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Treatment of Myelodysplastic Syndromes for Older Patients: Current State of Science, Challenges, and Opportunities

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Abstract

Purpose of Review Myelodysplastic syndromes/neoplasms (MDS) represent a diverse group of pathologically distinct diseases with varying prognoses and risks of leukemia progression. This review aims to discuss current treatment options for elderly patients with MDS, focusing on patients ineligible for intensive chemotherapy or allogenic hematopoietic stem cell transplantation (HSCT). The challenges associated with treatment in this population and emerging therapeutic prospects are also explored.

Recent Findings Recent advancements in molecular diagnostics have enhanced risk stratification by incorporating genetic mutations, notably through the molecular International Prognostic Scoring System (IPSS-M). Lower-risk MDS (LR-MDS) treatment ranges from observation to supportive measures and erythropoiesis-stimulating agents (ESAs), with emerging therapies like luspatercept showing promise. High-risk MDS (HR-MDS) is treated with hypomethylating agents (HMAs) or allogenic HSCT, but outcomes remain poor.

Summary Elderly MDS patients, often diagnosed after 70, pose challenges in treatment decision-making. The IPSS-M aids risk stratification, guiding therapeutic choices. For LR-MDS, supportive care, ESAs, and novel agents like luspatercept are considered. Treatment of HR-MDS involves HMAs or allogenic HSCT. Emerging treatments, including oral HMAs and novel agents targeting FLT3, and IDH 1/2 mutations, show promise. Future research should refine treatment strategies for this elderly population focusing on quality-of-life improvement.

Keywords Myelodysplastic syndrome · Elderly · Management · Prognosis

Introduction

Myelodysplastic syndromes/neoplasms (MDS) comprise a group of heterogenous pathologically distinct diseases with varied prognosis and natural risk of leukemia progression [1, 2]. MDS pathogenesis begins from different genetic alterations involving epigenetic, transcriptional, and/or splicing molecular pathways in the myeloid precursors and hematopoietic stem cells [3–5]. Such genetic insults lead to abnormal DNA synthesis and apoptosis of myeloid precursor cells, which underlies the multi-lineage peripheral cytopenia including anemia, thrombocytopenia, and neutropenia [2, 4, 6]. Clinically, cytopenia can manifest in MDS patients as fatigue, bleeding and infection risk. Consequently, MDS can be associated with a significant impairment on the quality of life (QoL) [7]. On the other hand, progression to acute myeloid leukemia (AML) is variable based on different risk factors including age, cytogenetic abnormalities, and specific mutations [8–11].

The treatment of MDS is based on a patient's risk for progression to AML and mortality [12–15]. Until recently, clinical and morphological features, later enhanced by cytogenetics, dominated the risk stratification of MDS patients. The international prognostic scoring system (IPSS) and the later revised version (IPSS-R) guided risk stratification, treatment selection, and eligibility for clinical trials in the past decades [8, 9]. However, different prognostic tools, including the recent molecular IPSS

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(IPSS-M), implemented molecular alterations for prognostic purposes [16, 17]. Lower-risk MDS (LR-MDS) treatment can range from observation and supportive transfusions/growth hormones to alleviate symptomatic cytopenia to treatment modalities typically reserved for patients with higher-risk MDS (HR-MDS) including hypomethylating agents (HMAs) and allogenic hematopoietic stem cell transplantation (HSCT) [12, 14]. Identifying patients at higher risk of progression is essential since more aggressive treatments may be required to prevent progression to HR-MDS or AML.

Overall, MDS is a disease of the elderly population with most patients being diagnosed when they are more than 70 years old [18]. As with many other cancers, advanced age is frequently associated with adverse outcomes and represents an obstacle in treatment [19]. Since allogeneic HSCT is the only available option to cure MDS, the identification of treatment goals in elderly patients is essential (Fig. 1). In addition, cardiopulmonary, renal, and hepatic disorders are more frequently encountered among elderly patients, making treatment selection, if needed, more challenging [20]. As a result, the participation of older patients

