Treatment of lower-risk myelodysplastic syndromes

Almuth Maria Anni Merz and Uwe Platzbecker

Department of Hematology, Cellular Therapy, Hemostaseology and Infectious Diseases, University Hospital of Leipzig, Leipzig, Germany

Correspondence: U. Platzbecker
uwe.platzbecker@medizin.uni-leipzig.de

Received: May 15, 2024.
Accepted: September 11, 2024.
Early view: October 24, 2024.

https://doi.org/10.3324/haematol.2023.284945

Abstract

Myelodysplastic syndromes (MDS) involve clonal hematopoiesis and cellular dysplasia, driven by genetic and epigenetic alterations. Spliceosome mutations and epigenetic dysregulation underscore the intricate pathogenesis of MDS. The bone marrow microenvironment, stromal dysfunction, chronic inflammation, and immune dysregulation contribute to disease progression. This complex pathogenesis underscores the necessity for targeted therapies, offering a personalized medicine approach, particularly in lower-risk patients. The development of risk scores such as the International Prognostic Scoring System (IPSS), its revision (IPSS-R), and the incorporation of molecular genetics into the IPSS-M have refined the diagnostic and prognostic framework of MDS. These scoring systems facilitate tailored treatment strategies and better prognostication, especially for lower-risk MDS patients. The progression from IPSS to IPSS-R and now to IPSS-M epitomizes the shift towards personalized medicine in the management of MDS. In this review we discuss recent developments and positive phase III studies in lower-risk MDS. The review concludes by proposing a treatment algorithm for lower-risk MDS and highlighting ongoing trials in this heterogeneous population of patients.

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis, leading to blood cell dysplasias and varying degrees of bone marrow failure.[1] Management strategies for MDS are dictated by the patient's risk category,[2] which is typically assessed using tools such as the Revised International Prognostic Scoring System (IPSS-R).[3] Treatment approaches for lower-risk MDS focus on improving quality of life (QoL), managing symptoms and delaying progression to higher-risk disease or acute myeloid leukemia (AML). This review article delves into the emerging treatment modalities for lower-risk MDS, with an emphasis on recent clinical trials including MEDALIST,[4] COMMANDS,[5] and IMerge,[6] which spotlight the potential of novel therapeutic agents in altering the course of the disease.

The MEDALIST trial provided significant progress for the management of patients with low-risk MDS who have ring sideroblasts and are refractory to erythropoiesis-stimulating agents (ESA).[4] Luspatercept, a recombinant fusion protein that acts as a ligand trap for transforming growth factor-β superfamily members, has emerged as a promising therapy in this context.[7] The trial's findings highlight luspatercept's ability to achieve transfusion independence in a significant proportion of patients. Transfusion independence is a critical marker of treatment success in lower-risk MDS because of the impact of anemia on QoL and overall health outcomes. In contrast, the COMMANDS trial compared the efficacy and safety of luspatercept *versus* epoetin alfa in ESA-naïve, transfusion-dependent, lower-risk MDS.[5] Meanwhile, the IMerge trial explored the use of imetelstat, a telomerase inhibitor, in patients with non-del(5q) lower-risk MDS refractory to ESA.[6] Imetelstat's mechanism of action, targeting the enzyme telomerase, introduces a novel and potentially targeted approach in the treatment landscape of MDS. Recently published data suggest that imetelstat not only improves hematologic parameters but may also alter the natural progression of MDS by having an impact on the underlying disease biology. These findings are crucial as they offer a potential shift from symptomatic management to a more definitive disease-modifying strategy.

The evolving landscape of treatment for lower-risk MDS as evidenced by these studies underscores a shift towards targeted therapies that not only ameliorate symptoms but potentially modify the disease's trajectory. This review an-

alyzes how these novel agents compare with traditional treatments such as ESA, immunosuppressive therapies and supportive care, and discuss their implications for clinical practice. Specifically, it considers how these treatments can be integrated into current management strategies and their impact on patients' outcomes.

