert panel did not reach consensus about the exact timing. Presence and acquisition of poor-risk mutations, such as TP53 mutations, may alter the prognosis at diagnosis or later (for details, see "Risk factors").

Failure of nontransplant strategies. Certain groups of lower-risk MDS patients are likely to respond to specific therapy, including ESAs (low erythropoietin [EPO] levels, low or absent transfusion requirements),[6,68] lenalidomide (presence of 5q−),[5] and RA with ringed

sideroblasts/RCMD with ringed sideroblasts with specific spliceosome mutations.[69] Therefore, these patients are generally considered for HSCT only after failure of these specific treatment options (Table 1; Figure 1). Higher-risk patients often receive cytoreductive or epigenetic-modifying treatment before considering HSCT and referral to a transplant center for various reasons. The recommendations for the selection and timing of patients who have been treated with ICT or HMA will be discussed in this section, taking into account the response to treatment at time of evaluation (complete/partial response, no response or progression after response).

After failure of ICT. The majority of MDS patients, transplanted after ICT, were transplanted after primary or secondary failure of ICT.[70] The 5-year disease-free survival (DFS) of patients transplanted not in complete remission (CR) after ICT was only 18%.[31] Patients with primary failure or relapse after first-line ICT are candidates for HSCT. Direct HSCT after failure of first-line ICT is recommended, if the BM blast percentage is <10% (recommendation level D). Also, patients relapsing within 1 year after reaching CR or showing resistance with higher percentages of marrow blasts are candidates for HSCT, but the preparation for transplantation is less clear. Additional studies are required in these patients (recommendation level D). However, if relapse occurs after prolonged CR-1 (>1 year), remission induction with ICT to induce CR-2 is recommended (recommendation level C). Both standard and alternative donors are recommended for those recipients (recommendation level C).

After failure of HMA treatment. Superior survival after treatment with HMA may be predicted in patients with a HMA therapy-specific risk score (zero points), based on absence of circulating blasts, presence of good-risk cytogenetics and low transfusion requirements (<4 units RBCs per 8 weeks) (Table 1).[71] TET2 or P53 mutations were associated with higher response rates to azacitidine treatment, but this did not translate into improved survival.[72-74] Median survival after failure of HMA therapy is usually <6 months.[75,76] Treatment after azacitidine failure in a study of 277 patients resulted in a median survival of 19 months in 37 patients treated with HSCT. This outcome was significantly superior to that obtained with other treatments or best supportive care only.[76] HMA failure should be considered an indication for HSCT where feasible (recommendation level D).

Factors relevant for the selection of cytoreductive treatment prior to transplant conditioning

Cytoreductive therapy to improve disease stage prior to the start of conditioning for HSCT. Large retrospective multicenter studies have demonstrated that the percentage of BM blasts at the time of transplantation significantly influences outcome after HSCT for MDS.[45,62,77] The retrospective nature of these studies usually leads to significant bias due to patient selection. The expert panel recommended upfront HSCT in higher-risk patients with <10% BM blasts (Figure 2).

Hypomethylating agents. The use of HMAs to prepare MDS patients with an excess of marrow blasts for HSCT has been reported in several retrospective studies.[78,79] The available evidence does not allow specific recommendations on the use of HMA for this purpose outside of clinical trials or prospective registry studies.[7,80,81] These studies need to address several important questions, including which factors could predict benefit from HMA therapy prior to the transplant conditioning and the optimal timing of HSCT. The expert panel did not reach consensus to continue HMA therapy or to propose HSCT if patients reached CR after HMA therapy. However, patients with stable disease after 6 or more courses of HMA therapy are considered candidates for HSCT (recommendation level D).