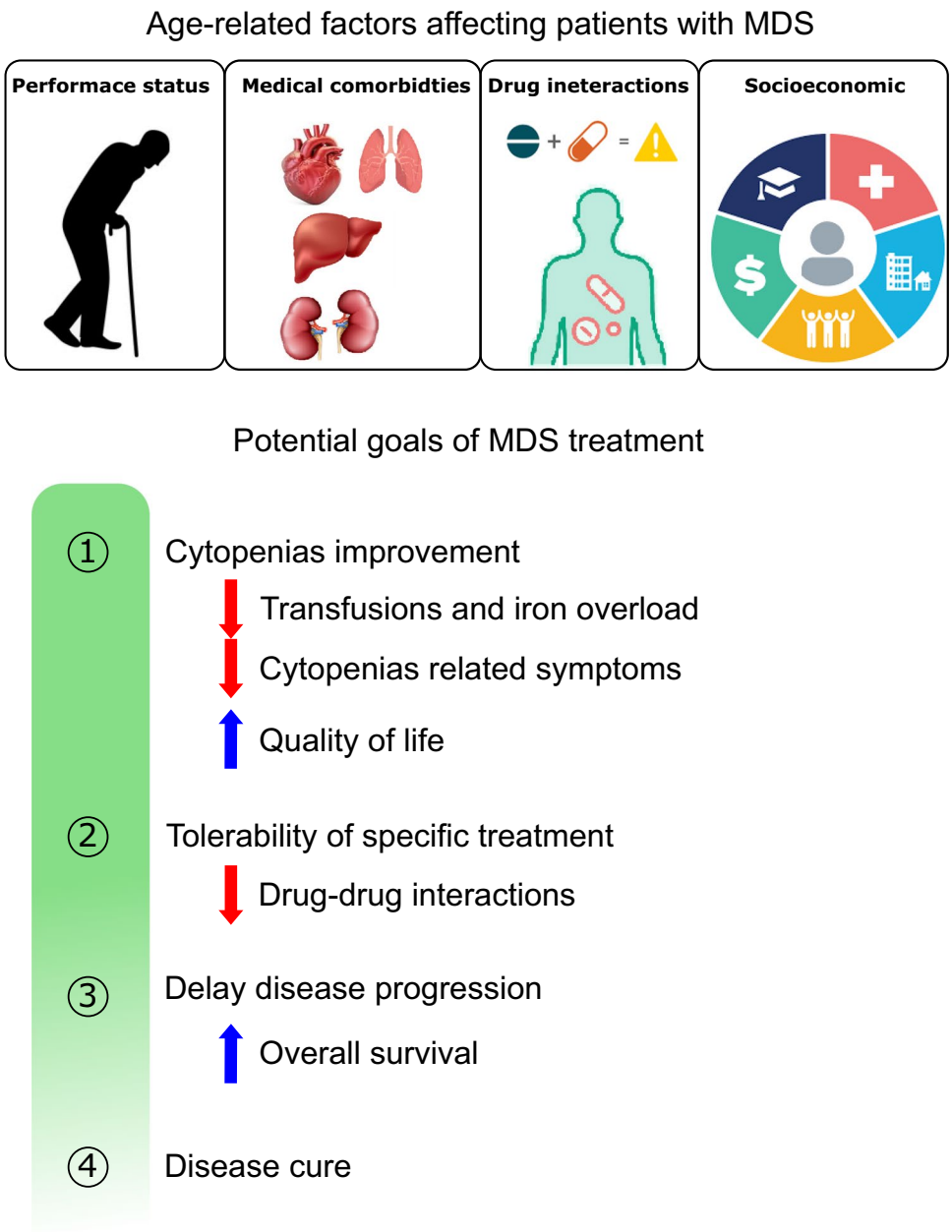

Fig. 1 Age-related factors affecting patients with MDS

in clinical trials is limited and many patients will pursue palliative options instead. Furthermore, many other factors including insurance coverage, socioeconomic status, and drug-drug interactions should be kept in mind when different treatments are considered. In this review, we discuss the current treatment options for elderly patients with MDS. Specifically, we will review treatment options for patients not eligible for intensive chemotherapy or allogenic HSCT due to medical comorbidities and/or age. We also address the potential challenges associated with treatment in this population. Finally, we will review emerging prospective therapeutics that can be considered.

Prognostication and Risk Assessment

Risk stratification is essential in MDS for proper treatment assignment, goals of care discussion, and long-term prognostication [21]. For many decades, risk classification for MDS patients was based on the IPSS and later its revised version (IPSS-R) [8, 9]. However, in recent years, advances in molecular diagnostics allowed for the discovery of multiple genetic alterations associated with specific morphological features and different clinical outcomes, including progression to AML. Genetic mutations have been incorporated with clinical features in the IPSS-M to help in better classification and risk assessment [16].

For this review, LR-MDS will include patients with IPSS-R less than 3.5 and HR-MDS will refer to patients with IPSS-R $\geq$ 3.5 [22], keeping in mind that high-risk features based on the IPSS-M score should be taken into consideration before assigning patients to risk group and should be addressed before making treatment decisions. Although IPSS-M has been validated in multiple settings [23–25], the utility of IPSS-M in identifying appropriate risk groups should be studied in the context of randomized clinical trials, and more prospective studies are needed before using molecular data to determine goal of care, since it has never been used before in these settings directly.

Another important aspect of prognostication in older population is the unique geriatric-related comorbidities. The use of geriatric assessment tools will help identifying patients at higher risk of treatment related side effects. Frailty among older patients with MDS has been associated with worse disease-related outcomes when compared to fit patients with same chronological age. Rockwood Clinical Frailty Scale can be used to identify patients with mild, moderate or severe frailty and was predictive for survival outcomes [26]. The implementation of such functional assessment tools will be essential before considering any treatments, especially for higher risk MDS patients.

LR-MDS

Observation with Supportive Measures

The treatment approach for LR-MDS in elderly patients is summarized in Fig. 2. In the absence of excess blast and high-risk cytogenetics, patients with asymptomatic cytopenia can be observed with supportive measures, such as transfusions, as needed only [27–29]. The intensity of follow-up and active surveillance should be determined according to the initial presentation. Patients with more pronounced cytopenia or with higher risk molecular alterations (*TP53*, *ASXL1, EZH2*, *RUNX1*, or *FLT3*) may require more closer follow-up [28]. Worsening cytopenia, increasing number of blasts, or new symptoms should be alarming for further work up including bone marrow (BM) biopsy to rule out disease progression and determine the need for treatment. So far, no approved treatment has been shown to change the natural history of very low and low-risk MDS in terms of progression to higher risk disease or AML.