Through a detailed examination of recent clinical trials and emerging therapies, this article aims to provide hematologists and oncologists with a comprehensive overview of the current and future landscape of lower-risk MDS treatment with a European focus, highlighting how these new developments can be harnessed to improve patients' care and outcomes. By focusing on novel agents that have demonstrated significant promise, this review explores the potential for these therapies to become cornerstones of treatment in lower-risk MDS.

Pathogenesis

The pathogenesis of MDS involves a complex and multifaceted process characterized by clonal hematopoiesis, cellular dysplasia, and ineffective hematopoiesis. These syndromes encompass a spectrum of hematologic disorders that result from various genetic and epigenetic alterations, environmental exposure and immune dysregulation, ultimately leading to bone marrow failure and an increased risk of transformation to AML.

The pathogenesis of MDS is primarily driven by genetic mutations and epigenetic modifications that disrupt normal hematopoietic cell function.[8] These alterations affect several key pathways including RNA splicing, DNA methylation, histone modification and chromatin remodeling. Mutations in genes such as *TP53*, *TET2*, *ASXL1* and *DNMT3A* are frequently observed in MDS patients.[9] These mutations often lead to impaired differentiation and increased apoptosis of hematopoietic cells.

Telomere erosion and dysfunctional telomerase activity has been identified as other hallmarks of the pathogenesis of MDS.[10] Telomere dysfunction leads to accumulation of secondary genetic events and impaired hematopoietic function. Therefore, targeting telomerase activity has become a promising new target for the treatment of MDS.

Spliceosome mutations, which are prevalent in about 50% of MDS cases, exemplify a critical pathogenic mechanism. Mutations in genes for spliceosome components, such as *SF3B1*, *SRSF2*, *U2AF1* and *ZRSR2* alter RNA splicing, leading to aberrant mRNA transcripts and dysfunctional proteins that disrupt cellular homeostasis and differentiation.[11] The high frequency of spliceosome mutations highlights their central role in MDS pathogenesis and offers potential targets for therapeutic intervention.

Epigenetic dysregulation also plays a significant role.[12] DNA methylation and histone modifications control gene expression without altering the DNA sequence. In MDS, dysregulation of these processes can lead to the silencing of tumor suppressor genes or the activation of oncogenes. Hypomethylating agents, which have become a mainstay in the treatment of MDS, target these aberrant epigenetic landscapes to restore normal gene function.

The bone marrow microenvironment, crucial for the maintenance and regulation of hematopoiesis, is notably altered in MDS.[13] Stromal cells, cytokines, and extracellular matrix components in the marrow can become dysregulated, contributing to the ineffective hematopoiesis and increased apoptosis characteristic of MDS. Abnormal signaling interactions between hematopoietic stem cells and the bone marrow stroma further promote the survival and expansion of the malignant clone while suppressing normal hematopoiesis.

Chronic inflammation and immune dysregulation are other key features of MDS pathogenesis.[14] Increased levels of inflammatory cytokines such as tumor necrosis factor-α and interferon-γ can induce apoptosis of hematopoietic cells and may contribute to the cytopenias observed in MDS. Additionally, autoimmunity and immune surveillance mechanisms are often impaired, allowing the clonal expansion of dysplastic cells. This immune dysregulation is not only a consequence of the disease but also contributes to its progression and severity.

Clinical implications of the pathogenesis

Understanding the complex pathogenesis of MDS is crucial for developing targeted therapies. With advances in genomic and epigenomic technologies, personalized medicine approaches are increasingly being applied to MDS treatment. These approaches aim to target specific mutations and pathways involved in an individual patient's disease, offering the promise of more effective and less toxic therapies, especially in lower-risk patients.

Risk scores for myelodysplastic syndromes

The diagnosis and prognostication of MDS have evolved significantly with the development of various scoring systems over the last decades, notably the International Prognostic Scoring System (IPSS),[15] its revision (IPSS-R),[3] and the most recent update, the IPSS-Molecular (IPSS-M).[16] Each of these scoring systems incorporates a range of clinical and laboratory features to classify patients into distinct risk categories, aiding in tailoring treatment strategies appropriately. This progression reflects a deeper understanding of the aforementioned biological complexity of MDS and has substantially impacted the management of lower-risk MDS.

