REVIEW SERIES

Treatment of high-risk myelodysplastic syndromes

Nicolaus Kröger

Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Correspondence: N. Kröger
nkroeger@uke.de

Received: October 11, 2024.
Accepted: November 19, 2024.
Early view: December 5, 2024.

https://doi.org/10.3324/haematol.2023.284946

Abstract

Myelodysplastic syndrome (MDS) is considered to be a heterogeneous myeloid malignancy with a common origin in the hematopoietic stem cell compartment and is generally divided into lower- and higher-risk forms. While the treatment goals for lower-risk MDS are to decrease transfusion requirements and transformation into acute leukemia, the major aims for higher-risk MDS are to prolong survival and ultimately cure the patient. Although novel agents such as luspatercept and imetelstat have recently been approved as new treatment options for lower-risk MDS, hypomethylating agents currently remain the only approved non-transplant option for higher-risk MDS and are the standard of care for patients not eligible for allogeneic hematopoietic stem cell transplantation (HSCT). Combinations with other drugs as first-line treatment have to date not proven more efficacious than monotherapy in higher-risk MDS, and outcome after the failure of treatment with hypomethylating agents is poor. The only potential cure and standard of care for eligible patients is HSCT and even though the number of transplanted – especially older – MDS patients has increased over time due to better management and greater donor availability, the majority of MDS patients will not be eligible for this curative approach. Current challenges include decreasing the relapse risk, the main cause of HSCT failure. This review summarizes current knowledge on the options of transplant and non-transplant treatment approaches for these patients and demonstrate the unmet clinical need for more effective therapies.

Assessment of patients and aims of treatment

Patients with myelodysplastic syndromes (MDS) present with a variety of disease manifestations ranging from indolent to severe, and have a high rate of progression of their MDS into acute leukemia over time. The treatment approach depends on disease-specific risk scores and the risk of transformation into acute leukemia. There is still consensus on distinguishing low-risk MDS from high-risk MDS (HR-MDS) based on the Revised International Prognostic Scoring System (IPSS-R) which would classify low, very low, and intermediate categories as low-risk MDS and high and very high categories as HR-MDS.[1,2] However, this classification does not consider the poor outcome of patients with low-risk MDS with severe cytopenia and bone marrow fibrosis and does not account for the importance of molecular genetics. Indeed, the genetic and molecular backgrounds of myelodysplastic tumor cells are heterogenous,[3] a finding that led to the introduction of the prognostically superior Molecular International Prognostic Scoring System (IPSS-M) risk stratification system. The IPSS-M, with its increased weight of molecular information, usually shifts patients from lower towards higher-risk categories, which means that recommendations for HR-MDS need to be reconsidered.[3,4] However it must be taken into account that the IPSS-M also included treated patients, which could have a potential impact on survival. The diagnostic procedure is based on the World Health Organization (WHO) classification and/or the International Consensus Classification (ICC), both published in 2022[5,6] and discussed in detail in another article of this review series. The clinical implications of clonal hematopoiesis of indetermined potential are outside the scope of this review. One difference between the two classifications is that the ICC defines patients with ≥10% marrow blasts as having “MDS/AML” while the WHO still uses the term MDS for these patients. With new therapies becoming more targeted and less governed by exact bone marrow blast percentages, the ICC approach could facilitate the approval by authorities of drugs that have been

mainly investigated in patients with acute myeloid leukemia (AML) also for patients with higher-risk MDS. Whether this would be useful and might lead to an improvement in the outcome of HR-MDS patients need to be determined. The data presented in this review are based on a classification of MDS with <20% blasts.

The management and treatment of HR-MDS should start with a thorough diagnostic and prognostic assessment including molecular and cytogenetic work-up. An in-depth analysis of the individual's symptoms, physical resources, and preferences is also important. Treatment recommendations should be discussed at multi-professional conferences including as many competences as possible.[3,5-7]

General treatment considerations

Even if patients can be classified as low risk according to the available MDS risk scores, the disease is a blood cancer with an overall poor prognosis. Patients with IPSS-R high and very high risk can expect a median survival of 1.6 and 0.8 years, respectively, while the median survival of those with IPSS-R intermediate, low, and very low risk is 3, 5.3, and 8.8 years, respectively.[2] Patients with IPSS-M moderate high to very high risk show a median survival of 1.7 and 1.0 years, while patients with moderate low and low risk have an overall survival of 4.6 and 6 years, respectively. Only patients in the very low-risk IPSS-M category have a median survival exceeding 10 years.[3] This means that therapeutic approaches at diagnosis, not only for HR-MDS patients, should aim to prolong survival and ultimately cure the patient. If a cure is not possible with available therapies, all other options, including survival prolongation, should be associated with an improved quality of life. All MDS types share their origin in the hematopoietic stem and progenitor cell compartment and it should be considered that over time most cases of low-risk MDS will progress into a higher IPSS-R or IPSS-M category. Investigations have tried to take the dynamics of the disease course into account by time-dependent analyses and proposed a cut-off of 3.5 points according to the IPSS-R to distinguish low-risk MDS from HR-MDS.[8] With a median age of about 75 years, co-morbidities and frailty contribute to the ability to tolerate various treatment options and most patients will not be eligible for curative allogeneic hematopoietic stem cell transplantation (HSCT). However, indications and eligibility for HSCT should always be explored early and during the course of disease. A proposed algorithm to determine "transplant eligibility" and counsel patients with regard to allogeneic HSCT is shown in Figure 1.

Supportive care

Supportive care is crucial in the management of patients with MDS, independently of whether they have low- or high-risk disease, and consists of active disease monitoring, transfusion support, and other aspects of dealing with cytopenias and increased risk of infection and bleeding. About half of MDS patients require red blood cell transfusion at the time of diagnosis.[9,10] Both the need for red blood cell transfusion at diagnosis and transfusion intensity over the course of disease are associated with impaired survival, quality of life, and progression-free survival.[11-13] Taking into account the option of allogeneic HSCT for HR-MDS (but also for low-risk MDS), only filtered blood products should be administered to minimize the risk of immunization.

The same holds true for thrombocytopenia which may be present at diagnosis but commonly occurs during treatment with chemotherapy and hypomethylating agents (HMA) as well as after allogeneic HSCT. The role of thrombopoietin agonists is controversial. Small phase II trials showed that thrombopoietin agonists increased platelet counts in patients with advanced MDS, but a randomized study in higher-risk MDS, in which a thrombopoietin agonist was used alone or in combination with azacitidine, failed to confirm this; in fact, the response rate was lower in patients receiving azacitidine + eltrombopag than in those receiving azacitidine alone.[14,15]

Infection prophylaxis is not specific for MDS and should follow general international guidelines. Granulocyte colony-stimulating factor is not licensed for low neutrophil counts associated with MDS but is frequently used as supportive care in cases of neutropenia caused by HMA treatment, especially after recurrent infectious events. While the role of iron chelation in transfusion-dependent, low-risk MDS is well accepted, its role in HR-MDS is controversial, due to the shorter life expectancy of the patients, but there is consensus to start chelation in transfusion-dependent HR-MDS if curative allogeneic HSCT is planned.

