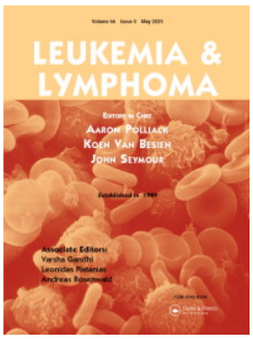

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REVIEW ARTICLE

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Allogeneic stem cell transplantation for MDS—clinical issues, choosing preparative regimens and outcome

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ABSTRACT

Despite the vast heterogeneity of myelodysplastic neoplasm (MDS), treatment options are limited and an allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative approach. While, subsequently, allo-HSCT is the treatment of choice in fit high-risk MDS patients younger than 70 years, it should only be considered in young and fit low-risk MDS patients who suffer from severe and life threatening cytopenias, and fail all available conservative treatment options. With the increasing use of mismatched or haploidentical donors, the majority of MDS patients will have a suitable donor available, however, matched donors should still be preferred if rapidly available. Strategies to prevent relapse after allo-HSCT are scarce, and include the use of donor lymphocytes or the experimental use of hypomethylating agents in patients with impeding relapse detected by MRD or chimerism evaluation. Here, we summarize current treatment options and factors to consider in the context of allo-HSCT in MDS.

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Myelodysplastic neoplasm; MDS; allogeneic stem cell transplantation; allo-HSCT; conditioning regimen

Introduction

Myelodysplastic neoplasm (MDS) constitutes a group of highly heterogeneous diseases, with clinical courses ranging from mild cytopenia with a nearly normal life expectancy to malignant neoplasm with outcomes similar to acute myeloid leukemia (AML). MDS are among the most common myeloid neoplasias in elderly patients [1–3] with a median age of more than 70 years at diagnosis [4,5]. About 50% of cases show cytogenetic abnormalities and 80–90% have at least one recurring myeloid mutation(median 3) at diagnosis [6], allowing together with other disease-related characteristics an estimation of overall (OS) and leukemia-free survival (LFS) for an individual patient [7,8]. The most frequently mutated genes are*TET2*, *SF3B1*, *ASXL1*, and *DNMT3A* (each present in >10% of patients) [9], whereas a complex karyotype and the presence of del(5q) are the most common cytogenetic abnormalities [10]. Despite advances in the treatment of MDS, allo-HSCT is still the only curative treatment available [11]. The wide range of clinical disease courses and the often advanced age of the patients at diagnosis pose a great challenge for physicians and patients in deciding pro or contra an allo-HSCT. For transplant-ineligible patients or those in which transplant can be deferred, possible therapy options depend on the individual disease risk. In asymptomatic lower risk patients, watch and wait can be sufficient, while in case of cytopenia, transfusions, erythropoiesis or thrombopoiesis stimulating agents, lenalidomide [12] (in case of MDS with del(5q)), or luspatercept [4,13] can be used. In higher risk individuals, hypomethylating agents (HMA) currently remain the only approved treatment option [14]. This review aims at highlighting indications for allo-HSCT, selecting suitable patients, choosing the optimal time point and discussing possible conditioning regimens and post-transplant strategies to prevent relapse.

Classifications in MDS

WHO und ICC

In 2022, the World Health Classification (WHO) disease classification system of 2016 was replaced by two

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parallel classifications, the WHO2022 [1] and the International Consensus Classification (ICC) [15]. Distribution in both systems overlap in the majority of cases, but some relevant differences remain. Both retained 20% blasts as threshold between MDS and AML. However, to highlight their biologic continuum, the ICC introduced the new category of MDS/AML (10–19% blasts in PB or BM), replacing the former MDS with elevated blasts (EB) 2. Fearing an overtreatment in these patients, the WHO2022 retained the 2016 blast thresholds, but renamed EB into 'increased blasts' (MDS-IB) [1].

The two classifications omitted the 2016 category 'MDS, unclassifiable,' and introduced a third genetically defined group in addition to MDS-*SF3B1* and MDS-del(5q), characterized by the high risk aberration mutated *TP53*. While in published real-world studies, <1% of included patients showed distinct diagnoses (MDS or AML) in WHO2022 and ICC [16], the existence of two competing classifications might confound patients or their treating physicians, and critically influence treatment decisions, as that for an allo-HSCT. Subsequently, merged classifications claiming to incorporate the strengths of both systems, have been proposed [17], and may be considered in future classifications.

To transplant or not to transplant

Allo-HSCT remains the only curative treatment for MDS, irrespective of the underlying disease risk. Potential candidates should therefore early be referred to a transplant center to assess eligibility (Figure 1). In general, allo-HSCT in MDS should be considered in fit patients up to age of 70–75 years with higher risk MDS or treatment-refractory and life-threatening cytopenias. However, the decision to undergo and the optimal timing of allo-HSCT has to be determined individually for every patient as it depends on a variety of disease-, patient- and transplant-related factors (Table 1). Although risk assessment changed over time, dividing patients into high- or low-risk remains necessary to estimate the optimal timepoint for allo-HSCT.

