In MDS, is higher risk higher reward?

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Patients with higher-risk myelodysplastic syndrome (HR-MDS) are defined by the original or revised International Prognostic Scoring System and specific genetic features. Treatment of HR-MDS is challenging. Allogeneic hematopoietic stem cell transplantation, the only curative approach, is feasible in a minority of fit or intermediate fitness patients aged <70 to 75 years who are willing to face the risks of the procedure. Response to azacitidine and decitabine, the only approved drugs for HR-MDS and considered the standard of care, is partial and transient in most patients. The development of novel more personalized and efficient drugs is an unmet medical need. During the last decade, there have been substantial advances in understanding the multiple molecular, cellular, and immunological disturbances involved in the pathogenesis of myelodysplastic syndrome. As a result, a number of clinical and translational studies of new more focused treatment approaches for HR-MDS patients are underway. In contrast to acute myeloid leukemia, they have not resulted in any new drug approval. This review addresses the benefits and limitations of current treatment alternatives, offers a practical individualized treatment approach, and summarizes the clinical trials in progress for HR-MDS.

Learning Objectives

- Identify MDS patients with a higher risk for AML transformation and death
- Understand available treatment modalities and those under investigation for patients with HR-MDS
- Select the most appropriate treatment for HR-MDS patients based on individual risk assessment, medical fitness, and goals of care

This review covers the current strategies for treatment of higher-risk patients with myelodysplastic syndrome (MDS) and describes how to use the available therapeutic options in a realistic and practical manner. With regard to patients in whom an allogeneic HSCT should be offered, several key issues, such as the role of bridging therapy, optimal conditioning regimen, role of genetic mutations, and selection of the best donor and graft source, are also discussed. Finally, the alternative treatment approaches for patients who are not suitable for transplantation, including hypomethylating agents (HMAs), intensive chemotherapy (ICT), and novel agents, most of which are under investigation, are also addressed.

Introduction

Patients with higher-risk myelodysplastic syndrome (HR-MDS) have a poor prognosis, and prolonging their survival is the primary goal of therapy for most patients, because the only curative treatment, allogeneic hematopoietic stem cell transplantation (HSCT), is restricted to fit patients up to 70 to 75 years of age. In contrast, for most patients with advanced age, bad performance status (PS), or severe comorbid medical conditions, less intensive therapies and/or palliative care are the only treatment options. A more difficult decision-making scenario exists for patients with an intermediate medical fitness or with specific genetic features. Some patients in this setting might be suitable for allogeneic HSCT, whereas others, depending on institutional/clinician approach and patient's preference, will choose a more or less intensive treatment, enrollment in a clinical trial, or even just supportive treatment.

Clinical case

A 67-year-old woman was referred from her general practitioner for evaluation of pancytopenia. Her medical history was unremarkable except for well-controlled essential hypertension and hypercholesterolemia. She had been fully active until 2 months before the onset of progressive fatigue. She was found to have a hemoglobin level of 8.2 g/dL, a white blood cell count of 1.4×10^9/L, a neutrophil count of 0.6×10^9/L, and a platelet count of 80×10^9/L. Physical examination was normal except for pallor. A bone marrow (BM) aspirate was hypercellular with multilineage dysplasia and 15% myeloblasts, which was consistent with MDS with excess blasts type 2. Cytogenetics showed deletion of 7q and trisomy 8 in 16 of 20 metaphases and 4 normal female metaphases. A mutational genetic panel showed mutations in *SRFS2* (variant allele frequency [VAF], 32%), *IDH2* (VAF, 27%), and *TET2* (VAF, 14%). An HLA-identical sibling was not available.

Definition of HR-MDS for therapeutic purposes

The International Prognostic Scoring System (IPSS)[1] and the subsequent Revised International Prognostic Scoring System (IPSS-R)[2] are the most widely used prognostic scoring systems for therapeutic decision making in MDS patients. The IPSS and the IPSS-R are able to stratify patients into 4 and 5 risk groups, respectively, in terms of survival and the risk of acute myeloid leukemia (AML) transformation. However, and primarily because of the paucity of available treatment alternatives, only 2 risk groups of patients, lower risk and higher risk, are recognized for therapeutic purposes. HR-MDS patients are defined as those with intermediate-2 or high-risk score by the IPSS or with intermediate (with >3.5 points), high, or very high risk score by the IPSS-R.[3] In some instances, patients not falling into those categories are considered to be deserving of the therapeutic alternatives used in HR-MDS patients. Thus, intermediate-1 risk patients by the IPSS are commonly upgraded to the higher-risk category in the presence of life-threatening cytopenias or genetic features of very poor prognosis, such as complex karyotypes or *TP53* mutations. The inclusion of other mutations or the number of mutations in this definition is still unclear. A large cooperative international group is building a molecular IPSS to confirm the negative independent prognostic impact of somatic mutations (eg, *TP53*, *RUNX1*, *EZH2*, *ASXL1*, *ETV6*, and *SRSF2*), comutation patterns, and the number of driver mutations; their preliminary results are eagerly awaited. The results of this study may be particularly relevant for younger fit patients categorized as lower-risk by the IPSS or IPSS-R.

Stratification by medical fitness and goals of care

Management of patients with HR-MDS is challenging and deserves a careful assessment of medical fitness, including physical and cognitive functioning, vulnerability, comorbid conditions, and quality of life. A prompt assessment of medical fitness is a critical step in the management of patients with HR-MDS, because it can accurately predict tolerability to ICT and allogeneic HSCT.