Due to a higher non-relapse mortality in patients with iron overload at the time of transplantation, timely chelation should be started but not postponing the transplant procedure.[16] Recent data suggest a significant reduction of labile plasma iron can be achieved if low-dose deferasirox is given during the conditioning therapy prior to allogeneic HSCT, although careful monitoring of busulfan is required.[16,17]

Hypomethylating agents

HMA are the only approved first-line treatment for higher-risk MDS. The mechanisms of action of HMA are complex, and most likely involve inhibition of DNA methyltransferase leading to transcriptional suppression[18] or reactivation of oncogenes, which can cause differentiation and might be cytotoxic.[19]

5-azacitidine, decitabine, and oral decitabine/cedazuridine are approved in the USA for all MDS subsets, the latter two for IPSS ≥intermediate-1, whereas in Europe only 5-azacitidine is approved for MDS and only for IPSS ≥intermediate-2.

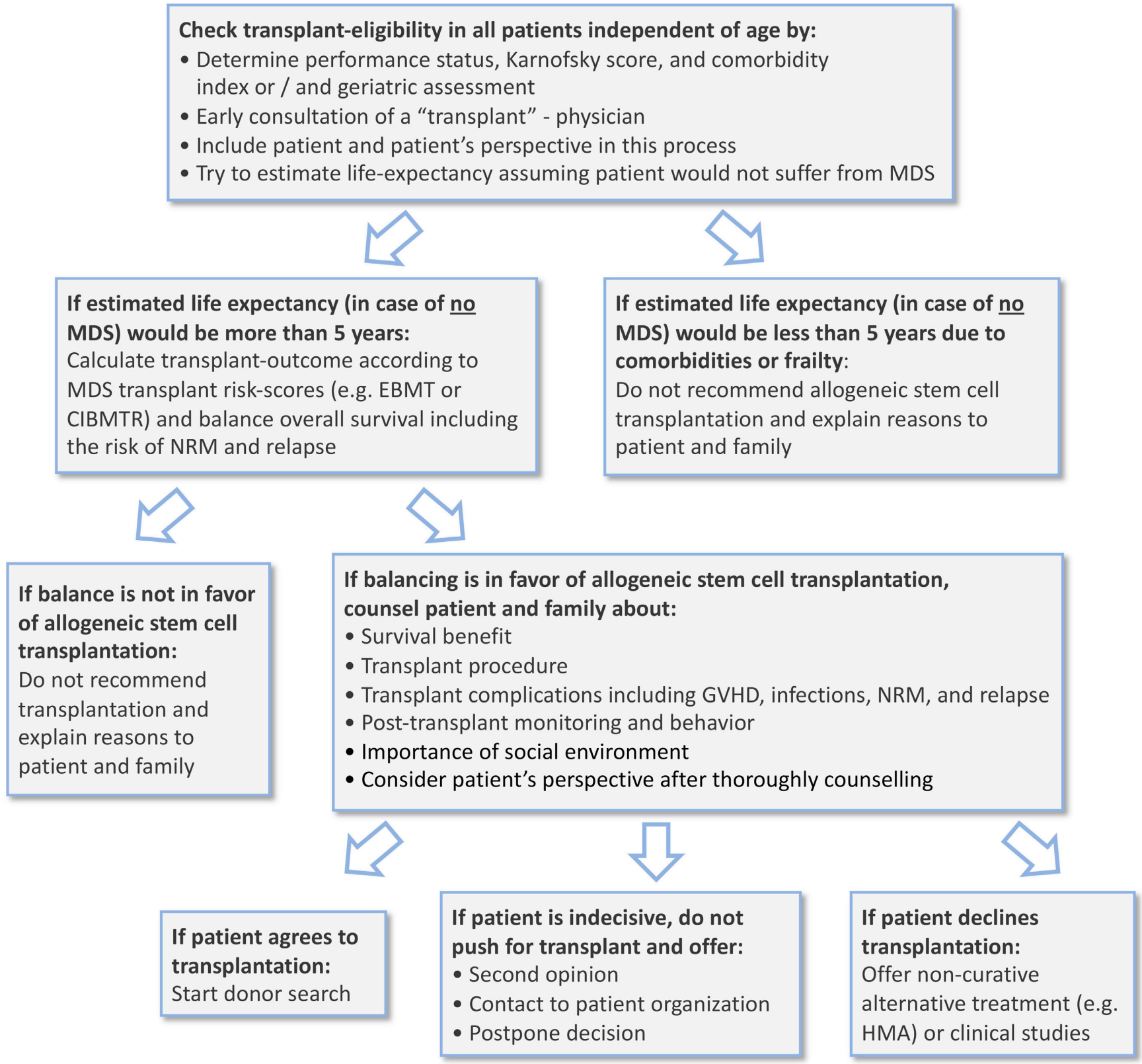

Figure 1. Proposal of how to assess transplant-eligibility and counsel patients with high-risk myelodysplastic syndrome. MDS: myelodysplastic syndrome; EBMT: European Blood and Marrow Transplantation group; CIBMTR: Center for International Blood and Marrow Transplant Research; NRM: non-relapse mortality; GvHD: graft-*versus*-host disease.

While no survival benefit could be shown for decitabine in randomized trials[20,21] the first randomized study of 5-azacitidine in higher-risk MDS showed significant improvements with respect to leukemic transformation and death for 5-azacitidine compared to best supportive care (CALGB 9221 study).[22] In the CALGB study, 191 MDS patients were randomized to 5-azacitidine or best supportive care. The overall response rate after azacitidine was 60% *versus* 5% in the best supportive care group (P<0.0001) and time to leukemic transformation or death was 21 *versus* 14 months (P=0.007), with improved survival after eliminating a confounding effect from early crossover.[22,23]

The subsequent AZA-001 international trial randomized 358 HR-MDS patients to either azacitidine or one of three conventional care regimens (best supportive care, low-dose cytarabine or conventional AML-like induction/consolidation therapy). There was significant improvement of median overall survival for patients treated with 5-azacitidine compared with standard care options chosen by the attending physicians (24.5 *vs.* 15 months, respectively).[24] The survival benefit was seen in all subgroups including older patients. Patients treated with 5-azacitidine also showed delayed progression

to AML, required fewer red blood cell transfusions, and had a lower rate of infectious complications.