Despite being the only curative option for MDS patients, an allo-HSCT has a significant risk for morbidity and treatment-related mortality [18]. This includes infectious complications during aplasia, where the risk for bacterial or fungal infections is highest, but also after neutrophil recovery due to the need for immunosuppressive treatment and severe impairment of B- and T-cell subsets early after allo-HSCT. The risk for cytomegalie virus (CMV)-reactivation and CMV-disease and other viral infections is high and warrants prophylactic treatment where possible [19]. Other pathogens requiring close monitoring and prophylactic treatment are *Pneumocystis jirovecii* and *Toxoplasma gondii* [20]. Post-engraftment, acute graft-*vs.*-host disease (GvHD) is also a major cause of mortality and morbidity. Milder forms of chronic GvHD may barely restrict quality of life whereas severe forms, especially pulmonary GvHD, are associated with high morbidity and mortality [21,22].

Disease risk: IPSS, IPSS-R, IPSS-M

The increasing importance of molecular markers in MDS is also reflected in the new version of the international prognostic scoring system (IPSS) published in 2022 [8] (IPSS-M Risk Calculator (mds-risk-model.com). Complementing the IPSS backbone of cytogenetics, bone marrow blasts, and cytopenias, the IPSS-molecular (IPSS-M) incorporates somatic mutations in 31 genes and distinguishes patients into six risk-groups. Still, for the decision regarding allo-HSCT, the IPSS, published in 1997 [23], as well as the revised version from 2012 (IPSS-R) [7] remain important and should be considered, as recent studies analyzing allo-HSCT in MDS are based on these risk classifications. Table 2 gives an overview for the risk of the number of analyzed patients, overall survival, and risk of AML transformation according to the IPSS, IPSS-R, and IPSS-M as given in the initial publications [8,23].

High-risk MDS

Several studies examined the effects of an immediate allo-HSCT in high-risk MDS patients, with varying modes of comparisons and definitions of high-risk MDS: In 2004, prior to the introduction of HMA into the clinical routine, a Markov decision model in prospectively collected IPSS intermediate-2 or high-risk MDS patients aged <60 years receiving myeloablative conditioning (MAC)allo-HSCT from a matched sibling donor (MSD) suggested a benefit from immediate allo-HSCT as compared to delaying allo-HSCT till progression to AML [24]. A subsequent analysis in the era of HMA as alterative treatment showed similar results for reduced-intensity conditioning (RIC)allo-HSCT from 8/8 HLA matched donors in patients aged 60–70 years [25]. Delaying allo-HSCT until intermediate risk disease was also shown to increase survival with regard to the IPSS-R [26]. All three studies considered quality of life (QoL), which did not change treatment recommendation. Three prospective donor-*vs*-no-donor analyses