Introduction of the International Prognostic Scoring System

Introduced in 1997, the original IPSS was a groundbreaking

tool that allowed for a standardized assessment of prognosis in MDS patients based on three variables: the percentage of bone marrow blasts, karyotype, and cytopenias.[15] Patients were classified into four risk groups (low, intermediate-1, intermediate-2, and high) which helped in guiding treatment decisions. The IPSS was primarily derived from untreated patients who were diagnosed with primary MDS, providing a baseline for the natural history of the disease.

For lower-risk MDS (low and intermediate-1 risk scores), the IPSS was instrumental in identifying patients who might benefit from supportive care or less intensive therapies, such as growth factor support or immunosuppressive treatment, instead of aggressive chemotherapy or stem cell transplantation. However, while effective, the IPSS had limitations in its ability to capture the full spectrum of genetic diversity and prognostic subtleties within MDS.

Transition to the revised International Prognostic Scoring System

The IPSS-R, introduced in 2012, was an advancement from the original system, offering refined risk stratification by incorporating additional cytogenetic abnormalities and more detailed gradations of marrow blasts and cytopenias.[3] The IPSS-R divides patients into five risk categories (very low, low, intermediate, high, and very high) and uses a more comprehensive cytogenetic scoring system that better reflects the prognostic impact of specific chromosomal abnormalities. For patients with lower-risk MDS, the IPSS-R provided a more nuanced approach to prognosis and treatment. It allowed for the identification of patients within the low and very low-risk categories who might have an even more indolent disease course and could be managed with minimal intervention or watchful waiting. Moreover, it helped in recognizing those at the higher end of the lower-risk spectrum who might benefit from early therapeutic intervention to prevent disease progression.

Emergence of the molecular International Prognostic Scoring System

The latest advancement, the IPSS-M, incorporates molecular genetic data into the risk stratification model, acknowledging the role of specific gene mutations in the pathogenesis and progression of MDS.[16] Established in 2022, this system integrates mutations in over 30 genes along with the traditional IPSS-R metrics of cytogenetics, marrow blasts, and cytopenias. This enhancement provides an even more precise prognostic classification and is particularly influential for patients with lower-risk MDS, in whom the detection of certain mutations can indicate a propensity for faster progression or transformation to AML.

In lower-risk MDS, the inclusion of molecular data allows clinicians to identify subgroups of patients who, despite having favorable scores based on cytogenetics and blood counts alone, may have poor outcomes due to the presence of high-risk mutations. This can lead to earlier and more aggressive treatments in patients who would otherwise be considered for conservative management based on older models.

The evolution from IPSS to IPSS-R and now to IPSS-M represents a trajectory towards increasingly personalized medicine in the management of MDS. These advancements underscore a growing understanding of the genetic and molecular underpinnings of the disease, facilitating more targeted and effective approaches in treating lower-risk MDS. This progress not only improves prognostic accuracy but also enhances patients' outcomes by aligning treatments with individual risk profiles, thereby optimizing therapeutic interventions and minimizing unnecessary exposure to potentially harmful treatments.

Recent phase III trials in lower-risk myelodysplastic syndromes

Historically, the treatment of lower-risk MDS was predominantly supportive, focusing on managing symptoms rather than altering the disease trajectory. The implementation of the IPSS-R and IPSS-M, combined with insights gained from the COMMANDS, MEDALIST, and IMerge trials, has dramatically changed this perspective. Results from the three trials are described below and summarized in Table 1. There is now a robust framework for a more proactive and targeted approach to treatment, which not only addresses symptoms and immediate complications but also aims to modify the underlying disease processes.

The integration of advanced risk stratification tools with new therapeutic options enables a more precise, personalized treatment regimen, potentially extending survival and improving QoL for patients with lower-risk MDS. As research continues to unveil the complexities of MDS pathophysiology and genetics, these strategies are likely to become even more refined, marking a new era in the management of a historically challenging group of disorders.