Assessment of physical and cognitive functioning and vulnerability

Physical functioning is commonly assessed by the Eastern Cooperative Oncology Group (ECOG) PS and the Karnofsky Performance Status (KPS). However, older adults may have impairments that are not appropriately considered in the PS scores, such as depression, cognitive impairment, decline in activities of daily living, and vulnerability to treatment. Some of the tools commonly used for measuring functional status in geriatrics, such as the Short Physical Performance Battery (SPPB) for evaluating lower extremity function,[4] different scales of impairment in basic and instrumental activities of daily living,[5] and geriatric assessment (GA) scores like the G8 score,[6] have demonstrated their value in cancer patients, including those with multiple myeloma.[7] Further, a specific and integral Geriatric Assessment in Hematology scale has recently been developed[8] but remains to be externally validated. The Geriatric Assessment in Hematology scale is as easy to use as the G8 score (10 minutes to fulfill), but in contrast to the G8 score it also includes comorbidity, which could be a potential advantage. However, it should be noted that none of those GA tools has been specifically evaluated in patients with MDS. Thus, a consensus on how to assess functional decline and vulnerability in older MDS patients has not been reached. A multicenter study on adults with MDS and AML showed that impairment in activities of daily living, KPS < 80%, and increased "fatigue" (≥50% by European Organization for Research and Treatment of Cancer

[EORTC] Quality of Life Questionnaire [QLQ]-C30) were independently associated with shorter overall survival (OS).[9]

Assessment of comorbidity

Comorbid conditions are very common in older adults with MDS and have important implications in their management.

Although the prognostic impact of comorbidity in HR-MDS is debatable, it clearly influences the choice of treatment. When relevant comorbidity is present, the likelihood of using disease-modifying therapies, especially allogeneic HSCT, is reduced. The comorbidity indexes that are used most frequently in MDS are the MDS-specific comorbidity index,[10] the Charlson comorbidity index,[11] and the Hematopoietic Cell Transplantation comorbidity index (HCT-CI).[12] The last is strongly recommended for assessing suitability for HSCT.

Categories of medical fitness and goals of care

Although age is an important factor, it is not always a determining factor when deciding the goals of care for patients with HR-MDS. Medical fitness, individual preference, and institutional approach should also be considered.

The medical fitness of the older patient with MDS can be categorized as fit, intermediate fitness, or frail, according to all of the factors discussed above. Table 1 shows the stratification criteria for defining medical fitness used at our center for older patients with HR-MDS and the therapeutic approach recommended for each category. Schematically, whenever possible, medically fit patients with HR-MDS should be considered for allogeneic HSCT. If for some reason transplantation is contraindicated or is not the preferred option for the patient, HMAs, ICT, and enrollment in a clinical trial are alternative treatment options. Some intermediate fitness patients may be suitable for allogeneic HSCT or ICT, assuming a higher risk for death, but most of them will be treated with HMAs. The choice of treatment for patients in this setting would be determined by the institutional approach, personal preference, availability of a caregiver, and, in some instances, by the presence of targetable genetic alterations. Care of medically frail patients, who are implicitly unsuitable for intensive therapy, should have only a palliative intention to relieve symptoms and improve quality of life. Supportive care alone could also be an option for certain fit and intermediate fitness patients of very advanced age or who lack a caregiver.

Translational research should be considered a priority in MDS, and patients should be included, whenever possible, in well-designed

Table 1. Goals of care and treatment approaches according to medical fitness in older patients with HR-MDS

Medical fitness*	Goals of care	First-choice treatment	Alternative option
Fit	Achieve long-term survival with the possibility of cure	HSCT	HMA ICT Clinical trial
Intermediate fitness†	Alleviate symptoms, improve quality of life, and/or prolong life.	HMA	Clinical trial
Frail	Palliation	Supportive care	Clinical trial (?)

*Fit: ECOG PS 0 or 1 and HCT-CI 0; intermediate fitness: ECOG PS 2 or HCT-CI 1 or 2 or SPPB score 9; frail: ECOG PS ≥ 3 or HCT-CI ≥ 3 or SPPB score < 9.
†Some intermediate fitness patients could be offered allogeneic HSCT with reduced intensity conditioning.

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prospective clinical trials driven to gain insight into our under-standing of MDS and improve the outcomes.

Treatment options

Because allogeneic HSCT is the only proven curative treatment in MDS, patients with HR-MDS should be evaluated shortly after diagnosis to assess their eligibility for this treatment option. For fit and intermediate fitness patients who are ineligible for transplantation, ICT or HMAs are first-line treatment options that should be considered. An algorithm for the management of HR-MDS patients is proposed in Figure 1.