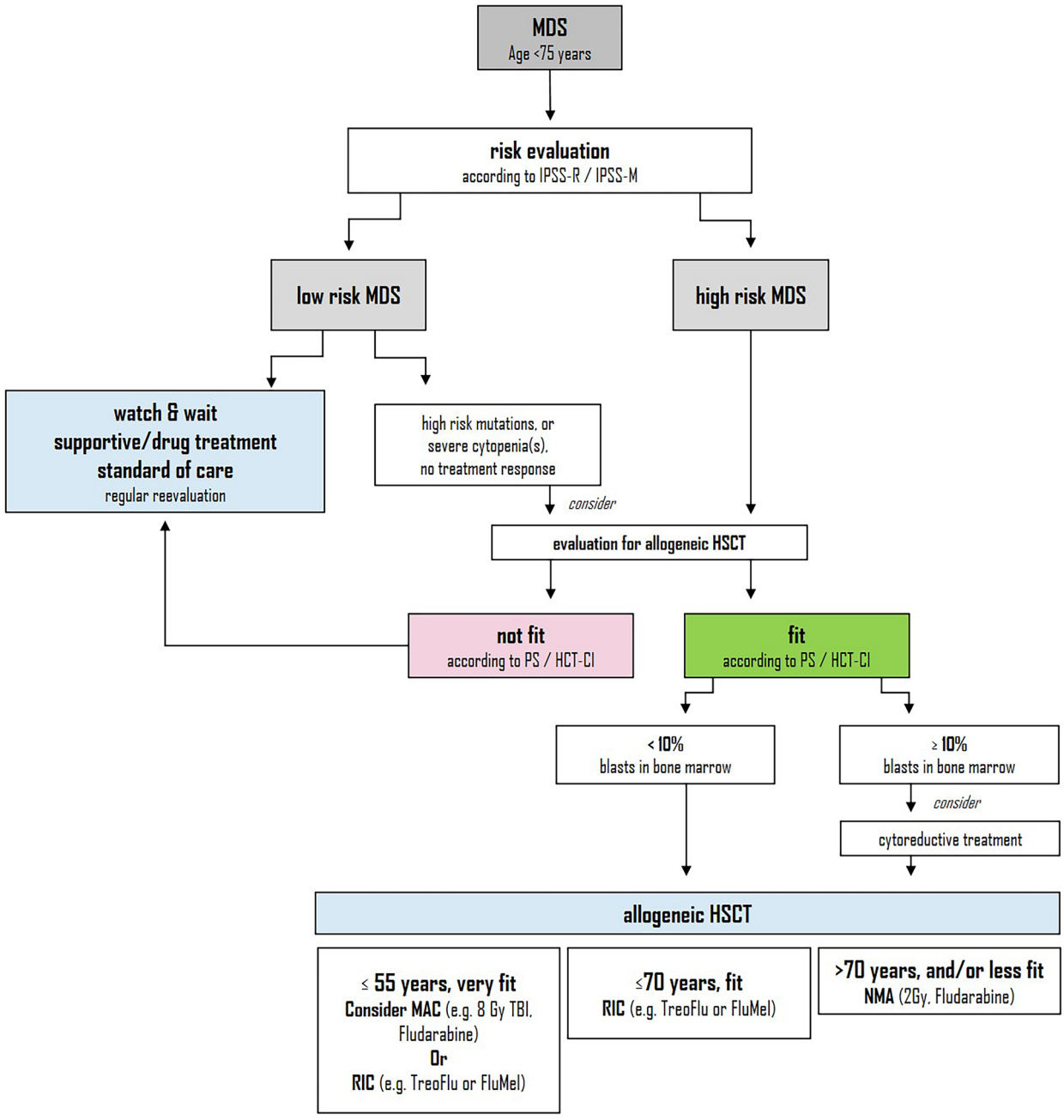

Figure 1. Decision tree for evaluation of patients with myelodysplastic neoplasm (MDS) regarding a potential allogeneic hematopoietic stem cell transplantation (allo-HSCT). HCT-CI: hematopoietic stem cell transplantation comorbidity index; HSCT: hematopoietic stem cell transplantation; MAC: myeloablative conditioning; MDS: myelodysplastic neoplasm; NMA: non-myeloablative conditioning; PS: performance score; RIC: reduced intensity conditioning.

confirmed the benefit from an allo-HSCT when a matched donor was available. First, in 2015, Robin et al. [27] published an MDS cohort (including therapy-related MDS and chronic myelomonocytic leukemia [CMML]) with high risk defined as IPSS intermediate-2/high or intermediate-1 with poor risk cytogenetics or platelet transfusion dependency aged 50–70 years. Treatment with intensive chemotherapy (ICT) or HMA was recommended in patients exceeding 10% bone marrow blasts, and RIC allo-HSCT in patients with a 10/10 MSD or matched unrelated donor (MUD). Of patients with a suitable donor available, 72% proceeded to allo-HSCT. While OS was similar during the first 24 months after inclusion into the trial, the donor group showed significantly longer OS thereafter (after 4 years: 37% donor *vs.* 15% no donor) [27]. The German VidazaAllo trial analyzed a similar patient population, but all received azacitidine before treatment allocation (4–6 cycles). Patients with a 10/10 donor proceeded to RIC allo-HSCT, while the no-donor group continued

Table 1. Relevant factors to consider in decision making for an allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Factors	Considerations	Clinical consequence
Medical patient-related factors	• (Biological) patient age • Performance score, CFS • Life expectancy • Organ function • Medical history and comorbidities, consider ○ HCT-CI	Consider allo-HSCT in fit younger patients (up to 70 years) without relevant comorbidities and adequate organ function.
Social patient-related factors	• Patient's preferred treatment choice • Patient's compliance • Social background/ support from family members and/or friends • Distance to allo-HSCT-center	Consider allo-HSCT in compliant patients with an adequately supportive social network.

Disease-related factors	• MDS relapse risk, consider
	  ○ Cytogenetics
	  ○ Molecular aberrations
	  ○ IPSS, IPSS-R, IPSS-M
	• (Life-threatening) cytopenias and transfusion-dependency
	• Frequency and severity of infections
	• Tolerability of current/ prior treatments
		Consider allo-HSCT in patients with high-risk disease or therapy-refractory and life-threatening cytopenias/high transfusion frequency.

Allo-HSCT-related factors	• Availability of an HLA-matched, mismatched or haploidentical donor • Donor age • CMV risk constellation • ABO match	Consider allo-HSCT in patients with a suitable stem cell donor, prefer younger, HLA-, CMV-, and ABO-matched donors.

allo-HSCT: allogeneic hematopoietic stem cell transplantation; CFS: clinical frailty scale; CMV: cytomegalie virus; HCT-CI: hematopoietic cell transplantation comorbidity index; HLA: human leukocyte antigen; IPSS: international prognostic scoring system; IPSS-M: molecular IPSS; IPSS-R: revised IPSS; MDS: myelodysplastic neoplasm.