Intensive chemotherapy. ICT in patients with MDS is associated with considerable toxicity, leading to treatment-related mortality (TRM) up to 16% after intensive remission-induction chemotherapy.[82,83] There was no evidence of a clear benefit in posttransplantation outcome associated with prior ICT for patients with MDS or AML after MDS.[26] However, a prospective study[84] showed a significantly superior survival in the donor group, in cases with intermediate- or poor-risk cytogenetic criteria according to IPSS. A large retrospective study[85] evaluated the impact of cytogenetic risk groups on outcome after upfront HSCT and HSCT in CR after ICT. The outcome of higher-risk MDS patients and poor-risk cytogenetics was inferior when patients were transplanted in CR, compared with comparable patients who received upfront HSCT. Further studies that will randomize patients to ICT vs no ICT are needed to appropriately address the benefit of ICT. The expert panel recommended to transplant higher-risk MDS with poor-risk cytogenetic characteristics in CR after ICT on investigational protocols only.

Usually, AML patients in CR received 1 or more consolidation courses prior to HSCT,[86] but ICT to consolidate CR in MDS patients is less efficient due to early relapses and prolonged hypoplasias.[4] Informative analyses concerning this issue are lacking. The expert panel advised to recommend that MDS patients who have entered CR after ICT proceed to HSCT without further attempts to consolidate CR (recommendation level D), but prospective studies are necessary to evaluate the value of consolidation courses in MDS patients who have entered CR after ICT.

The choice between HMA and ICT. A few retrospective studies have addressed the question, which cytoreductive approach prior to HSCT conditioning is associated with superior outcome.[78,87] The Seattle group compared pretreatment with ICT and HMA.[78] The relapse rates after HSCT for the 2 cohorts were similar after adjustment for several prognostic factors including cytogenetic risk groups, supporting the growing evidence that HMA therapy prior to the conditioning for HSCT might be associated with less toxicity than ICT and may allow for similar outcomes after HSCT. A French study reported on 163 MDS patients[87] who had received either ICT alone, HMA alone, or HMA after ICT. The multivariate analyses revealed no difference between the ICT and HMA pretreated groups.[87] A prospective randomized trial comparing ICT vs HMA therapy before HSCT is now accruing (www.clinicaltrials.gov, identifier NCT01812252).

The expert panel recommended reducing tumor load in fit higher-risk MDS patients with >10% marrow blasts and normal cytogenetics without a preference for ICT or HMA. However, in similar patients with complex karyotype or the approach is less clear (recommendation level D). The panel agreed to propose HSCT in these cases and agreed that cytoreductive therapy might be useful, but the type of cytoreductive therapy remained controversial.

Factors relevant for selecting the intensity of preparatory regimens

The expert panel defined the various preparatory intensities according to the classification used by EBMT[88] and the CIBMTR[89] with some minor modifications (supplemental Data Section 4). Most studies in patients with MDS report equivocal outcome after commonly used myeloablative (MA) regimens.[77,90-93] Many retrospective studies have assessed the value of RI conditioning (RIC) compared with MA regimens in patients with MDS.[12,17,94,95] These studies showed significantly increased relapse rates after RIC when compared with patients transplanted after MA regimens, but decreased NRM in the RIC cohorts, resulting in a comparable overall survival of both groups. Higher-risk patients with good performance status and no comorbidities are candidates for MA regimens, whereas less fit patients or patients

with comorbidities should be considered for RIC schedules (recommendation level C).

The MRD level of patients in 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 remission pre-HSCT, but 154 (54%) were MRD^+, whereas 65 (23%) were MRD^-. 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.[96] The expert panel recommended not to adopt pretreatment decisions based on intensity of planned conditioning, but to focus on posttransplant strategies, including chimerism and/or MRD monitoring, to prevent relapse (see "Posttransplantation strategies"; recommendation level D).