Allogeneic HSCT

The number of elderly patients receiving allogeneic HSCT has dramatically increased worldwide over the past decade, primarily as a result of the expansion of donors and sources of hematopoietic stem cells and wider applicability in older patients using reduced intensity conditioning (RIC) regimens. This has made HSCT, the only

* Consider targeted therapy for patients with targetable mutations

Figure 1. Therapeutic algorithm for HR-MDS. Arrow with shorter dashes indicates fit patients who, for some reason, are not candidates for HSCT (eg, patient's refusal, lack of donor), and arrow with longer dashes indicates intermediate fitness patients who are considered suitable for HSCT.

curative therapy in MDS, a realistic option for an increasing number of patients. In addition, transplantation offered superior clinical outcomes compared with nontransplantation approaches, including HMAs, in several retrospective studies of patients with HR-MDS up to 70 years of age.[13-15] Thus, using Markov decision models, 2 large series have showed that, in patients with HR-MDS (IPSS intermediate-2 and high risk) aged 60 years or younger[13] or aged 60 to 70 years,[14] life expectancy and quality-of-life–adjusted life expectancy are superior and maximized with early HSCT (using RIC regimens in patients aged 60 to 70 years) compared with best supportive care[13] or treatment with HMAs.[14] The results of a retrospective multinational study comparing 2 well-balanced cohorts of HR-MDS patients aged 60 to 70 years who received RIC HSCT (n = 103) or azacitidine (n = 75) based on donor availability or institutional policy also showed an advantage for HSCT-treated patients.[15] OS, disease-free survival (DFS), relapse rate (RR), and nonrelapse mortality (NRM) at 2 years were 39%, 37%, 30%, and 33%, respectively, for the HSCT-treated cohort and 23%, 14%, 52%, and 34%, respectively, for the azacitidine-treated cohort; treatment emerged as a strong independent factor for OS and DFS in multivariate analyses.[15] The superiority of RIC HSCT over azacitidine has been confirmed in a German prospective multi-center study reported in abstract form that compared azacitidine induction (4 to 6 cycles), followed by RIC HSCT, with continuous azacitidine, according to donor availability in 190 patients aged 55 to 70 years (median age, 63 years) with HR-MDS.[16] For several reasons, 81 patients exited the study prematurely (progressive disease, death, or adverse events in 46); only 109 patients were finally allocated to receive HSCT (n = 83) or continued azacitidine (n = 26). OS and DFS at 3 years were 49% and 35%, respectively, for HSCT and 22% and 0%, respectively, for continuous azacitidine treatment ($P = .027$ and $P < .001$, respectively).[16] A North American phase 3 multicenter clinical trial is also comparing RIC allogeneic HSCT with hypomethylating therapy or best supportive care in patients with intermediate-2 and high-risk MDS (Blood and Marrow Transplant Clinical Trials Network [BMT CTN] 1102). It is hoped that the full results of these studies will better inform decision making in the setting of HR-MDS. However, allogeneic HSCT is undertaken in roughly 10% of HR-MDS patients, and several issues regarding the best way to perform transplantation remain controversial.

Who should be considered for transplantation?. There is a general consensus that all patients aged up to 70 to 75 years with HR-MDS, good PS (ECOG PS ≤ 2 or KPS ≥ 80%), no severe comorbidities,[12] and suitable medical fitness should be transplanted whenever possible, unless the patient's preference is a nontransplant option. The Center for International Blood and Marrow Transplant Research (CIBMTR) risk score to predict outcome after HSCT[17] and some molecular features should also be considered.[18] According to current recommendations,[18] patients with an extremely low chance for cure with HSCT should be enrolled in clinical trials whenever possible.

Effect of somatic mutations at transplantation on transplantation outcomes. The role of genetic mutations present at transplantation on posttransplantation outcomes of patients with MDS has recently been investigated in 3 large cohorts of patients with interesting, but controversial, results.[19-21] In an Italian study of 401 patients with MDS and AML evolving from MDS (secondary AML [sAML]), multivariate analysis identified the presence of somatic mutations in *ASXL1* (hazard ratio [HR], 1.72 vs absence), *RUNX1* (HR, 1.59 vs absence), and *TP53* (HR, 1.82 vs absence) as being significantly associated with shorter OS after transplant. OS
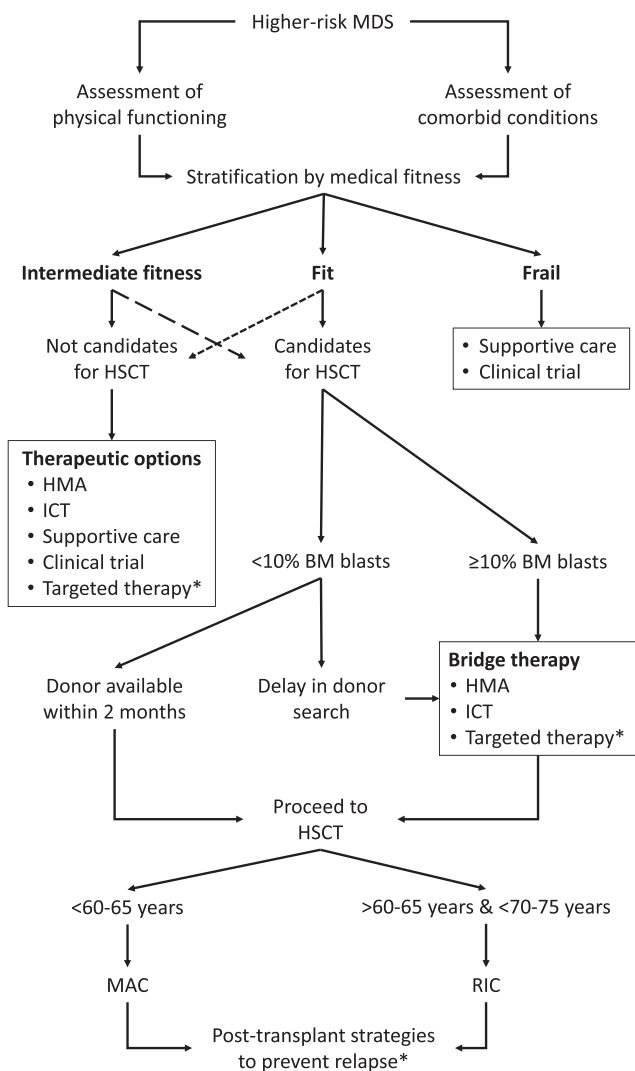
at 5 years for patients carrying ≥ 1 of those mutations was close to 30% and 10% in IPSS-R high-risk and very high-risk patients, respectively, whereas these figures were close to 50% and 25%, respectively, in nonmutated patients.[19] In a larger Japanese study of 797 patients with MDS, sAML, and MDS/myeloproliferative neoplasms, only *TP53* (HR, 1.49 vs absence), *CBL* (HR, 1.55 vs absence), and *RAS* pathway (HR, 1.64 vs absence) mutations were independently associated with OS (the later mutations only in patients with refractory anemia with an excess of blasts in transformation and sAML).[20] When ≥ 1 of those 3 mutations or a complex karyotype was present, OS at 5 years for patients in the IPSS intermediate-2 and high-risk groups was close to 30% and <10%, respectively, whereas for patients without those genetic lesions, the corresponding figures were >50% in both IPSS risk groups. Interestingly, in this series, the deleterious effect of *TP53* mutations on survival was confined to patients with a complex karyotype, who showed a dismal prognosis (OS at 2 years, 0%). In contrast, OS at 5 years for *TP53*-mutated patients without a complex karyotype was >30%.[20] Finally, a mutational analysis in a series of 1514 MDS patients (therapy-related MDS, 21%) reported to the CIBMTR confirmed that the presence of *TP53* mutations, irrespective of age and conditioning regimen, was the most powerful and independent predictor of OS (HR vs absence, 1.71) and RR (HR vs absence, 2.03).[21] OS at 3 years was 20% for patients harboring a *TP53* mutation and close to 50% for those who lacked this mutation. OS for patients with *TP53* mutations was similar regardless of whether a complex karyotype was present. This study also showed that, among patients aged ≥ 40 years without *TP53* mutations, the presence of *RAS* pathway mutations was associated with shorter OS in comparison with the lack of these mutations (30% at 3 years among patients with RAS pathway mutations) as the result of a higher RR, but only with RIC regimens (OS at 1 year, 42% if *RAS* pathway mutations were present and 20% if absent). In these older MDS patients, the presence of *JAK2* mutations (vs the absence of *JAK2* mutations) was associated with shorter OS because of a higher risk for NRM.[21]