Table 2. Risk scores, risk categories, and clinical outcomes in MDS.

	Patients	Overall survival	AML transformation
IPSS	*n* = 816	Median	Median years to 25% AML evolution
Low (0)	33%	5.7	9.4
Intermediate-1 (0.5–1)	38%	3.5	3.3
Intermediate-2 (1.5–2)	22%	1.2	1.1
High (≥2.5)	7%	0.4	0.2
IPSS-R	*n* = 7012	Median (95% CI)	Median years to 25% AML evolution
Very low (≤1.5)	19%	8.8 (7.8–9.9)	NR (14.5–NR)
Low (2–3)	38%	5.3 (5.1–5.7)	10.8 (9.2–NR)
Intermediate (3.5–4.5)	20%	3.0 (2.7–3.3)	3.2 (2.8–4.4)
High (5–6)	13%	1.6 (1.5–1.7)	1.4 (1.1–1.7)
Very high (>6)	10%	0.8 (0.7–0.8)	0.73 (0.7–0.9)
IPSS-M	*n* = 2701	Median (25–75% range)	% By 2 years
Very low (≤ −1.5)	14%	10.6 (5.1–17.4)	1.2%
Low (> −1.5 to < −0.5)	33%	6.0 (3.0–12.8)	3.4%
Moderate low (> −0.5 to 0)	11%	4.6 (2.0–7.4)	8.8%
Moderate high (>0 to 0.5)	11%	2.8 (1.2–5.5)	14.0%
High (>0.5 to 1.5)	14%	1.7 (1.0–3.4)	21.2%
Very high (>1.5)	17%	1.0 (0.5–1.8)	28.6%

AML: acute myeloid leukemia; CI: confidence interval; IPSS: international prognostic scoring system; IPSS-M: molecular IPSS; IPSS-R: revised IPSS; MDS: myelodysplastic neoplasm.
Source: Adapted from Greenberg et al. [7,23] and Bernard et al. [8]. Distribution, survival, and risk of AML transformation of MDS patients according to the risk stratifications of IPSS, IPSS-R, and IPSS-M.

azacitidine until progression. Three-year relapse-free survival(RFS) was superior after allo-HSCT compared to azacitidine (34 *vs.* 0%, $p < .001$), but non-relapse mortality(NRM) after 1 year was also higher (19 *vs.* 0%, $p = .007$) and there was no significant OS benefit for the allo-HSCT group (3-year OS: 50 *vs.* 32%, $p = .12$). Of note, the study reported a drop out rate of 33% before treatment allocation due to adverse events or disease progression, concluding that allo-HSCT should be performed as soon as a donor is available [28]. Finally, the BMT CTN 1102 trial included *de novo* MDS patients aged 50–75 years with IPSS intermediate-2 or high risk disease, where patients with a 10/10 matched donor should undergo allo-HSCT within 6 months of registration [29]. Despite 17% of patients in the donor group not proceeding to allo-HSCT, the donor group showed superior LFS (at 3-years: 36 *vs.* 21%, $p = .003$), and OS (at 3 years: 48 *vs.* 27%, $p < .001$). This data set was later assessed regarding molecular aberrations, especially focusing on high risk characteristics [30].

Here, the OS benefit of allo-HSCT was also seen in *TP53*mutated patients, irrespective of *TP53* allelic state, co-occurring complex karyotype, or *TP53* clearance before allo-HSCT. Only patients with IPSS-M very high risk with a co-occuring*TP53* mutation did not benefit from allo-HSCT. Finally, the authors also indicated the very high cure rate of MDS patients with germline *DDX41* mutations by RIC or non-myeloablative (NMA) allo-HSCT [30].

Till today, no prospective trial addressed the superiority of allo-HSCT using alternative donor sources, as mismatched unrelated (MMUD) or haploidentical, over HMA/best supportive care alone. However, registry analyses suggest outcomes using alternative donor sources to be only marginally inferior to that of matched allo-HSCT, especially when using post-transplant cyclophosphamide (PTCY) as GvHD prophylaxis [31–33].

Low-risk MDS

Low-risk MDS patients usually have favorable outcome after allo-HSCT due to a reduced relapse risk. Still, owing to the much higher NRM after allo-HSCT,

non-HSCT approaches still showed maximized OS and QoL in the above mentioned Markov decision models for IPSS low/intermediate-1 patients [24,25]. None of the mentioned donor-*vs.*-no donor studies [27–29] used molecular analyses to define high-risk MDS, hindering definite recommendations in patients with low IPSS but high-risk molecular aberrations. A retrospective EBMT study suggested superior outcomes in patients with IPSS low/intermediate-1 risk after allo-HSCT (3-year RFS 54% and OS 58%) compared to studies in higher risk MDS, although most patients (76%) had at least intermediate risk when reclassified according to the IPSS-R [34]. Subsequently, despite scarce data, allo-HSCT may be feasible in selected low-risk MDS patients with additional risk factors, as life threatening neutropenia, thrombopenia, erythropoiesis-stimulating agents- and/or luspatercept-refractory transfusion-dependent anemia, or high-risk mutations, as in *TP53* [11].