The hematologic response rate to HMA is about 40% but treatment rarely leads to complete remission (8%) and most patients eventually relapse. In the AZA-001 study, the overall response rate was higher for azacitidine than for best supportive care and low-dose cytarabine but not in comparison to intensive chemotherapy. The majority of patients responded within the first six cycles, which is the recommended number of cycles before efficacy assessment unless allogeneic HSCT is planned.[25] Despite the survival benefit associated with 5-azacitidine in this trial, real-world data have not confirmed this effect of HMA treatment and there is no scoring system to predict response to HMA.[26]

Decitabine was approved for use only in the US following a randomized phase III study in 170 MDS patients receiving either decitabine or best supportive care. The complete response rate was 9% in the decitabine group and 0% in the best supportive care group. A significant improvement in overall survival was seen only in HR-MDS (median: 12.0 months *vs*. 6.8 months, *P*=0.03). In a European study decitabine administered in a 3-day schedule failed to produce a survival benefit in comparison to best supportive care.[21] Another treatment approved only in the US is the oral formulation of decitabine coupled with cedazuridine to facilitate oral bioavailability; this approval is based on the comparable efficacy of the oral formulation and intravenously administered decitabine.[27]

CC-486, an oral form of 5-azacitidine, has been shown to improve survival in AML as post-consolidation therapy.[28] A randomized phase III study evaluating CC-486 in mainly lower-risk MDS showed a significant reduction of transfusion dependency and longer response duration compared to those achieved with placebo but did not result in improved survival.[29]

The approved 5-azacitidine dose that was used in the AZA-001 trial is 75 mg/m^2 for 7 days per cycle. Some centers use a 5+2+2 schedule or give the entire dose over 5 days to avoid treatment during weekends. A large study based on 449 MDS patients showed that complete response is often, but not always, associated with a clonal reduction (decrease in variant allele frequency) and that such a reduction is predictive of long-term outcome. The data are particularly strong for patients carrying *TP53* mutations, because *TP53*-mutated patients who were long-term survivors after subsequent HSCT showed a clonal reduction after treatment with 5-azacitidine.[30]

Hypomethylating agents in combination with novel agents

Over the last years several new drugs have been tested unsuccessfully in combination with 5-azacitidine in order to further improve patients' outcome. The randomized phase II SWOG trial compared standard azacitidine with azacitidine combined with either lenalidomide or vorinostat in 227 patients with HR-MDS and reported an overall response rate of 38% in the azacitidine group with no improvement in response or survival in the combination group.[31]

Likewise, pevonedistat, a selective inhibitor of NEDD-8 activating enzyme, in combination with 5-azacitidine failed to improve event-free survival in comparison to that achieved by 5-azacitidine alone in patients with higher-risk MDS (PANTHER trial).[32] After encouraging results of 5-azacitidine in combination with an anti-CD47 antibody, magrolimab, in an early phase Ib study,[33] a subsequent phase III study was discontinued due to lack of efficacy.

The recent approval of the use of a BCL-2 inhibitor, venetoclax, in combination with 5-azacitidine in AML prompted investigation of this combination also in MDS. The combination induced an overall response rate of 75% in HMA-naïve patients and 44% in patients after failure of HMA treatment.[34] These high response rates reported in early clinical studies await validation from the pending results of a recently completed randomized trial of 5-azacitidine with or without venetoclax.[35,36] It is of interest that the overall survival of 24.4 months observed in the AZA-001 trial has not been replicated so far and after single-agent azacitidine the median overall survival was only 15 months in the SWOG trial and 17.5 months in the PANTHER trial.[31,32] The combination of an anthracycline, idarubicin, with azacitidine produced a high response rate (41.5%) in a phase I/II study without additional toxicity compared to that of azacitidine alone. However, a subsequent randomized phase III study did not show that the combination improved response or overall survival in comparison to that achieved by azacitidine alone.[37,38]

Novel combinations producing high remission rates may become suitable alternatives to chemotherapy for reducing the number of blasts prior to allogeneic HSCT. Azacitidine has been tested in combination with sabatolimab, a TIM-3 inhibitor. TIM-3 regulates immune responses in malignancies[39] and is only expressed on immune cells and leukemic myeloid cells but not on normal hematopoietic stem cells.[39] After encouraging results from an early phase Ib study, with an overall response rate of 33% and a complete response rate of 20% including patients harboring *TP53*,[40] subsequent randomized phase II and III trials (STIMULUS-MDS-1 and MDS-2) of sabatolimab *versus* placebo both in combination with azacitidine failed to show significant improvements in complete remission (14% *vs*. 11%) or progression-free survival (17.8 *vs*. 19.2 months) for the sabatolimab plus azacitidine combination in comparison to placebo plus azacitidine.[41,42]

To conclude, HMA are currently the first-line treatment for higher-risk MDS patients not eligible for allogeneic HSCT and so far combination therapies with HMA have failed to improve overall survival in comparison to HMA alone in phase II studies.

Failure of hypomethylating agent treatment

The outcome of HR-MDS patients in whom HMA fail is poor. In 435 HR-MDS patients in whom HMA treatment failed, the median survival was only 5.6 months and the 2-year overall response rate was 15%. Allogeneic HSCT and investigated drugs were associated with better outcomes compared

to conventional clinical care.[43] Rigosertib did not improve outcome in comparison to best supportive care.[44] Currently there is no conventional therapy with significant activity for HR-MDS patients in whom HMA treatment fails and even though allogeneic HSCT still has a curative potential in this setting, current evidence recommends transplantation before treatment with HMA.[45-47] Several studies with novel agents are ongoing but out of the scope of this review and details are reported elsewhere.[48,49]

Targeted therapies

IDH1 or *IDH2* mutations occur in 5-15% of MDS patients and enasidenib and ivosidenib have been shown to produce responses in *IDH2*-mutated MDS patients.[50,51] 5-azacitidine in combination with APR-246 in *TP53*-mutated MDS patients induced complete responses in 50%,[52] but a subsequent phase III trial did not show a difference in outcome. Feasibility of APR-246 plus azacitidine as maintenance therapy after allografting has been demonstrated but randomized studies are lacking.[53] It may be mentioned that the new ICC, which classifies previous WHO 2016 MDS with ≥10% blasts as MDS/AML, would potentially allow the use of AML-approved drugs also in higher-risk MDS.[6]

Chemotherapy

AML-like chemotherapy protocols including anthracycline-cytarabine combinations have been used in MDS patients with high blast counts but with lower response rates and shorter lasting complete responses than those in patients with *de novo* AML. Furthermore, AML-like chemotherapy in older patients or in patients with unfavorable karyotype and/or *TP53* mutations resulted in even lower response rates with no clear benefit in comparison to 5-azacitidine treatment.[54-56] Less toxicity was achieved using CPX-351, a liposomal anthracycline, plus cytarabine-based chemotherapy with a 52% complete response rate in HR-MDS patients.[57] Currently AML-like chemotherapy is mainly used as induction therapy prior to allogeneic HSCT and is here recommended only in younger MDS patients without unfavorable karyotype or bi-allelic *TP53* mutations.