Anemia

Anemia is the most common cytopenia among MDS patients and is associated with a significant increased risk of cardiopulmonary compromise, mortality, and poor QoL [7, 30–32]. Erythropoiesis-stimulating agents (ESAs), including recombinant humanized erythropoietin or darbepoetin alpha, have been used for many years among MDS patients for anemia management [27, 33, 34] and continued to be the first line for MDS induced anemia in most settings. In a randomized double-blinded trial of 147 LR-MDS patients with hemoglobin less than 10 g/dL and serum erythropoietin (EPO) less than 500 IU/L, darbepoetin alpha was associated with significant hematologic improvement rate (14.7%) compared to the placebo group (0%). The effect of darbepoetin was more pronounced among patients with serum EPO level < 200 IU/L and with minimal history of blood transfusion [35]. In another randomized placebo-controlled trial, 130 patients with hemoglobin less than 10 g/dL were randomized in a 2:1 fashion to receive epoetin-alfa 450 IU/kg/week or placebo. Erythroid response based on the international working group (IWG) 2006 criteria was 45.9% in the epoetin arm compared to 4.4% for placebo ($p < 0.0001$) [34]. Overall, higher doses of ESAs are required for MDS treatment when compared to the doses used in anemia secondary to chronic kidney disease [36]. Weekly 60,000–80,000 units of recombinant humanized erythropoietin or 500 µg of darbepoetin alfa every 2–3 weeks are often needed to achieve optimal response in anemic lower risk MDS patients [15]. Focusing on

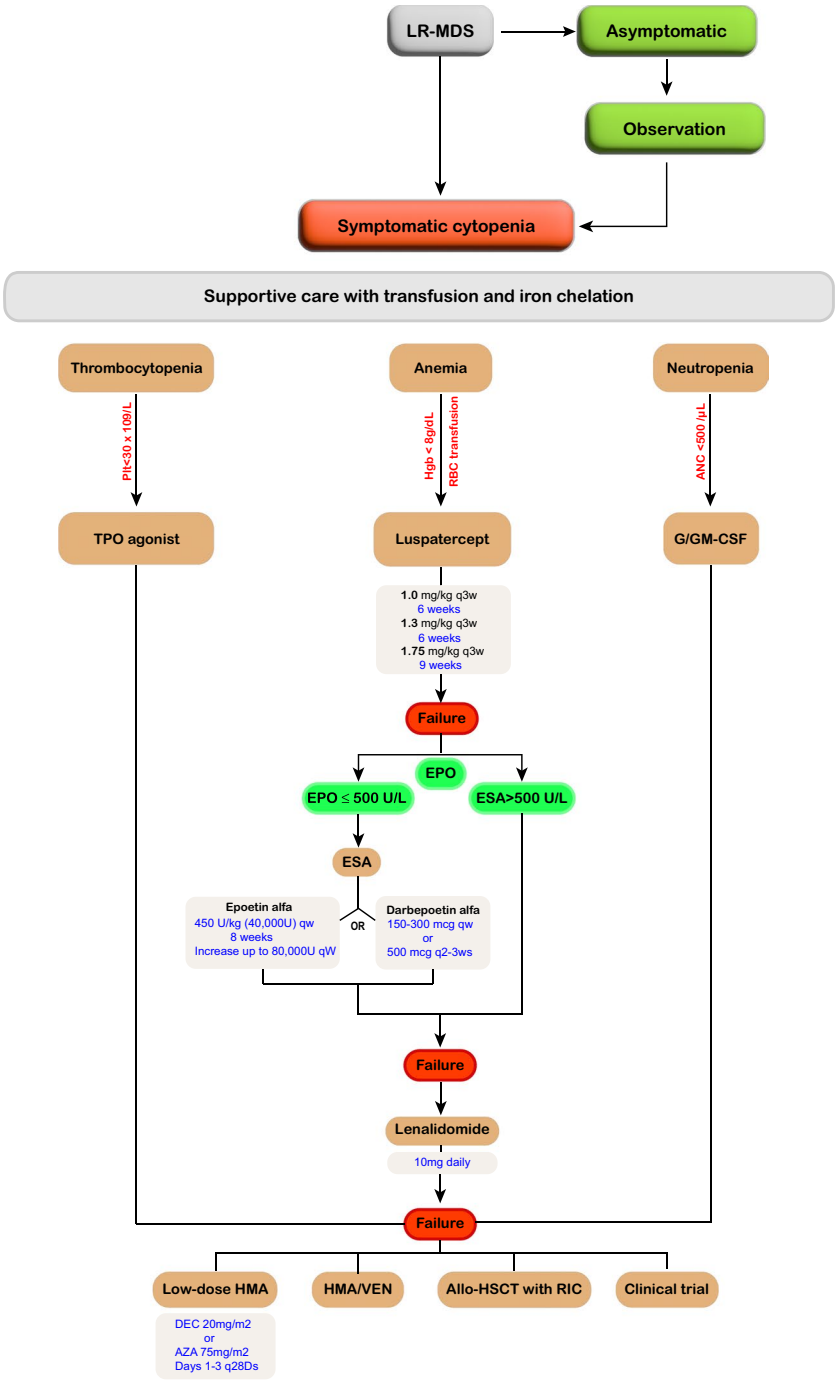

Fig. 2 Treatment of low-risk MDS (LR-MDS). Plt, platelet; Hgb, hemoglobin; ANC, absolute neutrophil count; TPO, thrombopoietin; G/GM-CSF, granulocyte/Granulocyte-Monocyte colony stimulating factor; EPO, erythropoietin; ESA, erythropoietin stimulating agent; HMA, hypomethylating agent; VEN, venetoclax; HSCT, hematopoietic stem cell transplantation; AZA, azacitadine; DEC, decitabine

older patients, age was not found to be an independent factor for ESA response prediction nor progression to AML [37–39].