The MEDALIST trial

In the MEDALIST phase III, double-blind, placebo-controlled trial, patients categorized as having very low-risk, low-risk, or intermediate-risk MDS according to the IPSS-R and presenting with ring sideroblasts were assigned to receive either luspatercept or placebo.[4] Patients needed to be red cell transfusion-dependent and refractory to or ineligible for ESA. Luspatercept was administered subcutaneously every 3 weeks, starting at a dose of 1.0 mg/kg, with possible escalations to 1.75 mg/kg depending on the patients' response. The primary endpoint was achieving at least 8 weeks of transfusion independence during the initial 24 weeks. A secondary endpoint was attaining at least 12 weeks of transfusion independence within the first 24 and 48 weeks. Among 229 enrolled participants, 153 received luspatercept and 76 were given a placebo. Achieving transfusion independence

Table 1. Summary of the design and results of recent positive phase III trials (MEDALIST, COMMANDS and IMerge) in lower-risk myelodysplastic syndromes.

	MEDALIST	COMMANDS	IMerge
N of patients	229	356	178
Age in years, median (range)	71 (26-95)	74 (69-80)	72 (65-78)
Indication	Transfusion-dependent very low, low or intermediate risk MDS refractory or not eligible for ESA with RS	Transfusion-dependent very low, low or intermediate risk MDS, ESA-naïve	Transfusion-dependent (≥4 units over 8 weeks) low or intermediate-1 (IPSS) risk MDS refractory or not eligible for ESA
Intervention	Double-blind, placebo-controlled, 1:2 randomization to placebo or luspatercept sc every 3 weeks for 24 weeks, starting with 1.0 mg/kg up to 1.75 mg/kg	1:1 randomization to luspatercept sc every 3 weeks for 24 weeks, starting with 1.0 mg/kg up to 1.75 mg/kg or epoetin alfa sc once weekly, starting with 450 IU/kg up to 1,050 IU/kg	Double-blind, placebo-controlled, 1:2 randomization to placebo or imetelstat IV every 4 weeks until progression or unacceptable side effects, 7.5 mg/kg
IPSS-R classification, N (%)			
Very low	24 (10)	33 (9)	5 (3)
Low	166 (72)	257 (72)	133 (75)
Intermediate	38 (17)	62 (17)	28 (16)
Primary endpoint	Transfusion independence for 8 weeks or longer during weeks 1-24	Transfusion independence for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL (weeks 1-24)	Transfusion independence for 8 weeks or longer
Results	38% *vs*. 13% (placebo)	59% *vs*. 31% (epoetin alfa)	40% *vs*. 15% (placebo)
Side effects in experimental arm	Fatigue, diarrhea, asthenia, nausea, dizziness	Fatigue, asthenia, nausea, dyspnea, hypertension, headache	Neutropenia, thrombocytopenia
Authors' conclusion	Lsupatercept reduces transfusions in lower-risk MDS in patients with RS who did not or are unlikely to respond to ESA.	Luspatercept is more effective than epoetin alfa in ESA-naïve, lower-risk MDS. Additional studies in patients without RS/*SF3B1* mutations are needed.	Imetelstat provides a unique treatment approach, reduces transfusions and potentially modifies disease biology of lower-risk, ESA-ineligible MDS patients.

MDS: myelodysplastic syndrome; ESA: erythropoietin-stimulating agents; RS: ring sideroblasts; IPSS: International Prognostic Staging System; sc: subcutaneous; IV: intravenous; IPSS-R: revised International Prognostic Staging System.

for at least 8 weeks was reported in 38% of the luspatercept group, which was significantly higher than the 13% observed in the placebo group (P<0.001). The luspatercept group also outperformed the placebo group in reaching the secondary endpoint of 12-week transfusion independence (28% *vs*. 8% during the first 24 weeks, and 33% *vs*. 12% up to 48 weeks; P<0.001 for both intervals). Notable adverse events associated with luspatercept included fatigue, diarrhea, asthenia, nausea, and dizziness, all of which decreased in frequency over time. Luspatercept significantly ameliorated anemia but had no impact on QoL in patients with lower-risk MDS and ring sideroblasts who were dependent on red-cell transfusions and either non-responsive to, intolerant of or not eligible for ESA. This study, supported by Celgene and Acceleron Pharma, underscores luspatercept's potential as an effective treatment for this population of patients.