Stem cell transplantation

Decision-making and timing of transplantation

Allogeneic HSCT is currently the standard-of-care treatment for HR-MDS patients eligible for the procedure and the only curative treatment but its inherent therapy-related morbidity and mortality necessitate careful selection of patients. Because the optimal timing of allogeneic HSCT in MDS has not been addressed in prospective, randomized clinical trials, comparisons between transplanted and non-transplanted MDS patients have been performed by using different statistical multi-state models. A Markov model was used in 184 non-transplanted patients and 868 patients with MDS <60 years old who underwent allogeneic HSCT after myeloablative conditioning from HLA-identical siblings. The authors found that life years increased if transplantation was delayed in patients with IPSS low- and intermediate-1-risk MDS, but for those with intermediate-2 or high-risk according to the IPSS, life expectancy was maximized by immediate transplantation.[58] A similar study compared the outcomes of 660 non-transplanted MDS patients with 449 MDS patients who received an allograft after myeloablative conditioning or reduced intensity conditioning and also included matched unrelated donors. In this study IPSS intermediate-1 and -2, and high-risk patients were best treated with early transplantation while low-risk patients benefited more from delayed transplantation.[59] Using IPSS-R scoring in a multi-state model, the outcome of 961 non-transplanted MDS patients was compared to that of 489 patients who received an allograft for MDS. Life expectancy was increased if transplantation was delayed in patients with low or intermediate IPSS-R scores while for those with IPSS-R high and very high scores, immediate transplantation after diagnosis improved outcome.[60]

The outcome after HSCT is strongly dependent on cytogenetics and molecular genetic features. Unfavorable cytogenetics such as complex karyotype or monosomal karyotype are associated with a higher risk of relapse and mortality.[61,62] The increasing importance of molecular genetics is reflected by the recently introduced IPSS-M.[3] *ASXL1*, *RUNX*[63] and *TP53*[63,64] as well as *RAS* pathway mutations are independent risk factors for relapse and mortality after HSCT and a combination of molecular genetics and cytogenetics may predict outcome after HSCT even better.[64,65] The IPSS-M usually shifts patients to a higher risk category and two retrospective studies reported a modest advantage in prognostication of MDS using IPSS-M before allogeneic HSCT. MDS patients classified as low risk according to the IPSS-R may be classified as higher risk according to the IPSS-M and, therefore, become candidates for allogeneic transplantation.[66,67]

Decision-making according to the IPSS-M in 7,118 MDS patients showed improved survival if transplantation was delayed in those with IPSS-M low or moderate-low risk MDS while survival was improved if transplantation was performed immediately in moderately high, high, and very high-risk patients.[4] Comparing decisions based on the IPSS-R or IPSS-M, transplant policy was changed in 15% of the patients from immediate transplant according to the IPSS-R to delayed transplant according to the IPSS-M, and 19% of the patients from delayed transplantation according to the IPSS-R into immediate transplant according to the IPSS-M.[4]

In three prospective donor *versus* no-donor comparisons, patients with IPSS-R intermediate-2 and high-risk and also IPSS-R intermediate-risk with high-risk cytogenetics with

available donors had a significantly better event-free survival and in two of them also an improved overall survival compared to those without donors.[45-47] In the BMT-CTN study, patients in the donor arm had an adjusted overall survival rate of 47.9% compared with 26.6% for those in the no-donor arm.[46] A similar prospective study (VidazaAllo) compared 5-azacitidine to allogeneic HSCT after 5-azacitidine induction in higher-risk MDS patients aged 55-70 years according to donor availability and reported an event-free survival at 3 years of 34% after HSCT and 0% after 5-azacitidine[45] which additionally support the use of allogeneic HSCT as standard care in higher-risk MDS, even in older patients (Table 1).[68,69]

Patients in whom HMA treatment fails, even if considered to have low-risk MDS, have a poor outcome and allogeneic HSCT should be considered in these patients.[43] The current recommendation for allogeneic HSCT in lower-risk MDS includes patients with severe cytopenia or progressive disease, and those in whom conventional treatment has failed. HSCT might also be indicated if additional unfavorable factors exist in addition to IPSS-R category, such as bone marrow fibrosis or unfavorable molecular genetics according to the IPSS-M.[70]

Despite patients with *TP53* mutations having a worse outcome after HSCT than patients without these mutations, *post-hoc* analysis of data from the BMT-CTN 1102 trial showed that, compared to non-transplant approaches, HSCT improved survival for *TP53* single-hit patients, *TP53* multi-hit patients and IPSS-M high-risk patients without *TP53* mutation.[71] Molecular testing prior to HSCT is recommended to exclude inherited bone marrow failure syndromes and germline mutations such as *GATA2*, *SAMD9*/*SAMD9L*, *RUNX1*, *ETV6*, and *DDX41* which have implications for conditioning regimens and donor selection.[72] After adjustment for other risk factors, age *per se* is not associated with worse overall survival[68] but poor performance status, comorbidity index, and Karnofsky index are associated with higher non-relapse mortality[68,73] even if not all comorbidities result in similar risks of non-relapse mortality.[74] To predict outcome after allogeneic HSCT for MDS, transplant scoring systems have been developed by cooperative groups as well as by the EBMT and CIBMTR; beside disease-specific risk factors, these systems take into account patient- and transplant-specific factors such as age, comorbidities, and donor match and are helpful for counseling patients regarding treatment decisions.[75-77]

Even if blast reduction prior to transplant has a positive impact on outcome and pre-transplant therapy in MDS with ≥10% blasts is recommended by international expert teams,[78] no prospective study comparing pre-transplant therapy *versus* no therapy exists and most of the retrospective studies that investigated HMA or chemotherapy did not show a significant impact on overall survival after transplantation,[79] also because patients progressed or died during pre-transplant therapy.[45,80]

A recent EBMT registry study on 1,482 MDS patients analyzed whether downstaging according to IPSS-R from diagnosis to transplant had an impact on survival after allogeneic HSCT.[81] Transplant outcome was moderately improved in patients treated with chemotherapy and who had an improved IPSS-R category at transplant, but worse if IPSS-R category increased at transplant after chemotherapy or HMA therapy. Improved IPSS-R risk category after HMA or other treatments did not affect outcome after transplantation.[81]

Retrospective studies of conditioning regimen intensity showed higher non-relapse mortality but fewer relapses with myeloablative conditioning regimens.[82] One prospective EBMT study (RICMAC) showed no difference in outcome between patients conditioned with myeloablative or reduced intensity regimens.[83] The BMT-CTN study of patients with AML or MDS showed a higher risk of relapse after reduced intensity conditioning, but the number of MDS patients included was limited.[84] Better outcome was seen in patients treated with a treosulfan/fludarabine-based reduced intensity conditioning regimen in comparison to a busulfan/fludarabine-based one[85] and there were fewer relapses associated with a melphalan/fludarabine-based reduced intensity conditioning regimen *versus* a busulfan/

Table 1. Prospective comparison of allogeneic stem cell transplantation and conventional therapy in high-risk myelodysplastic syndrome.