Luspatercept is a recombinant fusion protein that binds several transforming growth factor beta ligands and thus decreases SMAD2/SMAD3 signaling, thereby enhancing red blood cell maturation [40, 41]. Based on the MEDALIST trial, luspatercept (1.0–1.75 mg/kg) was initially approved on April 202 for the treatment of anemia with ring sideroblasts (with either ≥ 15% ring sideroblasts or ≥ 5% ring sideroblast with *SF3B1* mutation) in very low, low, and intermediate risk MDS patient's refractory or unlikely to respond to ESAs (endogenous erythropoietin > 200 U/L). Transfusion independence for more than 8 weeks (during 1 to 24 weeks) was higher in the luspatercept group (38% vs. 13%; $p < 0.001$). Importantly, luspatercept had no major safety signals with fatigue, diarrhea, nausea, and dizziness being the most common adverse events associated with luspatercept, but generally not severe and improve with time [40, 42, 43]. Interestingly, luspatercept was also shown to

be effective in the treatment of patients with non-RS and non-transfusion-dependent anemia according to the long-term follow-up of 108 LR-MDS patients from the phase II PACE-MDS study [42, 43]. Overall, erythroid hematologic improvement was observed in 36.4% of the non-RS patients and 70.6% of the non-transfusion-dependent cases. In addition, improvement in the platelet and absolute neutrophil counts were observed in 9.5% and 33.3%, respectively [43]. A post hoc analysis of the MEDALIST trial revealed the longer-term benefits of luspatercept in patients with transfusion-dependent LR-MDS with ring sideroblasts. After a median follow-up of approximately 38 months, luspatercept demonstrated a sustained reduction in the need for red blood cell transfusions. Among patients who were treated with luspatercept, 59% achieved a major erythroid response, a significant increase in hemoglobin levels, with a median duration of response lasting approximately 21 months. Importantly, 62% of these patients achieved transfusion independence for at least 8 weeks. This indicates that luspatercept offers a promising long-term solution for individuals with LR-MDS and ring sideroblasts, potentially reducing their dependance on blood transfusions and improving their overall quality of life [44].

Accordingly, the use of luspatercept in the first-line setting of low risk MDS patients with anemia was studied in the phase 3 COMMANDS trial. The comparative efficacy and safety of luspatercept and epoetin alfa were assessed in a cohort of patients with LR and intermediate risk MDS who had not previously received ESAs and were blood transfusion dependent (2–6 packed red blood cell units per 8 weeks for ≥ 8 weeks). The findings revealed significant advantages associated with luspatercept treatment: approximately 59% of patients treated with luspatercept achieved the primary endpoint of transfusion independence and a concurrent mean hemoglobin increase of at least 1.5 g/dL, a notably higher rate than the 31% observed in the epoetin alfa group. The overall response rate in the luspatercept group was approximately 53%, significantly surpassing the 26% response rate in the epoetin alfa group, suggesting a more pronounced improvement in hemoglobin levels and erythroid response. The study reported that luspatercept had a manageable safety profile consistent with prior studies, with no unexpected safety concerns. Based on that, luspatercept was approved on August 2023 for the treatment of anemia in ESAs-naive patients with LR-MDS who may require red blood cell transfusion [45].

Imetelstat is a first-in-class competitive inhibitor of the telomerase enzyme that has been found to be effective and safe in LR-MDS patients with non-del5q anemia after ESA treatment failure. A two-part phase II/III study investigated the efficacy and safety of imetelstat in patients with LR-MDS who were heavily transfusion-dependent and had relapsed or were refractory to ESAs. The study included 57 patients, and in the subset of non-del(5q) and HMA/lenalidomide-naïve patients ($n = 38$), imetelstat achieved an 8-week RBC transfusion independence rate of 42%, with a 24-week rate of 29%. The median duration of transfusion independence was approximately 21 months. In this subset, a hematologic improvement-erythroid response rate of 68% was observed, despite a high baseline transfusion burden (median, 8 units/8 weeks). Additionally, there was evidence of disease-modifying activity with reductions in cytogenetically abnormal clones and mutational allele burden. Imetelstat demonstrated a manageable safety profile, with predominantly reversible hematologic adverse events, and no new safety concerns were identified [46]. A following phase 2 trial long-term analysis, 11/28 patients (29%) had sustained transfusion independence for more than 1 year. Furthermore, 8/9 patients with molecular data showed > 50% reduction in the variant allele frequency (VAF) of *SF3B1* mutation which correlated with duration of transfusion independence and time to response. The most common side effects associated with imetelstat were reversible hematologic adverse events, with 94% of patients experiencing one or more treatment related adverse events, and 82% experiencing grade 3 or greater, primarily thrombocytopenia and neutropenia. Non-hematologic side effects, such as elevated AST levels and bronchitis, occurred in 18% of patients as grade 3 or greater events. Febrile neutropenia was rare, affecting 5% of patients, and there were no treatment-related deaths [47]. Recent news release from the phase 3 IMerge trial indicated that treatment with imetelstat (n = 118) resulted in transfusion independence rate of 39.8% at 8 weeks compared to 15% with placebo ($n = 60$), $p < 0.001$. The 24-week/1 year transfusion independent rates were 28%/13.6% vs. 3.3%/1.7%, respectively ($p < 0.001$). In addition, imetelstat resulted in 3.6 g/dL median increase in the hemoglobin as compared to 0.8 g/dL in the placebo group. No new safety signals were observed. However, imetelstat can cause neutropenia and thrombocytopenia which should be closely monitored and managed with dose modifications (interruptions and delays), growth factor, or prophylactic antibiotics as needed [48, 49].