The COMMANDS trial

Following the placebo-controlled MEDALIST trial, the COMMANDS study investigated luspatercept *versus* epoetin alfa in ESA-naïve patients with transfusion-dependent IPSS-R lower-risk MDS (very low risk, low risk, or intermediate risk) with less than 5% blasts.[4] Conducted across 142 sites in 26 countries, the trial enrolled patients who had not been previously treated with ESA and required regular red blood cell transfusions. Participants were randomly assigned to receive either luspatercept, administered subcutaneously at a dose of 1.0 mg/kg every 3 weeks (with escalation up to 1.75 mg/kg), or epoetin alfa, administered weekly starting at a dose of 450 IU/kg (with possible titration up to a maximum of 80,000 IU). Achievement of at least 12 weeks of red blood cell transfusion independence was the primary endpoint of the study, with a concurrent mean hemoglobin increase of at least 1.5 g/dL within the first 24 weeks. Out of the 301 patients analyzed in a prespecified interim analysis, 59% of those in the luspatercept group met the primary endpoint, compared to 31% in the epoetin alfa group, reflecting a significant response rate difference (P<0.0001). Additionally, median treatment exposure was longer in the luspatercept group. Adverse events observed with luspatercept included hypertension, anemia, dyspnea, neutropenia, thrombocytopenia, pneumonia, COVID-19, and syncope, whereas epoetin alfa was associated with similar issues, including iron overload. Treatment-related adverse events such as fatigue, asthenia, and headache were more frequent in the luspatercept group. These results demonstrate that

luspatercept is more effective than epoetin alfa in achieving transfusion independence and increasing hemoglobin levels in this patient population, apart from in patients without ring sideroblasts in whom responses to luspatercept and epoietin alfa were similar. Notably, QoL was not improved by luspatercept. Nevertheless, both the American Food and Drug Administration and the European Medicines Agency approved luspatercept as first-line treatment in all subgroups of patients with transfusion-dependent, lower-risk MDS.

The IMerge trial

Imetelstat is a first-in-class telomerase inhibitor, an enzyme that is preferentially active in clonal cells in MDS. Based on the positive results from the initial phase II study,[17] the international, double-blind, placebo-controlled IMerge phase III study investigated imetelstat in 178 patients (118 received imetelstat, 60 placebo) with ESA-relapsed, ESA-refractory, or ESA-ineligible lower-risk MDS (low or intermediate-1 risk disease as per IPSS criteria).[6] Participants received either imetelstat (7.5 mg/kg) or a placebo every 4 weeks as an intravenous infusion. The trial aimed to assess the efficacy of imetelstat in achieving red blood cell transfusion independence over 8 weeks. At the data cutoff, 40% of the imetelstat group achieved red blood cell transfusion independence for at least 8 weeks, compared to 15% in the placebo group. This marked a significant improvement, with a difference in response rate of 25%. Surprisingly, only marginal improvements in QoL were noted. However, higher rates of grade 3 or 4 treatment-emergent adverse events were noted in the imetelstat group, particularly neutropenia (68%) and thrombocytopenia (62%), which were significantly more common in this group than in the placebo group. Remarkably, 47% of patients in the placebo group suffered from at least one grade 3 or 4 treatment-emergent adverse event, underlining the general vulnerability of lower-risk MDS patients. Imetelstat represents a novel approach to the treatment of such patients, with its mechanism of telomerase inhibition, offering durable transfusion independence and potential disease-modifying effects in heavily transfused lower-risk MDS patients in second line irrespective of the presence of ring sideroblasts. The treatment appeared especially beneficial for those who had exhausted conventional options. However, the incidence of cytopenia events necessitates careful patient selection and management. Imetelstat was approved by the Food and Drug Administration in June 2024 for adults with low- to intermediate-1-risk MDS and transfusion-dependent anemia who need four or more red blood cell units over 8 weeks and are unresponsive to or ineligible for ESA. Approval from the European Medicines Agency is awaited shortly.