These findings support mutational analysis as an additional tool in decision making regarding transplantation in HR-MDS patients. Nonetheless, with the exception of *TP53* mutations, all of these results should be taken with caution before incorporating them into our daily practice. The heterogeneity of the patients included in the different studies, the divergent results, and the low number of patients with specific mutations, especially of those with low prevalence, do not allow us to draw definite conclusions, and further investigation is required. Patients with *TP53* mutations and a complex karyotype should not undergo a conventional HSCT. On the contrary, they should always be included in clinical trials driven to assess the efficacy of newer drugs or to prevent relapse after the transplant. No clear recommendation can be offered for patients with *TP53* mutations but without a complex karyotype. My personal advice would be to undergo HSCT, but favoring their participation in an investigative approach aimed to reduce RR.

Should patients receive cytoreductive bridging therapy before transplantation?. The role of cytoreductive ("bridging") treatment prior to transplant conditioning to reduce the burden of the disease in patients with HR-MDS is still controversial. Some retrospective studies suggested comparable outcomes whether patients proceeded directly to transplantation or received ICT[22,23] or azacitidine[24] prior to allogeneic HSCT. However, there are no randomized studies comparing the strategy of proceeding directly to transplantation with the use of bridging therapy in HR-MDS. The recent recommendation of an

international expert panel is to proceed to transplantation without pretreatment in patients with <10% BM blasts, whereas fit patients with >10% BM blasts should receive pretransplant treatment, without a preference for ICT or HMA.[18] This approach could also be an acceptable option for patients in whom HSCT is delayed for logistic reasons (eg, excessive delay in donor search is anticipated).

Two retrospective studies comparing azacitidine with ICT as pre-HSCT therapy were not able to demonstrate the superiority of any of these treatment alternatives on posttransplant outcomes.[25,26] In the large French series comparing ICT alone (n = 98) and azacitidine alone (n = 49) before the transplant, 3-year OS was 48% vs 55%, event-free survival was 44% vs 42%, RR was 37% vs 40%, and NRM was 20% vs 19%, respectively. These differences were not statistically significant in univariate and multivariate analyses.[26] Because HMAs, especially azacitidine, have a better toxicity profile than ICT, their use could be preferable, at least when an RIC regimen is planned. The results of an ongoing randomized phase 2 trial (NCT01812252) comparing the effect of pretransplant ICT vs HMAs will help to determine the optimal pretransplant cytoreductive treatment in MDS.

An alternative bridging therapy to allogeneic HSCT that has been suggested specifically for MDS patients with *TP53* mutations is a 10-day schedule of decitabine.[27] In a series including 21 patients with this mutation (12 with AML and 9 with MDS and 20 of them showing a complex karyotype), all patients responded to decitabine, with BM blast clearance to <5% and a reduction in VAFs to <5%; median OS was 12.7 months.[27] Because *TP53*-mutated AML and MDS are particularly resistant to ICT, the use of this decitabine schedule could be preferable to ICT in this setting.