Patients with del 5q and transfusion-dependent anemia can be treated with lenalidomide, which is a thalidomide analogue that promotes erythropoiesis [27, 33, 50]. ESAs are still often used in first-line management of transfusion-dependent anemia in del5q MDS patients; however, many of these patients are resistant to ESAs and the use of lenalidomide is warranted since transfusion independence can be achieved in more than 60% of the patients [51–53]. Patients with *TP53* mutations are less likely to respond to lenalidomide; this subgroup will need closer follow-up given the

increased risk of disease progression. Furthermore, a recent study showed that prior treatment with lenalidomide is associated with selective advantage for *TP53* mutations [54].

Lenalidomide has also clinical activity in non-del5q lower risk MDS patients with anemia, although its effectiveness is significantly lower compared to MDS with del-5q [50, 52]. In this setting, lenalidomide combined with darbepoetin alpha was associated with higher major erythroid response rate (28.3%) when compared to lenalidomide alone (11.5%), $p = 0.004$ [50]. In addition, for patient with LR-MDS and non-transfusion-dependent anemia, lenalidomide 5 mg daily for 2 years was associated with longer time to transfusion dependent (60.6 months) compared to placebo (11.6 months) in the phase III multicenter Sintra-Rev trial (NCT01243476) [55]. However, lenalidomide can be associated with higher rates of neutropenia, thrombocytopenia, as well as concerns about *TP53*-mutated clonal selection which warrant cautious use among elderly patients with other cytopenia and comorbidities.

Transfusion-dependent patients are at higher risk of iron overload which can eventually lead to end organ damage. Iron chelation therapy (ICT) is associated with reduced mortality risk, but its role among elderly patients is unclear [27, 56, 57]. In one study, Medicare data from older patients with MDS and ≥ 20 units of PRCB had a significant reduction in mortality with each incremental week of deferasirox use (HR 0.989, 95% CI 0.983–0.996) [57]. However, no overall survival benefit of ICT was observed in the TELESTO trial, which randomized patients with end-organ dysfunction and a ferritin > 1000 ng/mL to receive either deferasirox or placebo. Based on that, ICT can be considered in elderly patients with high transfusion burden or a ferritin > 2500 ng/mL with end organ damage [58]. In terms of the ideal ICT agent, oral deferasirox should be used with caution in elderly patients since it is associated with increased risk of renal failure, despite the favorable QoL with oral formulation. Subcutaneous deferoxamine is preferred in this situation.

Thrombocytopenia

Although thrombocytopenia is common among LR-MDS patients, severe thrombocytopenia that requires treatment is less common [27, 33, 59]. Treatment options include platelet transfusion and thrombopoietin receptor agonists (TPO-RA) [60]. In a double-blind, randomized, placebo-controlled trial, romiplostim was associated with 36% platelet response [61]. Similarly, eltrombopag showed 47% platelet response in another clinical trial [60]. There has been concerns regarding increased risk of progression to AML with romiplostim and eltrombopag, which does not seem to be the case in patients without excess blasts, though this concern requires counseling of patients and close monitoring and avoiding use in patients with excess blasts or in combination with HMA [62, 63]. The interim results of the EQOL-MDS Phase II clinical trial investigating the use of eltrombopag for LR-MDS with thrombocytopenia ($< 30 \times 10^3/mm^3$) have provided compelling insights. Notably, patients treated with eltrombopag (50–300 mg daily) demonstrated a significant improvement in platelet counts, with a median increase of $31 \times 10^3/mm^3$ compared to a much more modest $2 \times 10^3/mm^3$ in the placebo group. The clinical trial also revealed a remarkable reduction in the need for platelet transfusions among eltrombopag recipients, with 48% of these patients achieving transfusion independence, compared to only 1% in the placebo group. It is important to acknowledge that AML evolution and/or disease progression occurred in 17% for both groups. Nevertheless, this interim analysis strongly suggests that eltrombopag holds great potential as an effective treatment option for LR-MDS patients with thrombocytopenia, offering the possibility of substantially improved platelet counts and a reduced reliance on transfusions in this specific patient population [64].