Factors to consider prior to allo-HSCT

Optimal treatment before allo-HSCT

Till today, there are no randomized clinical trials (RCT) evaluating the optimal treatment before allo-HSCT. While patients without blast excess usually directly proceed to allo-HSCT, an international expert panel recommends prior cytoreduction in patients exceeding 10% blasts to reduce disease burden and allow time to identify a suitable donor [35]. Also, some retrospective analyses indicated a survival benefit in MDS patients achieving a blast clearance at allo-HSCT, arguing for the use of cytoreductive treatment [36–38], while others could not confirm these findings [39,40]. It is also unclear, whether the lower disease burden at allo-HSCT or rather a less malignant disease biology are responsible for the longer OS in responding patients. In addition, toxicity and disease progression might impede a planned allo-HSCT, as shown in the VidazaAllo study [28].

With the caveat of missing drop outs before allo-HSCT, as well as a selection bias toward younger age and lower blast percentages in patients receiving upfront allo-HSCT, two retrospective studies indicated that upfront allo-HSCT was at least not inferior to prior cytoreduction with regard to cumulative incidence of relapse (CIR) and OS. This was shown for patients with MDS-EB1 [41] or EB2 [41,42], irrespective whether ICT or HMA were given, and is further strengthened by recent data showing even lower CIR and longer OS after upfront allo-HSCT, compared to pretreatment with HMA [41].

The second question would be whether ICT or HMA should be used as cytoreduction, for which again, no RCT exists. A Markov analysis suggested pretreatment with HMA to be beneficial in advanced MDS, especially in older patients [26]. While superior OS due to lower NRM was shown for patients receiving decitabine compared to a historical cohort treated with ICT [43], most other studies showed equivalent CIR, NRM, and OS in cohorts where HMA patients were usually older and had lower bone marrow blasts at treatment initiation [40,44,45]. Of note, patients who failed either ICT or HMA and received both treatments sequentially had shorter OS due to higher NRM and more extensive chronic GvHD. Subsequently, treatment intensification before allo-HSCT may increase NRM without reducing CIR in non-responding patients [45].

For older patients with myelodysplasia-related AML an OS benefit for CPX-351, the liposomal formulation of cytarabine and daunorubicin, compared to standard 7+3 was shown, especially after a consolidation allo-HSCT [46]. To evaluate whether CPX-351 may also provide improved RFS over azacitidine or 7+3 in high-risk MDS patients scheduled to undergo allo-HSCT, the randomized PALOMA trial (NCT04061239) recently finished recruitment, with first results expected in 2026.

Patient-associated factors

Since the incidence of MDS increases with age, comorbidities are frequent and patient-fitness is an important factor for transplant decision-making. However, the definition of 'fit' and 'unfit' is not unified. For general evaluation, tools like the Eastern Cooperative Oncology Group performance status (ECOG-PS), Karnofsky-PS (KPS)and clinical frailty scale (CSF) [47] can help to objectify a patient's physical abilities. While for KPS a threshold of >80 *vs.* ≤80% is repeatedly used and shows prognostic significance [48,49], in unselected cohorts including MDS patients, ECOG-PS and CSF were reported with less consistency.

To specifically evaluate comorbidities, the Charlson Comorbidity Index (CCI) [50] or the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) [51] are frequently used. A comparison of the two scores in 171 MDS patients showed that HCT-CI was able to detect more comorbidities, and allowed for a better outcome prediction prior to allo-HSCT [52].

Also, inflammatory markers show applicability as prognostic biomarkers in the context of allo-HSCT in MDS. In a cohort of 175 MDS patients undergoing allo-HSCT, CRP >10 mg/l and albumin <3.5 g/dl were associated with higher mortality. The results served to

develop a formula based on CRP, albumin, and ferritin leading to three biomarker risk-groups which were prognostic for NRM and OS [53]. Another study evaluated the inflammatory and nutritional status in 143 patients ≥60 years undergoing allo-HSCT, including 30 patients with MDS. Here, a high CRP/Albumin-ratio (CAR, i.e. >0.6) associated with poor ECOG-PS (i.e. ≥1), male sex, and high disease risk and remained an independent prognostic factor for OS. Of note, age alone did not associated with higher NRM or shorter OS in patients up to 70 years of age [54].