What is the optimal conditioning intensity and regimen?. The current evidence does not provide support for specific recommendations on the optimal intensity of the conditioning regimen. Two randomized studies comparing RIC and myeloablative conditioning (MAC) in patients up to 65 years of age are available with conflicting results.[28,29] In the BMT CTN 0091 trial, which included only MDS patients with <5% blasts in BM, OS, relapse-free survival, and RR (NRM not available) at 18 months were 81.5% vs 85.2%, 77.8% vs 55.6%, and 3.7% vs 37% for MAC and RIC regimens, respectively; the differences in RR were statistically significant.[28] Thus, this study supports that MDS patients younger than 65 years of age with acceptable HCT-CI scores should receive MAC to reduce the RR. In contrast, in a study by the European Society of Blood and Marrow Transplantation (EBMT) that included patients with MDS and AML secondary to MDS with <20% blasts in BM, OS, relapse-free survival, and RR at 2 years and NRM at 1 year were 76%, 62%, 17%, and 17%, respectively, for RIC and 63%, 58%, 15%, and 25%, respectively, for MAC.[29] Although there were no statistically significant differences between MAC and RIC for all of these outcomes in univariate analyses, RIC resulted in improved OS in multivariate analyses, supporting that it is a valid alternative to MAC in MDS patients.[29] Whether the results of these randomized trials are fully applicable to HR-MDS is uncertain, because more than half of the patients in both series had lower-risk MDS, and advanced disease at transplantation is a well-recognized poor prognostic factor for transplantation outcomes.

In general, the choice of a preparative regimen is made by considering the patient's age, as well as comorbidities, expected RR, patient preference, and institutional approach. MAC is generally offered to

younger (<60-65 years) fit patients, whereas RIC is preferred for older patients and/or those with significant comorbidity. In addition, MAC is usually recommended to patients with a high RR, whereas RIC is more commonly preferred in those with a lower RR. Mutational analysis could also be of value for fine tuning the intensity of the conditioning regimen. Older patients with *RAS* pathway mutations should receive MAC if possible, whereas strategies aimed at reducing toxicity and NRM should be explored in those with *JAK2* mutations.[21]

With regard to the components of MAC regimens, total-body irradiation is generally less preferred than chemotherapy because of long-term toxicities, including secondary malignancies.[30] In the absence of MDS-specific data, based on a recent phase 3 trial of patients with AML,[31] busulfan plus fludarabine has also been adopted as the standard of care for older patients with MDS, because it is associated with lower transplant-related mortality (TRM) than busulfan plus cyclophosphamide but retains potent antileukemic activity.

Fludarabine has become a central component of RIC regimens that is generally combined with a reduced dose of busulfan or melphalan.[31] Treosulfan is also a promising drug to be combined with fludarabine. Results of a randomized trial comparing treosulfan-fludarabine vs busulfan-fludarabine in adult AML and MDS patients ineligible for standard MAC regimens (NCT00822393), reported in abstract form, have demonstrated a significant improvement in OS after treosulfan-based conditioning.[32] This benefit was primarily attributed to the reduction in TRM while preserving antileukemic efficacy.

Who is the preferable donor and what is the best graft source?. Despite the fact that outcomes of matched unrelated donor (MUD) HSCT have improved in recent years, a matched related donor (MRD) is still considered the optimal donor for patients with myeloid malignancies. For patients lacking a matched donor, haploidentical and umbilical cord blood (UCB) allografting offer alternative HSCT strategies. Although no randomized comparisons of these strategies are available, some retrospective and registry-based studies in AML, but not in MDS, reported comparable outcomes between MUD HSCT and haploidentical allografting[33] or cord blood transplantation.[34] A large EBMT and CIBMTR joint retrospective study in patients with acute leukemia has recently compared the outcomes of patients after haploidentical transplants including posttransplantation cyclophosphamide vs HLA-matched sibling donor transplants.[35] Irrespective of the recipient's age, haploidentical transplants had a lower incidence of chronic graft-versus-host disease (GVHD) compared with HLA-matched sibling transplants. Patients aged ≥55 years grafted from an HLA-matched sibling had a longer OS, a lower NRM, and a lower graft rejection rate than did patients who were grafted from a haploidentical offspring. For patients aged <55 years, OS, NRM, and the graft rejection rate did not differ between the 2 graft sources.[35] Another EBMT study has suggested that haploidentical transplantation with posttransplant cyclophosphamide could be superior to UCB transplantation in MDS patients.[36] All of these data support that haploidentical family members or UCB are also acceptable donor options for adults with myeloid malignancies when a MUD is not available or a transplant is urgently needed. Institutional preferences and experience with these strategies may influence the choice of donor source.