Neutropenia

At least 20% of MDS patient will have neutropenia and up to 40% of mortality among MDS patients can be related to infections [65]. Absolute neutrophil count of less than 500 cells/μL was found to be associated with increased risk of infections [66]. Primary prophylaxis with antibiotics or antifungal was generally not associated with significant impact on overall survival and its use is controversial in MDS [67–69]. In addition, the use of granulocyte colony stimulating factor (G-CSF) or granulocyte-monocyte colony stimulating factors (GM-CSF) was not shown to be associated with lower risk of infections or increased overall survival and is not generally recommended to manage neutropenia [70–72]. In elderly patients with recurrent infections or those receiving myelosuppressive therapy, supportive measures including antibiotic prophylaxis should be strongly considered.

Hypomethylating Agents in LR-MDS

Azacitidine and decitabine are recommended for patients with LR-MDS who failed to respond or relapsed after more conservative approaches [73, 74]. LR-MDS patients with mainly severe neutropenia or thrombocytopenia are less likely to respond to conventional agents used in LR-MDS. Studies showed that HMAs can achieve 30–60% transfusion independence in LR-MDS [15, 75, 76]. However, the optimal HMA (azacitidine vs. decitabine), dosing, and regimen are still unclear. In a recent clinical trial, patients with low/intermediate-1 risk MDS by IPSS were assigned to receive either 20 mg/m^2 decitabine daily or 75 mg/m^2 azacitidine daily on days 1 to 3 every 28 days. The overall response

rate was better for decitabine (67%) compared to azacitidine (48%) with better rates of transfusion independence. Among 59 patients with baseline transfusion dependency, 19 (32%) reached transfusion independence (decitabine, 16 of 39 [41%] and azacitidine, 3 of 20 [15%]; $p = 0.039$). However, no control arm for comparison was included and the study used IPSS for risk stratification which can underestimate the risk [75]. As compared to 5 days or 7 days regimens, 3-day regimen is expected to be associated with better QoL and less side effects and can be considered for elderly patients with LR-MDS if HMAs to be used.

The AZA-MDS-003 study explored CC-486, an oral HMA, in LR-MDS patients with transfusion-dependent anemia and thrombocytopenia. The study demonstrated that CC-486 significantly increased red blood cell transfusion independence rates, improved hemoglobin and platelet counts over time, and had a generally manageable safety profile. While overall survival remained similar between the CC-486 and placebo arms, there was a reduced rate of AML progression with CC-486 treatment. Safety concerns arose due to early deaths, primarily related to infections, in the CC-486 arm, particularly in patients with significant pretreatment neutropenia and thrombocytopenia. Further investigation is needed to refine patient selection and maximize the benefits of CC-486 in MDS therapy [77].

High-Risk MDS

Hypomethylating Agents

Treatment approach for HR-MDS in elderly patients is summarized in Fig. 3. HMA or DNA methyltransferase inhibitors were initially approved in 2004 for the treatment of high risk MDS. The AZA-001 trial showed OS benefit among patients treated with azacitidine as compared to conventional therapy [78]. In addition, multiple real-world analysis demonstrated no differences between patients treated with azacitidine and decitabine which led to the approval of the later [76]. Azacitidine is typically given at a dose of 75 mg/m^2 daily for 7 consecutive days in a 28-day cycle. Decitabine is administered at a dose of 20 mg/m^2 daily for 5 consecutive days in a 28-day cycle. Although approved, the OS of elderly HR-MDS patients treated with HMAs remains poor [79, 80]. In a SEER-Medicare study, only a 3-month OS improvement was observed for patients with a median age