Based on the introduction of luspatercept and imetelstat into the treatment landscape of lower-risk MDS, we propose the following treatment algorithm, which is summarized in Figure 1.

Treatment algorithm for lower-risk myelodysplastic syndromes

The overarching principle of treatment of patients with lower-risk MDS is adequate supportive care, consisting of transfusions in the case of symptomatic, transfusion-dependent anemia, iron chelation, as well as reducing the risk of bleeding events and infectious complications. Furthermore, recent studies demonstrated that patients with MDS are at higher risk of bone loss.[18] Therefore, improving bone health in patients with lower-risk MDS and osteopenia or overt osteoporosis has become another focus of supportive care.

In the case of isolated symptomatic thrombocytopenia, administration of thrombopoietin agonists, although still not approved, is safe and effective including a reduction in the risk of bleeding events.[19]

Patients with symptomatic anemia should be delineated according to transfusion dependency. Based on two randomized trials, all patients with transfusion-dependent or -independent MDS with del(5q) should be treated with lenalidomide.[20,21] If this treatment fails, the strategy used for non-del(5q) patients should be followed.

In non-transfusion-dependent patients, ESA remain the standard of care for first-line treatment. Comparable to the transfusion-dependent setting, lenalidomide can be used after treatment failure in patients harboring del(5q).[22] Autoimmune phenomena are common in patients with MDS.[23] Moreover, hyperactivation of T cells can lead to suppression of hematopoiesis and the presence of paroxysmal nocturnal hemoglobinuria or large granular lymphocyte clones is common in patients with hypoplastic MDS.[24] In hypoplastic MDS patients, immunosuppressive treatment with horse anti-thymocyte globulin and cyclosporine should be implemented. Immunosuppression leads to hematologic improvement and transfusion independency was attained in 30% of patients, with 11% achieving a complete remission.[25]

In the non-del(5q) group of transfusion-dependent patients, treatment should be stratified by the presence or absence of ring sideroblasts and/or *SF3B1* mutations. In patients presenting with an erythropoietin level exceeding 200 U/L, luspatercept should be administered as the primary treatment based on the findings from the COMMANDS study. For individuals with erythropoietin levels below 200 U/L, ESA may be considered, particularly for those without ring sideroblasts, although both treatments remain viable options. Notably, patients with ring sideroblasts generally exhibit better overall response rates with luspatercept than with ESA.

In the transfusion-dependent group without ring sideroblasts or *SF3B1* mutations, ESA remain the mainstay of first-line therapy if justified by low erythropoietin levels given that in the COMMANDS trial responses to ESA were similar to those to luspatercept. If nonresponsive to ESA or treatment failure occurs, imetelstat should be con-