Although some retrospective studies reported better results with mobilized peripheral blood (MPB) for MRD HSCT in patients with MDS,[37,38] BM is also an acceptable source in this setting. However, for MUD grafts, BM should be considered preferable to MPB,

because long-term follow-up of a large BMT CTN randomized clinical trial comparing BM and MPB from MUDs demonstrated better patient-reported outcomes in recipients of BM.[39] Patients receiving BM grafts had less long-term toxicity, including better psychological well-being and less burdensome chronic GVHD symptoms, and were more likely to return to work (52% vs 40%) at 5 years after transplantation than were patients receiving MPB; however, there were no clear differences between the 2 graft sources with regard to OS (40% vs 39%), RR (32% vs 29%), and TRM (29% vs 32%). Available studies have significant limitations with regard to the ability to draw any definite conclusions about the optimal graft source in the haploidentical setting.[40]

With regard to donor age, younger donors are generally preferred. However, it is often more likely that an older recipient with MDS also has an older healthy MRD in whom some somatic mutations associated with clonal hematopoiesis of indeterminate potential (CHIP) are frequently present.[41,42] Some transplant units are screening for the presence of CHIP in older family donors and searching for a younger MUD if present; however, this approach is questionable. A recent study has evaluated the effect of donor CHIP status on transplantation outcomes in 500 related donor transplants.[43] CHIP was present in 80 (16%) donors, with a higher prevalence in donors for recipients with myeloid malignancies compared with lymphoid malignancies (19.2% vs 6.3%, respectively). Recipients from CHIP donors had a higher incidence of chronic GVHD and lower RR, but donor CHIP status had no effect on OS or NRM. In almost all instances (24/25), clones with mutations engrafted showed a clear expansion in half of them, and 2 patients developed donor-derived leukemia. Until more information becomes available, these data suggest that CHIP donors are safe, at least in terms of OS.[43]

On the other hand, HSCT from a younger MUD rather than from an older HLA-identical sibling could be preferable in older MDS patients. In an EBMT study of transplant recipients older than 50 years of age, transplantation from younger MUDs (<30 years) resulted in a significantly improved 5-year OS in comparison with MRDs (40% vs 33%, respectively).[44]

Preventing and treating relapse after transplantation. Relapse is the main cause of failure after allogeneic HSCT, especially after RIC. Potential treatment approaches for MDS overt relapse after transplant include supportive care, cytoreductive therapy with HMAs or ICT, and cellular immunotherapy with donor lymphocyte infusions (DLIs) or second allogeneic HSCT. In a French series of 147 consecutive patients, OS at 2 years was clearly better with cellular immunotherapy (32%) than with cytoreductive therapy (6%) or supportive care (2%).[45] The combination of azacitidine and DLIs resulted in an impressive 2-year OS of 66% in 28 MDS patients relapsing after transplant, but these results require confirmation.[46]

Other areas under investigation to reduce the risk of relapse after transplant include the prophylactic or preemptive use of azacitidine in patients with a high relapse risk[47] or in those with measurable residual disease by quantitative polymerase chain reaction or declining donor chimerism, considered signs of impending relapse.[48] In a prospective multicenter study assessing the latter approach in 198 patients with AML or advanced MDS, 38 of 53 patients who developed measurable residual disease after transplant received 7-day cycles of azacitidine. Relapse-free survival at 12 months was 46%, which suggests that preemptive therapy with azacitidine could prevent or delay hematological relapse.[48] However, these encouraging results

should be considered preliminary. The recent demonstration of a higher risk for disease progression among patients with MDS in whom persistent disease–associated mutations were detected in the BM 30 days after transplantation constitutes another setting for potential preemptive therapeutic intervention.[49]

ICT

Outside of bridging therapy, the role of AML-type chemotherapy alone for HR-MDS is marginal. Although up to half of younger fit patients can achieve CR with ICT, long-term results after AML-type chemotherapy are very poor, unless it is followed by postremission allogeneic HSCT. In patients ineligible for allogeneic HSCT, the use of HMAs is generally preferred to AML-type chemotherapy. A possible exception is CPX-351, a liposomal formulation with a fixed 5:1 molar ratio of cytarabine and daunorubicin that has been recently licensed for elderly patients with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes. This drug is being explored for HR-MDS patients who are suitable for intensive treatment and HSCT (NCT03572764), as well as after HMA failure (NCT03957876).

HMAs

In the last few years, HMAs have become the standard of care for patients with HR-MDS who are not candidates for allogeneic HSCT. Compared with best supportive care, azacitidine and decitabine have clearly been show to delay progression to AML in randomized trials,[50-53] but only azacitidine has showed a significant advantage in OS compared with conventional care (median OS, 24.5 vs 15 months, respectively).[52] Additionally, azacitidine has shown a survival benefit over low-dose cytarabine,[54] as well as in patients older than 75 years of age.[55] However, none of these drugs have demonstrated significant survival superiority compared with ICT.

Lacking prospective data comparing azacitidine and decitabine head to head, the available indirect evidence cannot reliably confirm the superiority of either agent. In a recent systematic review and network meta-analysis, azacitidine was less likely to induce a complete response compared with decitabine, but there were no clear differences between these drugs in any of the remaining outcomes analyzed.[56] Thus, there are no arguments to favor the use of one of them. One possible exception, as previously discussed, is the preferable use of a 10-day schedule of decitabine for patients with TP53 mutations.[27] However, it should be noted that both commercially available HMAs, azacitidine and decitabine, are approved in the United States for the treatment of all MDS subtypes, whereas azacitidine is licensed solely for HR-MDS in Europe, and decitabine is not licensed at all.

It should be highlighted that the benefit reported for azacitidine in clinical trials has not always been reproduced in real-life. In several series of azacitidine-treated patients from different national or regional registries, the median OS ranged from 12 to 18 months.[57-60]

The optimal schedules, doses, and duration of therapy have not been fully defined for HMAs. The approved schedule for azacitidine is 75 mg/m^2 per day subcutaneously for 7 consecutive days every 28 days. However, other alternative schedules that avoid weekend administration are commonly used in daily practice, such as 5 or 6 consecutive days or 5 days on, 2 days off, and 2 days on (5-2-2 schedule), with apparently similar efficacy.[57]

Although the dose schedule of decitabine used in the randomized trials was 15 mg/m^2 IV over 4 hours, 3 times a day for 3 days in 6-week

cycles,[51,53] other alternatives are commonly used, such as 20 mg/m^2 IV daily for 5 days.[61]

Treatment with azacitidine or decitabine should be given for ≥6 cycles in the absence of unacceptable toxicity or disease progression. For patients who show a clinical response, treatment should continue as long as the subject continues to benefit.