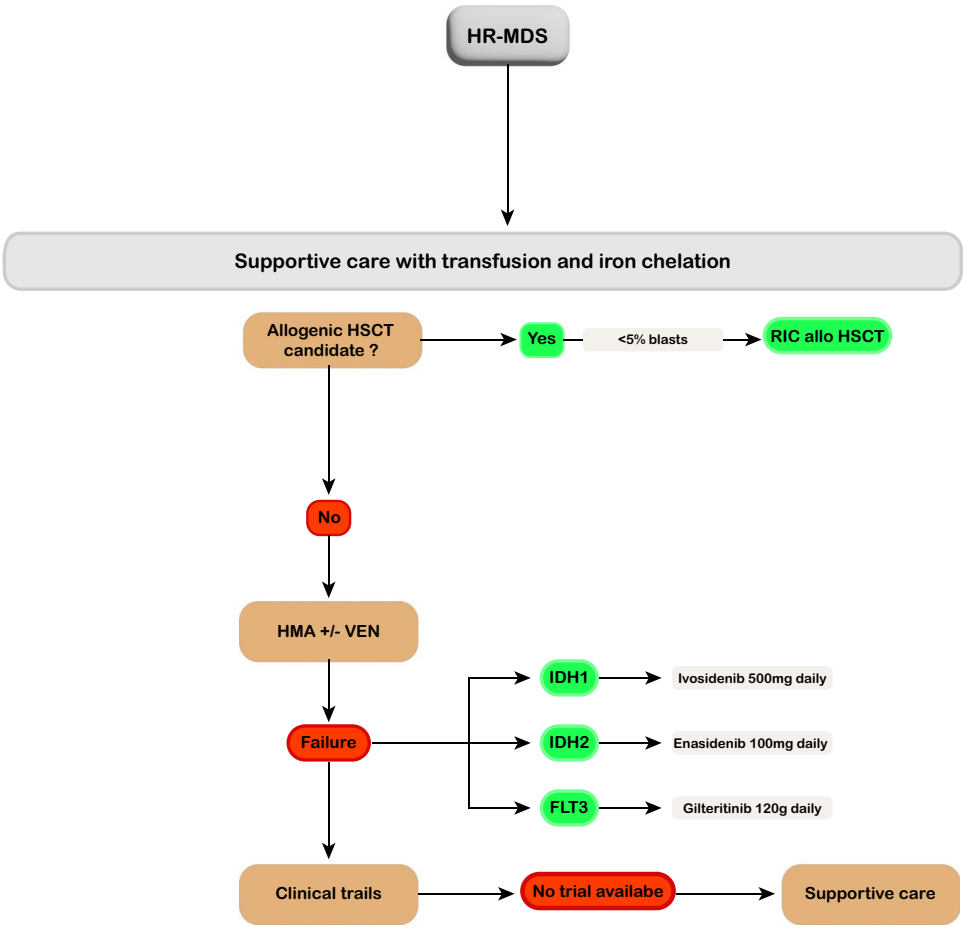

Fig. 3 Treatment of high-risk MDS (HR-MDS). HSCT, hematopoietic stem cell transplantation; RIC, reduced intensity conditioning; HMA, hypomethylating agent; VEN, venetoclax

of 79 years treated with HMA [76]. In long-term analysis of a study involving patients with LR-MDS who were treated with low-dose HMA, 41% of transfusion-dependent patients in the decitabine group achieved transfusion independency, with a third of patients achieving complete remission (CR). Achieving CR resulted in reduced disease progression and improved survival. The median number of treatment cycles was 15, with a significant portion of patients maintaining their responses over extended periods. The study highlighted the potential benefits of low-dose HMA therapy in LR- MDS patients, particularly in terms of reducing transfusion dependence and preventing disease-related complications [75].

The use of injectable HMAs is associated with repeated visits to the clinic or the hospital to receive the medication. According to that, multiple attempts were made to develop oral formulation of azacitidine and decitabine. ASTX727 is an oral compound of the cytidine deaminase inhibitor cedazuridine incorporated with decitabine. ASTX727 showed comparable safety and exposure similar to intravenous (IV) formulation which led to the approval of ASTX727 for the treatment of MDS [81]. A phase 2 randomized cross over study showed that the efficacy and the safety of the cedazuridine/decitabine combination were consistent with IV decitabine in MDS and MDS/MPN patients. The study included patients with a median age of 69 years [81]. In the ASCERTAIN phase 3 clinical trial, the patients received a median of 9 treatment cycles, and the follow-up period lasted for an average of 32 months. Notably, 22% of the participants achieved a CR, 26% underwent HSCT, and 53% achieved independence from transfusions for both red blood cells and platelets. The safety profile observed in both the phase 2 and phase 3 studies was consistent with the anticipated adverse events associated with intravenous decitabine, including grade ≥ 3 adverse events such as thrombocytopenia, neutropenia, anemia, febrile neutropenia, and leukopenia [81, 82].

Oral azacitidine is approved (CC-486) for the treatment of adult patients with AML in first CR who are not eligible for allogenic bone marrow transplant based on outcomes form the randomized phase III QUAZAR AML-001 trial which showed median OS advantage of 10 months with oral azacitidine compared to placebo [82]. However, oral azacitidine has not been approved for the treatment of HR-MDS or LR-MDS patients [77].

Allogenic Hematopoietic Stem Cell Transplantation

Allogenic HSCT remains the only cure option for LR and HR MDS [12, 20, 27, 83, 84]. Essential to mention is that there is no hard age cut-off that makes patients in-eligible for allogenic HSCT. As expected, only a minor proportion of elderly patients are eligible to transplant, and studies showed that only 2–10% of older patients with myeloid malignancies were treated with allogenic HSCT [85, 86]. In older patients, reduced intensity conditioning (RIC) is favorable since it has shown to be associated with lower transplant-related mortality. However, using RIC is on the expense of higher rates of disease relapse. Hence, the use of bridging therapy is recommended to achieve bone marrow blast of < 5% before proceeding to allogenic HSCT [83, 87]. In prospective clinical trials, liposomal cytarabine (CPX-351) was used as bridge to allogenic HSCT. A phase 2 multicenter trial evaluated CPX-351 in 31 treatment-naïve patients with HR-MDS > 70 years old. Overall, 23% of the patients achieved CR and 89% of the patients with BM blast > 10% achieved BM blast < 5% after induction. The data suggested the feasibility of CPX-351 induction chemotherapy as a bridge to transplant [88].

Outcome advantages (disease-free survival) have been reported in clinical trials that randomized patients to allogenic HSCT with RIC vs. continuous HMAs, even among patients aged > 70. In another multicenter assignment trial, patients aged 50–75 years treated with allogenic HSCT with RIC has 3-year OS rate of 47.9% as compared with 26.6% ($p = 0.0001$) for patients treated with conventional therapy [89]. Overall, elderly fit patients who are eligible to transplant with either HR-MDS or LR-MDS resistant to conventional therapy should be evaluated for allogenic HSCT with RIC.