Posttransplantation strategies

Monitoring of mixed chimerism and residual disease. Several techniques can be used to monitor chimerism before and after HSCT to detect single nucleotide polymorphisms between donor and recipients in whole BM and sorted subpopulations.[97-99] Declining donor chimerism or mixed chimerism early after HSCT are usually considered signs of imminent relapse. Monitoring of chimerism in sorted CD34 cells has been used as MRD monitoring after HSCT in MDS.[98] Molecular monitoring after HSCT has been performed retrospectively in 36 MDS/myeloproliferative neoplasm patients. Patients with detectable mutations (ASXL1, CBL, TET2, or NRAS) after HSCT had a higher incidence of relapse than in patients with undetectable mutations.[100]

Prevention and treatment of relapse after HSCT. Relapse remains the leading cause of failure after HSCT,[70,95] especially after RIC.[88,99] Treatment options for MDS relapse after HSCT consist of palliative care, low-dose care, treatment with HMA or ICT, and cellular immunotherapy, either donor lymphocyte infusions (DLIs) or second HSCT. DLIs can be administered prophylactically (pDLI) at time of persisting or declining mixed donor/recipient chimerism[101] or in recipients without signs of graft-versus-host disease (GVHD)[102] or therapeutically in cases of confirmed relapse (DLI). DLI to treat relapsed MDS after HSCT has moderate efficacy with prolonged post-DLI event-free survival ranging from 15% to 31%.[101,103-105] The combination of DLI and azacitidine to treat relapse after HSCT in 154 patients MDS or AML with MDS-related changes showed a promising 2-year survival of 66% ± 10% of the 28 MDS patients with relapse.[106] Cellular immunotherapy for treatment of 147 patients with MDS relapse after HSCT was associated with superior survival, when compared with cytoreductive therapy or supportive care only.[107] Using a different donor than the one used in the first HSCT does not seem to add further benefit.[108] Prophylactic DLI has shown promising results with long-term event-free survival after starting pDLI up to 77%.[102] Increasing doses of azacitidine to prevent relapse in patients at high risk for relapse after HSCT have been tested in a phase 2 study[109] with a median event-free survival of 18 months. A recent study showed that monthly courses of azacitidine after HSCT induced a cytotoxic CD8 T-cell response to several tumor antigens[110] and an improved relapse-free survival.[111] The expert panel recommended in MDS patients with mixed (<90% donor cells) or increasing recipient chimerism (>10% recipient) after HSCT, rapid tapering of immunosuppression followed by pDLI in case of absent GVHD (recommendation level C). The expert panel could not recommend any specific intervention if MDS relapsed clinically within 6 months after HSCT. The panel recommended a type of immune modulation in cases in which relapse occurred beyond 6 months after HSCT. However, more prospective studies are necessary to identify the most appropriate approach for MDS relapsed after HSCT, including studies combining HMAs and DLIs (recommendation level D).

Monitoring and prevention/treatment of iron overload. Iron toxicity may be caused by frequent RBC transfusions, release of toxic iron radicals by the transplant conditioning, causing cytotoxicity and ineffective hematopoiesis, as well as by other less well-defined processes.[112] Several noninvasive tests are available to assess iron overload and iron toxicity (supplemental Data Section 5). 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.[113] Reduction of iron overload by iron chelation prior to HSCT was associated with improved survival and reduced NRM in a pediatric HSCT study.[114] The expert panel agreed that MDS patients with a transfusion history of >20 units of RBCs, who are potential candidates for HSCT should receive appropriate iron chelation therapy prior to conditioning for transplantation, similar to several other guidelines[7] (recommendation level D).

Iron overload after HSCT may be treated by phlebotomies or by iron chelation (supplemental Data Section 5).[115,116] The expert panel agreed to recommend treatment of iron overload after HSCT in patients with a high transfusion burden, but the choice between phlebotomies and iron chelation remained open due to the lack of prospective studies (recommendation level D).

Overall conclusions

HSCT is increasingly applied in the treatment of MDS after the introduction of RIC regimens and the increased availability of well-matched unrelated donors. Several new developments may influence the outcome and application of HSCT. The recently introduced new techniques may change the predictive models. These techniques may allow better monitoring of minimal residual disease and improve both nontransplant and transplant strategies. Several new classes of drugs are being tested in MDS patients. Positive outcome of these studies may change the need for upfront and delayed HSCT in MDS. Currently, the MDS working group of the ELN is developing an interactive website (https://mds-europe.eu) supported by the MDS-Right Project (funded by the EU Horizon 2020 project no. 634789), which will support fast incorporation of new developments in the current HSCT recommendations.

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