The recognition of predictive factors for a response to HMAs is of the utmost relevance because of the limited efficacy and potential hematologic toxicity of these agents; however, available data are very limited. In the largest series to date, assessing clinical variables in 228 HR-MDS patients, previous low-dose cytarabine treatment, BM blasts > 15%, and abnormal karyotype independently predicted lower response rates to azacitidine, whereas ECOG PS > 2, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and red blood cell transfusion dependency > 4 units in 8 weeks independently predicted poorer OS.[59] The predictive impact of specific somatic mutations on HMA response rate, response duration, and survival remains controversial.[62] TP53 mutations have generally been associated with shorter response duration and survival after HMA treatment.[63] In contrast, the higher response rate to azacitidine reported in patients carrying TET2 mutations[64] has not been consistently confirmed.[62,65]

Novel treatment approaches

Given the limited efficacy of HMAs and the small fraction of patients who can benefit from HSCT or ICT, the development of new treatment approaches for HR-MDS patients is an urgent unmet need. This is particularly true for patients failing HMAs, whose expected median survival is <6 months. Thus, most new drugs are being evaluated in this setting.

Second-generation HMAs. Guadecitabine is an HMA that allows a more prolonged DNA exposure to decitabine. In a phase 2 study of guadecitabine after azacitidine failure in 56 patients with MDS or low-blast-count AML, the response rate was 14%, and median OS was 7.1 months. Median duration of response was 11.5 months, and median OS in responders was 17.9 months. None of the 11 patients with TP53 mutations responded.[66] This drug is being evaluated in a phase 3 clinical trial in patients who have failed azacitidine or decitabine (NCT02907359). An oral combination of decitabine and cedazuridine (ASTX727) that emulates IV decitabine pharmacokinetics[67] is also under evaluation (NCT03306264).

Combinations of azacitidine and another partner drug. Several promising drugs, such as vorinostat, lenalinomide, and eltrombopag, have been combined with azacitidine in an attempt to improve its efficacy; however, none of these combinations has shown a significant benefit compared with azacitidine alone.[68,69] In general, the combinations increased hematological toxicity, suggesting that a lower dose of azacitidine, when combined with other agents, could be worthy of study.

A randomized clinical trial evaluating the addition of pevonedistat, a first-in-class inhibitor of the NEDD8-activating enzyme, to azacitidine as first-line treatment in HR-MDS patients (NCT03268954) is underway. Preliminary results for the use of venetoclax, a BCL-2 inhibitor, with azacitidine or decitabine in 145 elderly patients with AML not suitable for ICT have shown a 67% response rate (complete remission [CR] or CR with incomplete count recovery), median duration of response of 11.3 months, and median OS of 17.5 months. Nonetheless, toxicity (mainly hematological) was substantial, with

41% of the patients experiencing febrile neutropenia. Other very common (>30%) adverse events were nausea, diarrhea, constipation, fatigue, hypokalemia, and decreased appetite.[70] The combination of venetoclax and azacitidine is being evaluated in phase 1 trials in treatment-naive HR-MDS patients (NCT02942290) and after HMA failure (NCT02966782).

Targeted molecular therapies. IDH1 (ivosidenib) and IDH2 (enasidenib) inhibitors, which provide durable remissions in a proportion of older AML patients with those mutations, are under investigation in higher-risk IDH1- or IDH2-mutated MDS when administered alone or in combination with azacitidine (NCT03383575, NCT03503409, NCT02719574). The preliminary results with ivosidenib in 12 patients with relapsed or refractory MDS who have IDH1 mutations have showed an adequate safety profile and a high overall response rate (91.7%; CR, 41.7%; marrow CR, 50%), with ∼60% of the patients maintaining a response at 12 months.[71] HR-MDS with *FLT3* mutations, particularly in patients whose disease evolved to AML, is another targetable setting to be investigated. Other targeted approaches now under investigation are upregulation of the transcriptional activity of mutant and wild-type *TP53* with APR-246 (NCT03072043) and ALRN-6924 (NCT02909972), respectively, and spliceosome modulation with H3B-8800 (NCT02841540). In a phase 1b/2 trial of APR-246 plus azacitidine in 12 patients with HMA-naive *TP53*-mutant HR-MDS or oligoblastic AML, the response rate was 100% (11/11 evaluable patients; 9 CR and 2 marrow CR); the median OS has not been reached at a median follow-up of 7 months. The most common adverse events were grade 3/4 hematological toxicity, as well as grade 1/2 nausea and vomiting, dizziness, headache, and neuropathy.[72]