Authors	Conditioning	Compared to	Age in years	Donor (matched) *vs.* no donor, N	LFS, %	OS, %
Robin *et al.*[47]	RIC and MAC	HMA (76%) and others	50-70	112 *vs.* 50	ND	at 4 years: 37 *vs.* 15 *P*=0.02
Nakamura *et al.* (BMT-CTN 1102)[46]	RIC (different regimens)	HMA or best supportive care	50-75	260 *vs.* 124	at 3 years: 35.8 *vs.* 20.6 *P*=0.03	at 3 years: 47.9 *vs.* 26.6 *P*=0.001
Kröger *et al.* (VidazaAllo-Study)[45]	RIC (busulfan-based)	Azacitidine	50-70	81 *vs.* 27 [no donor: treated with azacitidine]	at 3 years: 34 *vs.* 0 *P*<0.0001	at 3 years: 50 *vs.* 32 *P*=0.12

LFS: leukemia-free survival; OS: overall survival; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; HMA: hypomethylating agents; ND: not done.

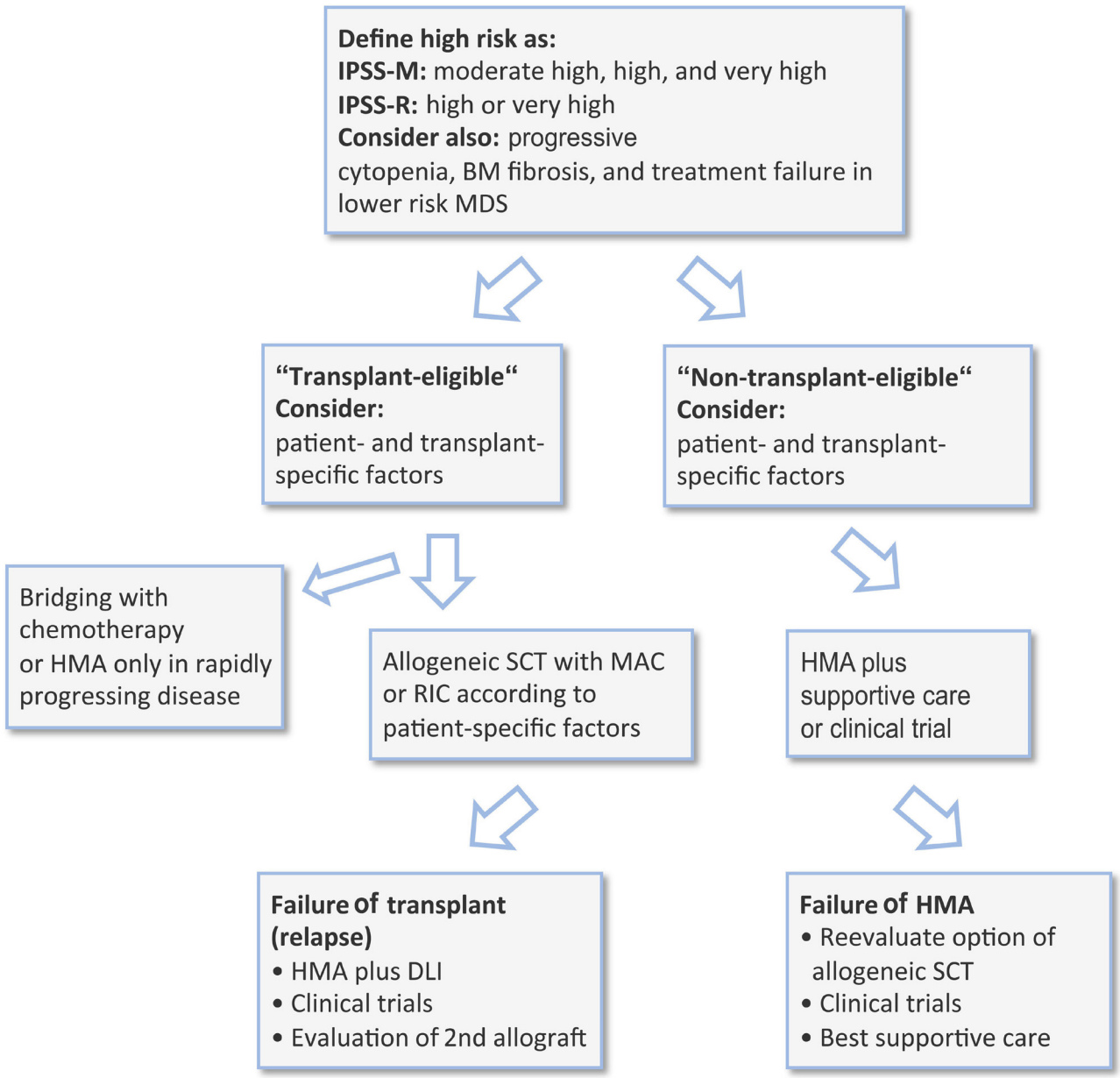

Figure 2. Treatment of high-risk myelodysplastic syndrome. IPSS-M: Molecular International Prognostic Scoring System; IPPS-R: Revised International Prognostic Scoring System; BM: bone marrow; MDS: myelodysplastic syndrome; HMA: hypomethylating agent; SCT: stem cell transplantation; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; DLI: donor lymphocyte infusion.

fludarabine-based one.[86] The broader availability of unrelated donors and the introduction of post-transplant cyclophosphamide as prophylaxis against graft-*versus*-host disease in haploidentical HSCT has further increased the donor pool and the number of allogeneic transplants for MDS and registry studies suggest that the outcome of haploidentical HSCT with post-transplant cyclophosphamide is similar to that with matched unrelated donors.[87]

Post-transplant relapse prevention strategies

Because relapse is the most frequent treatment failure after HSCT in MDS, reducing the risk of relapse by introducing post-transplant maintenance strategies is a hot topic and currently under intense clinical investigation. Post-transplant monitoring by assessment of chimerism or molecular markers with sensitive sequencing methods is helpful in guiding post-transplant interventions.[88,89] However, the largest study so far with 5-azacitidine maintenance for AML and MDS patients failed to show a reduction of relapse after HSCT.[90] Novel approaches to prevent or delay relapse are eprenetapopt plus 5-azacitidine in *TP53*-mutated MDS, enasidinib for *IDH2*-mutated MDS, or pre-emptive 5-azacitidine triggered on the basis of minimal residual disease findings.[53,91,92] Donor lymphocyte infusions alone or in combination are indicated in relapsed patients but available data on this strategy as prophylactic treatment are not conclusive.[93,94] Results from ongoing prospective studies on pre-emptive donor lymphocyte infusions, as well as maintenance with oral 5-azacitidine or 5-azacitidine/venetoclax combinations are pending, thus no valid recommendations can be given at present.