HSCT-related factors—donor choice

The main determinant for selecting a donor is the degree of histocompatibility between donor and recipient. In general, antigen and allele matched donors at the HLA-A, B, C, DRB1, and DQB1 loci are considered optimal as with decreasing histocompatibility the risk for graft rejection as well as GvHD rises significantly [55]. Possible stem sources include matched (10/10) or mismatched (8–9/10) sibling or unrelated donors as well as alternative donors, such as haploidentical (at least 5/10 matched) related donors, or cord blood. Currently, an MSD is preferred over a MUD or alternative donors, but RCT are lacking. However, several retrospective analyses showed similar or even better outcomes after allo-HSCT from younger MUD compared to older MSD [56–58]. In cases with several HLA-identical donors, matched CMV- and ABO-constellations should be preferred.

The introduction of PTCY greatly improved outcomes after allo-HSCT from a MMUD or haploidentical donor, and is increasingly used, especially in the non-white population [59,60]. Several retrospective analyses by the EBMT even indicated that PTCY might associate with longer OS, compared to ATG as GvHD prophylaxis after MMUD and MUD allo-HSCT [61,62], also in patients with MDS [63]. A RCT comparing PTCY to ATG in MUD allo-HSCT, that will hopefully answer this question, is currently recruiting (NCT05153226).

HSCT-related factors—conditioning intensity and conditioning regimens

The choice of conditioning intensity remains controversial and only few RCT exist. A trial by the EBMT randomly assigned MDS patients up to 65 years to either receive a busulfan-based MAC or RIC allo-HSCT [64]. Engraftment rates, NRM, and CIR did not differ between groups, resulting in similar 2-year OS. Recently published long-term results confirmed the initial results, although the 4-year OS was numerically better after MAC (70%) *vs.* RIC (58%) allo-HSCT, while patients with low-risk cytogenetics benefited more from RIC [65].

A similar trial by the BMT CTN recruited patients with MDS ($n=54$) and AML ($n=218$) with <5% blasts pre allo-HSCT but was closed early due to higher CIR and shorter RFS in the RIC group [66]. Long-term follow up of the trial showed a longer OS after MAC allo-HSCT, but also a very significant late NRM [67]. The very high CIR and low NRM in the RIC cohort and the allowed oral busulfan application of this trial suggest potentially inadequate busulfan-exposure. Still, both RCT indicate that MAC can be feasible in fit MDS patients up to the age of 65 years.

A CIBMTR publication compared RIC and MAC in patients with MDS and AML with regard to the cytogenetic risk and disease status at allo-HSCT using the well-established Disease Risk Index (DRI) [68,69]. In patients with low/intermediate DRI, RIC resulted in less NRM but higher CIR, leading to an inferior RFS compared to MAC, while RFS was similar between RIC and MAC in the high/very high DRI cohort. The authors concluded that MAC should be preferred in patients with AML and MDS with low or intermediate DRI.

The standard busulfan/fludarabine (BuFlu) RIC used in the above mentioned trials was challenged by a phase 3 RCT for patients with MDS or AML not eligible for MAC [70], testing treosulfan-based (TreoFlu) conditioning. TreoFlu was non-inferior to BuFlu regarding engraftment, acute and chronic GvHD, CIR, and OS. This was also true for the subgroup of MDS patients and even more pronounced in patients with high or very high IPSS-R. Longer follow up revealed an RFS (at 3 years: 60 *vs.* 50%) and OS (at 3 years: 67 *vs.* 50%) advantage for TreoFlu, mainly due to a lower NRM [71].

A recent retrospective analysis compared TreoFlu, fludarabine/melphalan (FluMel) RIC, and busulfan-based MAC in patients aged 50–70 years [72], and showed similar outcomes for FluMel and TreoFlu RIC in MDS patients, whereas 2-years OS was higher with TreoFlu compared to MAC. Finally, another retrospective analysis compared RIC regimens to a 2 Gy total body irradiation (TBI)-based NMA conditioning in patients with MDS and MDS/MPN. Here, NMA associated with higher NRM and shorter OS in patients younger than 65 years [73], due to a higher rate of graft rejection (12 *vs.* 2%) and chronic GvHD, leading to the conclusion that MDS patients should receive a more intensive RIC regimen whenever possible.

A novel approach is the inclusion of anti-CD117-antibodies into conditioning, which have been shown to deplete MDS hematopoietic stem cells (HSC) and to facilitate transplantation of normal human HSC in murine MDS models [74]. Results from a phase 1 trial

combining the anti-CD117-antibody briquilimab with NMA conditioning showed promising results in patients with wildtype*TP53* MDS or AML [75].

Predicting relapse after allo-HSCT

Chimerism

Chimerism represents an established tool for engraftment analysis as well as relapse prediction in various hematologic malignancies after allo-HSCT. Usually, single tandem repeats are detected, whereas XY-FISH can be used in sex-mismatched donor-recipient constellations [76,77]. While chimerism analyses can be derived from both bone marrow and peripheral blood, bone marrow usually provides higher specificity and sensitivity [78]. In MDS, detection of a mixed bone marrow chimerism after allo-HSCT associated with a higher risk for overt relapse and subsequent shorter OS [79,80].