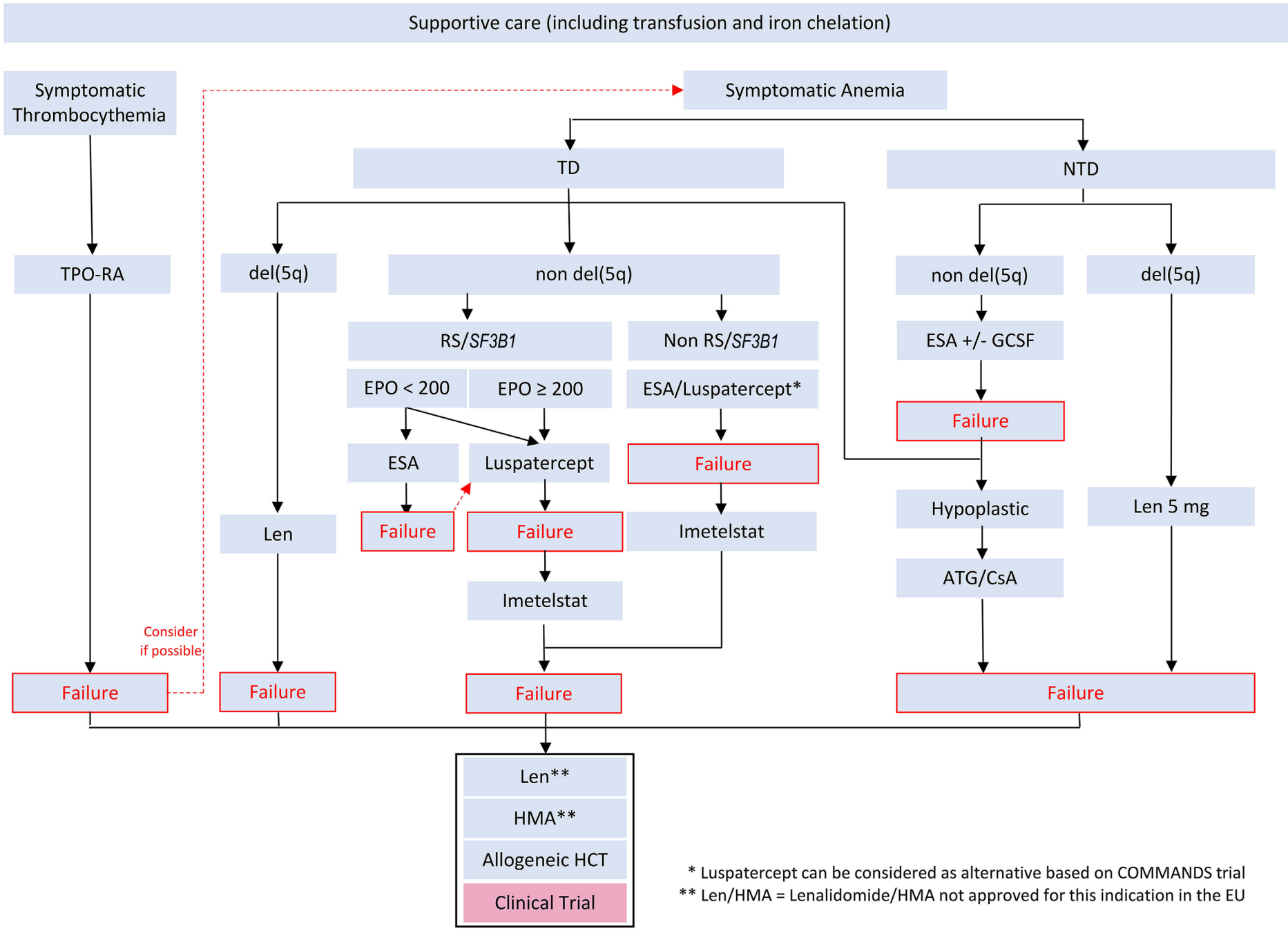

Figure 1. Treatment algorithm for lower-risk myelodysplastic syndromes. Flow chart summarizing a treatment approach to lower-risk myelodysplastic syndromes. TPO-RA: thrombopoietin receptor agonist; TD: transfusion dependent; NTD: non-transfusion dependent; del(5q): deletion of chromosome 5q; RS: ring sideroblasts; ESA: erythropoiesis-stimulating agents; Len: lenalidomide; EPO: erythropoietin; GCSF: granulocyte colony-stimulating factor; HMA: hypomethylating agents; HCT: hematopoietic cell transplantation; ATG: antithymocyte globulin; CsA: cyclosporine A; EU: European Union.

sidered in second line. However, based on the findings of the phase II MDS-PACE study, which enrolled 44 patients without ring sideroblasts among the entire cohort of 108 patients,[26,27] luspatercept (although not approved) can be considered as an alternative to imetelstat in second-line treatment of non-del(5q) transfusion-dependent patients without ring sideroblasts or *SF3B1* mutations after the failure of ESA therapy.