Future Prospective and Emerging Treatments

Multiple clinical trials for novel therapeutics are undergoing for HR and LR MDS. As we discussed above, the telomerase enzyme inhibitor imetelstat will most likely be approved for the treatment of ESA refractory anemia based on results of the phase 3 IMerge trial [47, 48]. However, most novel therapeutics are mainly focusing on HR-MDS.

The BCL-2 inhibitor venetoclax in combination with HMAs or low-dose cytarabine is approved for the treatment of elderly patients ≥ 75 years with AML and patient's ineligible for intensive chemotherapy [90–92]. Similarly, the efficacy and the safety of the similar combination for HR-MDS patients were conducted. In the phase Ib M15-522 trial, 40% of the relapsed/refractory HR-MDS patients ($n = 38$) achieved CR plus marrow CR. Similar CR rate of 40% was observed among treatment naïve HR-MDS patients ($n = 78$) in the phase Ib MDS-513 trial [93]. Another phase 1b clinical study evaluated the efficacy and safety of combining venetoclax (escalating doses of oral venetoclax: 100, 200, or 400 mg daily for 14 days every 28-day cycle) and azacitidine for the treatment of patients suffering from relapsed or refractory HR-MDS. The trial involved 67 patients, where a majority had experienced

prior treatment failures. The results were quite promising, with a clinical response rate of 71%, showcasing the effectiveness of this combination. Moreover, 64% of the patients achieved hematologic improvement. Notably, 47% of patients achieved transfusion independence for red blood cells, a critical aspect of improving the QoL for MDS patients. The median duration of response was estimated to be around 9.6 months. The most common adverse events included febrile neutropenia, anemia, and thrombocytopenia [94].

Given these results, the combination is currently being evaluated in the phase 3 VERONA study with standard azacitidine dosing and 14 days of 400 mg venetoclax (NCT04401748). The application of this combination among elderly patients needs to be addressed since it will be expected to have higher rates of cytopenia that may limit its use among elderly patients.

CD47 is a cell surface protein that prevents phagocytosis by macrophages. Studies showed that CD47 is upregulated in MDS cells, and its expression can be augmented by HMAs [95, 96]. Magrolimab is a monoclonal antibody targeting CD47 and enhancing phagocytosis. Magrolimab in combination with standard azacitidine was initially studied in a phase 1b clinical trial of 95 untreated HR-MDS patients. CR was 33%. CR was achieved in 40% (10/15) *TP53*-mutated patients. Magrolimab was placed on brief clinical hold from February to April 2022 due to on-target effect of hemolytic anemia but clinicals resumed enrollment after [97]. Currently, the phase 3 randomized ENHANCE trial is comparing magrolimab plus azacitidine to azacitidine alone; the study is fully accrued and results will be available soon (NCT04313881).

Mutations in *FLT3*, *IDH1*, and *IDH2* can be detected in up to 5% of MDS patients [3]. Studies of *FLT3* inhibitors monotherapy or in combination with HMAs/low dose cytarabine were negative for patients with myeloid malignancies [98, 99]. Combination studies of gilteritinib with azacitidine and venetoclax in patients with AML and HR-MDS are underway (NCT04140487), although FLT3 mutations are not common in MDS patients. Ivosidenib is an *IDH1* inhibitor that was approved for the treatment of relapsed/refractory HR-MDS based on interim analysis of a phase 1/2 trial that showed 42% CR [100]. Ivosidenib monotherapy (NCT03503409) or in combination with azacitidine (NCT03471260) are currently being investigated for HR-MDS patients. Enasidenib is an *IDH2* inhibitor with promising results in relapse/refractory MDS. Interim analysis of the phase 1/2 trial showed a CR of 55% (NCT03744390) [101]. Multiple trials of enasidenib monotherapy or in combination with other treatment are undergoing. *FLT3* and *IDH/IDH2* inhibitors are orally administered. *IDH/IDH2* inhibitors are associated with increased risk of differentiation syndrome, which can lead to profound consequences among elderly patients with cardiovascular or pulmonary comorbidities.

The interleukin 1 receptor–associated kinases (IRAKs) are involved in multiple inflammatory pathways associated with hematologic malignancies. IRAK4 inhibitor (CA-4948) is under development for HR MDS patients (NCT04278768).

Conclusion

The management of MDS in elderly patients is challenging. Age is associated with higher prevalence of comorbidities, frailty, and mortality. Risk stratification remained essential for the appropriate selection of treatment approach. It is important to remember that age alone is not a contraindication for allogenic bone marrow transplant and all patients who are eligible should be evaluated for all-HSCT since it is the only available cure.

Clinical trials in elderly patients should embrace QoL and patients reported outcomes (PRO) as primary endpoints to address the special needs of this group of MDS patients. The palliative intent approach is more reasonable in patients with lower risk disease focusing on better QoL, reducing transfusion requirements, and symptoms burden. Targeted novel therapeutics may allow for personalized patient-focused approach with improvement of mortality, morbidity, and QoL in this unique population. Well-designed clinical trials focusing on QoL improvement are needed to provide more options for the management of MDS in elderly patients.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest Maximilian Stahl consulted for Curis Oncology and Boston Consulting; served on the advisory board for Novartis and Kymera, GSK, Rigel, Sierra Oncology; and participated in GME activity for Novartis, Curis Oncology, Haymarket Media and Clinical care options (CCO).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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