MRD

The evaluation of measurable residual disease (MRD) is an even more sensitive method that detects small amounts of surviving malignant cells and is widely used for response assessment in AML. While data in MDS increasingly emerges, we currently lack unanimous recommendations.

In MDS, MRD detection by various methods before allo-HSCT was associated with adverse post-transplant outcomes. First MRD data in MDS was published for *WT1* overexpression and multiparameter flow cytometry (MFC) MRD, showing higher CIR and shorter OS for MRD-positivity at HSCT [81–84]. Additionally, clearance of known mutations before allo-HSCT correlated with improved outcomes, as shown for *TP53* mutated patients receiving HMA therapy [85–87], or other MDS-associated mutations [87]. Retrospective data suggested that conditioning intensification (from RIC to MAC) may improve outcomes in MRD-positive MDS patients, identified by persisting mutations or cytogenetics [87,88].

Similarly, after allo-HSCT, MRD allows the detection of patients at high risk of relapse. Very recently, sensitive molecular MRD monitoring by digital droplet PCR in a large MDS cohort ($n = 266$) was shown to reliably predict relapse post allo-HSCT with short turn-around time and low costs, including every mutation present at diagnosis [89]. The same correlation toward higher relapse risk and shorter OS has been shown for MFC MRD [90,91], and especially for molecular and MFC MRD combined [92].

Preventing relapse after allo-HSCT

In overt relapse, response to treatment with HMA and donor lymphocyte infusion (DLI) are low and outcomes dismal [93]. Thus, strategies peri- and post-HSCT should focus on preventing hematological relapse, using either prophylactic or preemptive approaches. However, allo-HSCT alone might be curative in some patients, and potential overtreatment with its associated toxicities must be weighed against the poor prognosis of patients relapsing after allo-HSCT. Subsequently, preemptive treatment using reliable and sensitive MRD markers seems promising if it provides a therapeutic window of opportunity before open relapse occurs.

Prophylactic treatment approaches

The curative potential of DLI in high risk myeloid neoplasm was already reported in the last millennium [94], and two trials showed high response rates at the expense of high rates of acute and chronic GvHD [95,96]. Schmid et al. explored a different approach in patients with high-risk MDS and AML using sequential chemotherapy followed by immediate RIC allo-HSCT and rapid tapering of immunosuppression. Afterward, prophylactic DLI in escalating doses were given to patients without GvHD after day +120, starting at least 30 days after discontinuation of immunosuppression [97]. Here, 66/75 patients achieved a complete remission (CR), but rates of acute and chronic GvHD were high (61 and 45%, respectively), and only 12 patients fulfilled the criteria to receive prophylactic DLI.

The preemptive use of DLI has also been investigated in a study using MFC or *WT1*MRD in MDS, AML, and acute lymphocyte leukemia (ALL) after allo-HSCT [98]. The 13% of patients with MRD relapse received low dose IL-2, DLI, or both, which resulted in a 3-year CIR of 22% in the whole group (18% in patients remaining MRD-negative, and 64 and 28% in the IL-2 and DLI group, respectively), while the 3-year OS was 66% in the MRD-negative group, 28% after IL-2, and 58% after DLI.

Currently, no prospective trials exist for the combination of DLI and HMA in the preemptive setting, although retrospective data showed promising results [99]. Other cellular therapies, such as CAR T-cells are currently being explored in phase 1 trials (NCT05457010, NCT03291444).

HMA has also been tested as maintenance therapy after allo-HSCT in MDS by several groups. In 2010, Lima et al. investigated different azacitidine doses and number of treatment cycles starting 40 days after allo-HSCT in 45 patients with AML and MDS, of whom

67% were not in CR at the time of HSCT [96]. NRM was 9%, and 53% of participants relapsed, while the rates of acute and chronic GvHD were 9 and 37%, respectively. An RCT then tested azacitidine against no intervention in 187 patients with MDS or AML after allo-HSCT [100]. With a median number of 4 cycles received, median RFS and OS did not differ (2.1 and 2.5 years with azacitidine *vs.* 1.3 and 2.6 years without).

Platzbecker et al. chose an MRD-guided strategy to initiate preemptive treatment. A decline in the CD34-sortedchimerism below 80% triggered a therapy with 4 cycles of azacitidine in 27/59 of screened patients after a median of 169 days [101]. In 16 patients the CD34-sortedchimerism stabilized or improved and hematological relapse could be prevented. Encouraged by these results, a second larger trial was set up in MDS and AML after intensive chemotherapy or allo-HSCT, using mutant *NPM1*, AML-specific fusion genes, and the CD34-sortedchimerism as MRD markers [102]. Of 198 screened patients, 30% suffered an MRD relapse and received up to 24 azacitidine cycles. Patients achieving MRD-negativity after 6 cycles were candidates for treatment de-escalation. RFS at 12 months was 46% in the whole group and 88% in the group of patients with MRD-negativity at 6 months, underlining the efficacy and feasibility of this approach.