Summary

Treatment of HR-MDS remains a major challenge. Allogeneic HSCT is curative and the standard-of-care treatment for eligible patients. Outcomes after transplantation have improved in recent years due to a reduction of toxicity and better management of infectious complications. All

"higher-risk" MDS patients with good performance status and no severe comorbidities should be considered for curative allogeneic HSCT (Figures 1 and 2). Age should not be considered *per se* as a contraindication. In any case, the risk of HSCT must be balanced against the life expectancy with and without transplantation, also taking the patient's perspective into account. However, even if transplantation for HR-MDS can be offered to older patients as well, the majority of subjects with HR-MDS are still not eligible for this approach. Major clinical research efforts should be made to provide a commonly accepted definition of "transplant-eligibility" and to further reduce therapy-related morbidity and mortality. For patients who are not eligible for transplantation, treatment options are limited and HMA remain the standard treatment. Despite novel insights into the disease and encouraging results from early clinical trials investigating novel agents, subsequently performed randomized trials have not shown improvements to the outcomes achieved with standard therapy with HMA alone, which is still the only approved treatment forf HR-MDS, thus underlscoring the unmet need for better, effective treatment.

Disclosures

NK has received honoraria from Mallinckrodt, Novartis, Kite/Gilead, BMS, Takeda, Medac, Neovii, and Sanofi.

References

1. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013;122(17):2943-2964.
2. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood. 2012;120(12):2454-2465.
3. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for myelodysplastic syndromes. NEJM Evid. 2022;1(7):EVIDoa2200008.
4. Tentori CA, Gregorio C, Robin M, et al. Clinical and genomic-based decision support system to define the optimal timing of allogeneic hematopoietic stem-cell transplantation in patients with myelodysplastic syndromes. J Clin Oncol. 2024;42(24):2873-2886.
5. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
6. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
7. Hellstrom-Lindberg ES, Kroger N. Clinical decision-making and treatment of myelodysplastic syndromes. Blood. 2023;142(26):2268-2281.
8. Pfeilstocker M, Tuechler H, Sanz G, et al. Time-dependent changes in mortality and transformation risk in MDS. Blood. 2016;128(7):902-910.
9. Moreno Berggren D, Folkvaljon Y, Engvall M, et al. Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS Register. Br J Haematol. 2018;181(5):614-627.
10. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007;25(23):3503-3510.
11. Cazzola M, Malcovati L. Myelodysplastic syndromes--coping with ineffective hematopoiesis. N Engl J Med. 2005;352(6):536-538.
12. de Swart L, Crouch S, Hoeks M, et al. Impact of red blood cell transfusion dose density on progression-free survival in patients with lower-risk myelodysplastic syndromes. Haematologica. 2020;105(3):632-639.
13. Stauder R, Yu G, Koinig KA, et al. Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study. Leukemia. 2018;32(6):1380-1392.
14. Mittelman M, Platzbecker U, Afanasyev B, et al. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): a randomised, placebo-controlled, phase 2 trial. Lancet Haematol. 2018;5(1):e34-e43.
15. Dickinson M, Cherif H, Fenaux P, et al. Azacitidine with or without eltrombopag for first-line treatment of intermediate- or high-risk MDS with thrombocytopenia. Blood. 2018;132(25):2629-2638.
16. Penack O, Peczynski C, van der Werf S, et al. Association of serum ferritin levels before start of conditioning with mortality after alloSCT - a prospective, non-interventional study of the EBMT Transplant Complications Working Party. Front Immunol. 2020;11:586.
17. Essmann S, Heestermans M, Dadkhah A, et al. Iron chelation with deferasirox suppresses the appearance of labile plasma iron during conditioning chemotherapy prior to allogeneic stem cell transplantation. Transplant Cell Ther. 2023;29(1):42.e1-42.e6.
18. Stomper J, Rotondo JC, Greve G, Lubbert M. Hypomethylating agents (HMA) for the treatment of acute myeloid leukemia and myelodysplastic syndromes: mechanisms of resistance and novel HMA-based therapies. Leukemia. 2021;35(7):1873-1889.
19. Liu YC, Kwon J, Fabiani E, et al. Demethylation and up-regulation of an oncogene after hypomethylating therapy. N Engl J Med. 2022;386(21):1998-2010.
20. Garcia-Manero G, Fenaux P. Hypomethylating agents and other novel strategies in myelodysplastic syndromes. J Clin Oncol. 2011;29(5):516-523.
21. Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol. 2011;29(15):1987-1996.
22. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the