Immunotherapy approaches. Based on studies that have demonstrated an aberrant expression of PD-L1, PD-L2, PD-1, and CTLA4 proteins in patients with MDS, as well as the fact that this expression is enhanced by HMAs, multiple clinical trials with immune-checkpoint inhibitors (eg, pembrolizumab, ipilimumab, nivolumab, durvalumab, atezolizumab) are ongoing (NCT01953692, NCT02530463, NCT02397720, NCT02775903, NCT02508870). In a phase 2 study of nivolumab or ipilimumab, with or without azacitidine, given as front-line treatment or after HMA failure, the response rate and median OS were 75% (15/20 patients) and 12 months, respectively, for nivolumab plus azacitidine; 71% (15/21 patients) and not reached, respectively, for ipilimumab plus azacitidine; 13% (2/15 patients) and 8 months, respectively, for nivolumab; and 35% (7/20 patients) and 8 months, respectively, for ipilimumab. CR was higher in patients receiving combined therapy.[73] A recent review with the preliminary data from some studies of checkpoint inhibitors, with or without HMAs, is also available.[74]

The potential role of bispecific antibodies and chimeric antigen receptor T cells targeting CD123 or CD33 is still uncertain. Efficacy was limited in 24 patients (19 AML and 5 MDS) treated with the anti-CD123 antibody talacotuzumab, with an overall response rate of 20%, a median duration of response of 3 months, and a median OS of 3.2 months.[75]

Other drugs. Despite the lack of a clear benefit in OS compared with best supportive care (median OS, 8.2 months vs 5.9 months) reported with IV rigosertib, a multikinase inhibitor, in a randomized phase 3 study in HR-MDS patients after HMA failure, the response rate for rigosertib-treated patients was higher than for patients receiving best supportive care (53% vs 17%), and post hoc analyses showed that patients with early HMA failure, as well as those with very high-risk

IPSS-R or age < 75 years, could potentially have benefited from rigosertib.[76] For those reasons, a study with rigosertib focused to patients with early HMA failure is now ongoing (NCT02562443). An oral formulation of rigosertib in combination with azacitidine is also under investigation. In a phase 2 expansion study including 31 patients with HR-MDS or low-blast-count AML (14 HMA naive and 17 HMA failure), the overall response rate was 68% (59% for the HMA-failure cohort and 79% for the HMA-naive cohort), and the most common adverse event was hematuria (grade 1-2, 16%; grade ≥3, 5%).[77]

Discussion: clinical case

Applying the IPSS and IPSS-R, the patient under discussion would be classified as high and very high risk, with a predicted median survival of 0.5 years and 0.8 years, respectively. In addition, the *SRSF2* mutation present in the patient has been associated with poor outcomes in MDS patients. The next step would be to evaluate her medical fitness. She had a normal life until anemia appeared, no limiting comorbidities were evident, her KPS was 100% after transfusion of 2 units of packed red blood cells, and her HCT-CI was 0. Therefore, she was considered fit for allogeneic HSCT. At this time point, some patients prefer a potentially curative, but risky, treatment, whereas others select a less intensive treatment that is able to provide a better quality of life and prolong survival. The pros and cons of treatment alternatives, including allogeneic HSCT, HMAs, and clinical trials, were discussed in detail with the patient. Off-label use of enasidenib, an IDH2 inhibitor, was ruled out because the drug is not licensed in Europe, and no clinical trial in this setting was available. The patient decided to proceed to allogeneic HSCT, and a search for a MUD was started. In an attempt to reduce disease burden and avoid disease progression, bridging treatment with azacitidine was initiated while waiting for a donor. The use of ICT was ruled out because our institutional policy is to use ICT only in younger (<60 years) MDS patients with favorable risk cytogenetics. It should be highlighted that a substantial number of patients may not undergo allogeneic HSCT after bridging treatment with azacitidine because of disease progression or toxicity (eg, severe infections).[16,78] After 3 cycles of azacitidine, the patient had profound neutropenia and remained dependent on red blood cell transfusions, but her platelet count was normal (140 × 10⁹/L), and BM blasts had decreased to 7% (partial remission with platelet response). Cytogenetic response and mutation clearance had not occurred. She underwent an allogeneic HSCT from a 10/10 HLA-matched MUD with a RIC regimen that consisted of thiotepa, busulfan, and fludarabine. Posttransplant cyclophosphamide was used in an attempt to reduce the incidence and severity of GVHD. The use of azacitidine after transplantation to reduce the relapse risk was discussed, but the patient refused this treatment. An active surveillance for the presence of measurable minimal residual disease, with controls every 3 months, was instituted. The evaluation with enhanced exome sequencing of mutation clearance 30 and 100 days after transplantation could also be helpful in deciding whether some kind of maintenance or salvage treatment should be given. The risk for disease progression at 1 year in patients with a preexisting mutation at VAF ≥ 0.5% was 53% and 67% at 30 and 100 days after transplantation, respectively, whereas it was 13% and 0%, respectively, in the absence of such a mutation.[49] Two years after transplantation, the patient is in remission, without GVHD, and is enjoying a normal life.

Concluding remarks

The complex and heterogeneous pathophysiology of MDS is likely the major cause underlying the limited effectiveness of current treatment approaches for HR-MDSs. More focused and personalized

strategies targeting specific gene mutations or cellular pathways involved in the development and progression of these disorders to AML are being intensively investigated in multiple clinical trials. This strategy has already been relatively successful in older patients with AML and has resulted in the recent approval of several novel drugs in that setting, such as those targeting *FLT3* and *IDH* mutations or inhibiting the *BCL-2* pathway. Although the clinical benefit of these and other drugs targeting commonly mutated genes in HR-MDS remains unproven, there are good reasons for hope. In fact, HR-MDS and AML in older patients share many biological characteristics, and there is a thin line between the 2 diseases. Enrollment of patients with HR-MDS in clinical trials should always be considered a priority.

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