The combination of HMA and venetoclax is standard of care in newly diagnosed AML patients not eligible for ICT. Encouraged by its high efficacy, a phase 3 trial evaluating the combination as maintenance after allo-HSCT has finished recruitment (NCT04161885). In MDS, HMA/venetoclaxis currently still explored in treatment-naïve high-risk and relapsed MDS, with promising activity in early Phase 1/2 trials [103–105]. The combination of HMA and eprenetapopt might be another maintenance approach in MDS or AML after allo-HSCT [106].

IDH1/2 mutations occur in ~5% of patients with MDS [107]. The role of IDH1/2 inhibitors as maintenance strategy after allo-HSCT in MDS and AML is currently explored in several trials (e.g. NCT04522895, NCT03744390).

Treating open relapse after allo-HSCT

In patients suffering open relapse after allo-HSCT approved treatment options are scarce, and in most cases of palliative intention. Studies evaluating substances in the relapsed setting usually also included patients with AML, impeding final conclusions for MDS.

In relapsed MDS or AML patients post allo-HSCT (AML: $n=116$, MDS: $n=65$), 25% showed an objective response to azacitidine, and 13% reached a CR [84]. Decitabine may be an alternative, especially in patients harboring a complex karyotype and/or *TP53* mutation, as this population seemed to have the highest benefit in first-line treatment of MDS or AML, but has no approval in the relapsed setting [108].

Newer combination partners for HMA [84], as the CD47-antibody magrolimab [109], orsabatolimab [110] showed sobering results in the front-line setting, and have not yet been evaluated in MDS patients relapsing post allo-HSCT [111,112]. More promising results were seen with the mutant*TP53*reactivator eprenetapopt [86], with an overall response rate of 73% (50% CR) in patients with HMA-naïve and relapsed/refractory*TP53*-mutated MDS. As mentioned, hope lies in the combination of HMA and venetoclax with trials in MDS ongoing.

Only a few mutations with targeted treatment options exist, and none have been evaluated in MDS patients alone. In *FLT3* mutated patients, gilteritinib was evaluated in a small study as salvage therapy at relapse in high-risk MDS patients (blasts >10%) or AML [113], showing 60% molecular responses, 45% of patients converting to MRD-negativity and a 2-year-OS of 80% [114]. A phase 1 study evaluated quizartinib in HMA-naïve and relapsed/refractory MDS and MDS/MPN patients with *FLT3* or *CBL* mutations, and showed an overall response of 83% and a 57% *FLT3* clearance rate [115].

In the relapsed AML setting, the *IDH1* inhibitor ivosidenib [116] and*IDH2* inhibitor enasidenib [117] achieved CR rates of 22 and 20%, respectively, which led to FDA approval. First data also suggests efficacy in MDS relapsed after HMA with a composite CR rate of 35% [118].

Second allo-HSCT?

A second allo-HSCT for relapsed MDS post allo-HSCT remains a potentially curative treatment. In a multi-center cohort of 99 patients receiving second allo-HSCT after MDS relapse, 5-year OS, CIR, and NRM were 25, 44, and 35%, respectively [119]. Risk factors associated with inferior outcome were relapse within 18 months after the first allo-HSCT and a poor performance status (i.e. ECOG 2–4) before second allo-HSCT. In a second study, 15 patients who received a second allo-HSCT also had dismal OS (after 2 years: 20%) [120]. Again, early relapse (here defined as within 6 months post first allo-HSCT) was found as risk factor for inferior outcomes after second allo-HSCT. Other studies reporting outcomes after second allo-HSCT included

only small proportions of MDS patients without further subanalyses [121]. Still, in fit patients with late relapse after the first allo-HSCT, a second allo-HSCT is an option and should be evaluated.

Conclusion

While an allo-HSCT currently remains the only curative treatment in MDS, we largely lack RCT with regard to patient selection, pretreatment, conditioning regimen, and post-HSCT strategies. The optimal transplant candidates are younger individuals without significant comorbidities and lacking promising alternative treatments. While patients with lower-risk MDS, when indicated, directly proceed to allo-HSCT, cytoreductive treatment before HSCT might be indicated in higher-risk cases, especially when exceeding 10% blasts. However, significant drop-out rates in prospective clinical trials before allo-HSCT argue for performing HSCT as soon as a suitable donor is identified. In younger patients with high-risk disease, MAC regimen may be an option, while TreoFlu or FluMel -based RIC are associated with the best outcomes for less fit individuals. NMA may be considered in older and more comorbid patients. As prognosis for patients relapsing after allo-HSCT are dismal, and only a minority of patients are candidates for a second HSCT, new treatment strategies, ideally adapting MRD-directed approaches, are urgently needed.

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