myelodysplastic syndrome: a study of the Cancer and Leukemia Group B. J Clin Oncol. 2002;20(10):2429-2440.
23. Kornblith AB, Herndon JE 2nd, Silverman LR, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol. 2002;20(10):2441-2452.
24. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223-232.
25. Greenberg PL, Stone RM, Al-Kali A, et al. Myelodysplastic syndromes, version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(1):60-87.
26. Zeidan AM, Salimi T, Epstein RS. Real-world use and outcomes of hypomethylating agent therapy in higher-risk myelodysplastic syndromes: why are we not achieving the promise of clinical trials? Future Oncol. 2021;17(36):5163-5175.
27. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood. 2020;136(6):674-683.
28. Wei AH, Dohner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. N Engl J Med. 2020;383(26):2526-2537.
29. Garcia-Manero G, Santini V, Almeida A, et al. Phase III, randomized, placebo-controlled trial of CC-486 (oral azacitidine) in patients with lower-risk myelodysplastic syndromes. J Clin Oncol. 2021;39(13):1426-1436.
30. Nannya Y, Tobiasson M, Sato S, et al. Postazacitidine clone size predicts long-term outcome of patients with myelodysplastic syndromes and related myeloid neoplasms. Blood Adv. 2023;7(14):3624-3636.
31. Sekeres MA, Othus M, List AF, et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. J Clin Oncol. 2017;35(24):2745-2753.
32. Ades L, Girshova L, Doronin VA, et al. Pevonedistat plus azacitidine vs azacitidine alone in higher-risk MDS/chronic myelomonocytic leukemia or low-blast-percentage AML. Blood Adv. 2022;6(17):5132-5145.
33. Sallman DA, Al Malki MM, Asch AS, et al. Magrolimab in combination with azacitidine in patients with higher-risk myelodysplastic syndromes: final results of a phase Ib study. J Clin Oncol. 2023;41(15):2815-2826.
34. Ball BJ, Famulare CA, Stein EM, et al. Venetoclax and hypomethylating agents (HMAs) induce high response rates in MDS, including patients after HMA therapy failure. Blood Adv. 2020;4(13):2866-2870.
35. Bazinet A, Darbaniyan F, Jabbour E, et al. Azacitidine plus venetoclax in patients with high-risk myelodysplastic syndromes or chronic myelomonocytic leukaemia: phase 1 results of a single-centre, dose-escalation, dose-expansion, phase 1-2 study. Lancet Haematol. 2022;9(10):e756-e765.
36. Asayama T, Tamura H, Ishibashi M, et al. Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. Oncotarget. 2017;8(51):88904-88917.
37. Sebert M, Stamatoullas A, Braun T, et al. Azacitidine (AZA) combined with idarubicin in higher risk MDS - results of a phase I/II study by the Groupe Francophone Des Myelodysplasies (GFM). Blood. 2015;126(23):2884.
38. Ades L, Duployez N, Guerci-Bresler A, et al. A randomised phase II study of azacitidine (AZA) alone or with lenalidomide (LEN), valproic acid (VPA) or idarubicin (IDA) in higher-risk MDS or low blast AML: GFM's "pick a winner" trial, with the impact of somatic mutations. Br J Haematol. 2022;198(3):535-544.
39. Wolf Y, Anderson AC, Kuchroo VK. TIM3 comes of age as an inhibitory receptor. Nat Rev Immunol. 2020;20(3):173-185.
40. Brunner AM, Esteve J, Porkka K, et al. Efficacy and safety of sabatolimab (MBG) in combination with hypomethylating agents (HMAs) in patients (Pts) with very high/high-risk myelodysplastic syndrome (vHR/HRMDS) and acute myeloid leukemia (AML): final analysis from a phase Ib study. Blood. 2021;138(Supplement 1):244.
41. Zeidan AM, Ando K, Rauzy O, et al. Sabatolimab plus hypomethylating agents in previously untreated patients with higher-risk myelodysplastic syndromes (STIMULUS-MDS1): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Haematol. 2024;11(1):e38-e50.
42. Zeidan AM, Xiao Z, Sanz G, et al. Primary results of the phase III STIMULUS-MDS2 study of sabatolimab + azacitidine vs placebo + azacitidine as frontline therapy for patients with higher-risk MDS or CMML-2. Hemasphere. 2024. EHA Library. Zeidan A. 06/13/2024; 422284; S180.
43. Prebet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol. 2011;29(24):3322-3327.
44. Garcia-Manero G, Fenaux P, Al-Kali A, et al. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. Lancet Oncol. 2016;17(4):496-508.
45. Kroger N, Sockel K, Wolschke C, et al. Comparison between 5-azacytidine treatment and allogeneic stem-cell transplantation in elderly patients with advanced MDS according to donor availability (VidazaAllo study). J Clin Oncol. 2021;39(30):3318-3327.
46. Nakamura R, Saber W, Martens MJ, et al. Biologic assignment trial of reduced-intensity hematopoietic cell transplantation based on donor availability in patients 50-75 years of age with advanced myelodysplastic syndrome. J Clin Oncol. 2021;39(30):3328-3339.
47. Robin M, Porcher R, Ades L, et al. HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome. A prospective study on behalf of SFGM-TC and GFM. Leukemia. 2015;29(7):1496-1501.
48. Awada H, Gurnari C, Xie Z, Bewersdorf JP, Zeidan AM. What's next after hypomethylating agents failure in myeloid neoplasms? A rational approach. Cancers (Basel). 2023;15(8):2248.
49. Merz AMA, Sebert M, Sonntag J, Kubasch AS, Platzbecker U, Ades L. Phase to phase: navigating drug combinations with hypomethylating agents in higher-risk MDS trials for optimal outcomes. Cancer Treat Rev. 2024;123:102673.
50. DiNardo CD, Venugopal S, Lachowiez C, et al. Targeted therapy with the mutant IDH2 inhibitor enasidenib for high-risk IDH2-mutant myelodysplastic syndrome. Blood Adv. 2023;7(11):2378-2387.
51. DiNardo CD FJ, Watts JM, et al. Ivosidenib (IVO) in patients with IDH1-mutant relapsed/refractory myelodysplastic syndrome (R/R MDS): updated enrollment of a phase 1 dose escalation

and expansion study. HemaSphere. 2020:EHA Library. DiNardo C. 06/12/2020; 294743; EP826.
52. Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and azacitidine in TP53-mutant myelodysplastic syndromes. J Clin Oncol. 2021;39(14):1584-1594.
53. Mishra A, Tamari R, DeZern AE, et al. Eprenetapopt plus azacitidine after allogeneic hematopoietic stem-cell transplantation for TP53-mutant acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol. 2022;40(34):3985-3993.
54. Wattel E, De Botton S, Luc Lai J, et al. Long-term follow-up of de novo myelodysplastic syndromes treated with intensive chemotherapy: incidence of long-term survivors and outcome of partial responders. Br J Haematol. 1997;98(4):983-991.
55. Bally C, Ades L, Renneville A, et al. Prognostic value of TP53 gene mutations in myelodysplastic syndromes and acute myeloid leukemia treated with azacitidine. Leuk Res. 2014;38(7):751-755.
56. de Witte T, Suciu S, Verhoef G, et al. Intensive chemotherapy followed by allogeneic or autologous stem cell transplantation for patients with myelodysplastic syndromes (MDSs) and acute myeloid leukemia following MDS. Blood. 2001;98(8):2326-2331.
57. Peterlin P, Le Bris Y, Turlure P, et al. CPX-351 in higher risk myelodysplastic syndrome and chronic myelomonocytic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Haematol. 2023;10(7):e521-e529.
58. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004;104(2):579-585.
59. Alessandrino EP, Porta MG, Malcovati L, et al. Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. Am J Hematol. 2013;88(7):581-588.
60. Della Porta MG, Jackson CH, Alessandrino EP, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised International Prognostic Scoring System. Leukemia. 2017;31(11):2449-2457.
61. Onida F, Brand R, van Biezen A, et al. Impact of the International Prognostic Scoring System cytogenetic risk groups on the outcome of patients with primary myelodysplastic syndromes undergoing allogeneic stem cell transplantation from human leukocyte antigen-identical siblings: a retrospective analysis of the European Society for Blood and Marrow Transplantation-Chronic Malignancies Working Party. Haematologica. 2014;99(10):1582-1590.
62. van Gelder M, de Wreede LC, Schetelig J, et al. Monosomal karyotype predicts poor survival after allogeneic stem cell transplantation in chromosome 7 abnormal myelodysplastic syndrome and secondary acute myeloid leukemia. Leukemia. 2013;27(4):879-888.
63. Della Porta MG, Galli A, Bacigalupo A, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. J Clin Oncol. 2016;34(30):3627-3637.
64. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med. 2017;376(6):536-547.
65. Yoshizato T, Nannya Y, Atsuta Y, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. Blood. 2017;129(17):2347-2358.
66. Gurnari C, Gagelmann N, Badbaran A, et al. Outcome prediction in myelodysplastic neoplasm undergoing hematopoietic cell transplant in the molecular era of IPSS-M. Leukemia. 2023;37(3):717-719.
67. Sauta E, Robin M, Bersanelli M, et al. Real-world validation of Molecular International Prognostic Scoring System for myelodysplastic syndromes. J Clin Oncol. 2023;41(15):2827-2842.
68. Atallah E, Logan B, Chen M, et al. Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage With Evidence Development study. JAMA Oncol. 2020;6(4):486-493.
69. Niederwieser C, Kroger N. Hematopoietic cell transplantation (HCT) in MDS patients of older age. Leuk Lymphoma. 2024;65(5):570-584.
70. DeFilipp Z, Ciurea SO, Cutler C, et al. Hematopoietic cell transplantation in the management of myelodysplastic syndrome: an evidence-based review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. Transplant Cell Ther. 2023;29(2):71-81.
71. Versluis J, Saber W, Tsai HK, et al. Allogeneic hematopoietic cell transplantation improves outcome in myelodysplastic syndrome across high-risk genetic subgroups: genetic analysis of the Blood and Marrow Transplant Clinical Trials Network 1102 study. J Clin Oncol. 2023;41(28):4497-4510.
72. Kennedy AL, Shimamura A. Genetic predisposition to MDS: clinical features and clonal evolution. Blood. 2019;133(10):1071-1085.
73. Carre M, Porcher R, Finke J, et al. Role of age and Hematopoietic Cell Transplantation-Specific Comorbidity Index in myelodysplastic patients undergoing an allotransplant: a retrospective study from the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2020;26(3):451-457.
74. Penack O, Peczynski C, Mohty M, et al. Association of pre-existing comorbidities with outcome of allogeneic hematopoietic cell transplantation. A retrospective analysis from the EBMT. Bone Marrow Transplant. 2022;57(2):183-190.
75. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood. 2014;123(15):2333-2342.
76. Shaffer BC, Ahn KW, Hu ZH, et al. Scoring system prognostic of outcome in patients undergoing allogeneic hematopoietic cell transplantation for myelodysplastic syndrome. J Clin Oncol. 2016;34(16):1864-1871.
77. Gagelmann N, Eikema DJ, Stelljes M, et al. Optimized EBMT transplant-specific risk score in myelodysplastic syndromes after allogeneic stem-cell transplantation. Haematologica. 2019;104(5):929-936.
78. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017;129(13):1753-1762.
79. Niederwieser C, Kroger N. Current status of pretransplant intensive chemotherapy or hypomethylating agents for myelodysplastic syndrome. Best Pract Res Clin Haematol. 2021;34(4):101332.

80. Kroger N. Induction, bridging, or straight ahead: the ongoing dilemma of allografting in advanced myelodysplastic syndrome. Biol Blood Marrow Transplant. 2019;25(8):e247-e249.
81. Scheid C, Eikema DJ, van Gelder M, et al. Does IPSS-R downstaging before transplantation improve the prognosis of patients with myelodysplastic neoplasms? Blood. 2024;144(4):445-456.
82. Martino R, Iacobelli S, Brand R, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006;108(3):836-846.
83. Kroger N, Iacobelli S, Franke GN, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a prospective randomized phase III study of the EBMT (RICMAC trial). J Clin Oncol. 2017;35(19):2157-2164.
84. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol. 2017;35(11):1154-1161.
85. Beelen DW, Trenschel R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. Lancet Haematol. 2020;7(1):e28-e39.
86. Oran B, Ahn KW, Fretham C, et al. Fludarabine and melphalan compared with reduced doses of busulfan and fludarabine improve transplantation outcomes in older patients with myelodysplastic syndromes. Transplant Cell Ther. 2021;27(11):921.e1-921.e10.
87. Grunwald MR, Zhang MJ, Elmariah H, et al. Alternative donor transplantation for myelodysplastic syndromes: haploidentical relative and matched unrelated donors. Blood Adv. 2021;5(4):975-983.
88. Duncavage EJ, Jacoby MA, Chang GS, et al. Mutation clearance after transplantation for myelodysplastic syndrome. N Engl J Med. 2018;379(11):1028-1041.
89. Tobiasson M, Pandzic T, Illman J, et al. Patient-specific measurable residual disease markers predict outcome in patients with myelodysplastic syndrome and related diseases after hematopoietic stem-cell transplantation. J Clin Oncol. 2024;42(12):1378-1390.
90. Oran B, de Lima M, Garcia-Manero G, et al. A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients. Blood Adv. 2020;4(21):5580-5588.
91. Fathi AT, Kim HT, Soiffer RJ, et al. Enasidenib as maintenance following allogeneic hematopoietic cell transplantation for IDH2-mutated myeloid malignancies. Blood Adv. 2022;6(22):5857-5865.
92. Platzbecker U, Middeke JM, Sockel K, et al. Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial. Lancet Oncol. 2018;19(12):1668-1679.
93. Schroeder T, Stelljes M, Christopeit M, et al. Azacitidine, lenalidomide and donor lymphocyte infusions for relapse of myelodysplastic syndrome, acute myeloid leukemia and chronic myelomonocytic leukemia after allogeneic transplant: the Azalena-trial. Haematologica. 2023;108(11):3001-3010.
94. Guisnel C, Schirmer L, Morisset S, et al. On behalf of the SFGM-TC: prophylactic donor lymphocyte infusion in patients treated with allogeneic stem-cell transplantation for high-risk myelodysplastic syndrome and acute myeloid leukemia. Acta Haematol. 2023;146(3):230-239.