Although the abovementioned treatment suggestions for the different groups of lower-risk MDS provide a comprehensive, risk-adapted and clinically as well as molecularly informed approach, treatment failure due to side effects, lack of response or progression to AML reflect the natural history of the disease. Therefore, allogeneic transplantation is ultimately the only curative treatment option for MDS patients.[28,29] Hypomethylating agents or lenalidomide (although not approved in most of the countries) have become the standard of care for transplant-ineligible, lower-risk MDS patients who have none of the aforementioned therapeutic options. Still, patients should always be evaluated for eligibility for enrollment into clinical trials.

Ongoing trials and a look at future treatment options in lower-risk myelodysplastic syndromes

ELEMENT-MDS

In the phase III COMMANDS study luspatercept significantly increased the number of ESA-naïve, lower-risk MDS pa-

tients achieving transfusion independence for 12 weeks or more, coupled with a hemoglobin increase of at least 1.5 g/dL, performing significantly better than ESA. However, its effectiveness in transfusion-independent, lower-risk MDS patients remains unexplored.

The ELEMENT-MDS study (NCT05949684), a phase III, randomized, multicenter trial, is underway to evaluate the safety and effectiveness of luspatercept *versus* epoetin alfa in preventing the progression to transfusion dependence in ESA-naïve, transfusion-independent adult patients with lower-risk MDS.[30] The study targets enrolling 360 patients with anemia categorized as having very low-, low-, or intermediate-risk MDS according to the IPSS-R. Candidates are adults with a confirmed diagnosis of MDS, baseline serum erythropoietin levels of 500 U/L or less, and clinically significant anemia.

Eligible participants will be randomized equally to receive either luspatercept every 3 weeks starting at a dose of 1.0 mg/kg (with possible escalation to 1.75 mg/kg), or weekly epoetin alfa starting at a dose of 450 IU/kg (with a potential increase to 1,050 IU/kg). The primary measure of the study is to determine the proportion of patients becoming transfusion-dependent during any 16-week period within the initial 96 weeks of treatment. Secondary outcomes include duration of transfusion independence, time to first transfusion dependency, improvement in hemoglobin levels, and overall QoL. Safety assessments will focus on types and severity of adverse events, and their connections to the treatment as well as progression into AML. This ongoing research is pivotal in determining the potential of luspatercept as a viable alternative for lower-risk, non-transfusion-dependent MDS patients.

AG-946

Inhibiting pyruvate kinase in patients with lower-risk MDS is another principle that is currently being investigated in a phase IIa/b study.[31,32] AG-946 acts as a small-molecule, allosteric activator of both wild-type and mutated pyruvate kinase R isoforms. Pyruvate kinase R is a crucial enzyme in the glycolysis pathway, and its activation by AG-946 aims to boost ATP production, thereby potentially alleviating the anemia associated with MDS by improving red blood cell survival and promoting healthier erythropoiesis. The study of AG-946 consists of two phases: an open-label, proof-of-concept phase (phase IIa) and a randomized, double-blind, placebo-controlled phase (phase IIb). The study involves adult patients with anemia due to lower-risk MDS, categorized by their transfusion needs into three groups: non-transfusion-dependent, low transfusion burden and high transfusion burden. Key inclusion criteria include having documented lower-risk MDS as per the IPSS-R, with a risk score of ≤3.5 and less than 5% bone marrow blasts, and hemoglobin levels below 11.00 g/dL. In phase IIa, 5 mg of AG-946 will be administered daily for up to 172 weeks to 20 patients. The primary endpoints for this phase are to achieve a significant hemoglobin response (an average increase of ≥1.5 g/dL from baseline between weeks 8 and 16) and transfusion independence (no transfusions for ≥8 consecutive weeks) among patients with a low transfusion burden. Safety, changes in hemoglobin levels, reduction in transfusion requirements, and drug pharmacokinetics/pharmacodynamics are also key areas of focus. Should phase IIa meet its predefined success criteria, phase IIb will proceed with 96 patients randomized to receive varying doses of AG-946 or a placebo for up to 180 weeks. The primary endpoint for phase IIb is the modified hematologic improvement-erythroid response, which includes sustained hemoglobin response, transfusion independence, and a 50% reduction in transfusion requirements across different groups of patients. Secondary outcomes include overall safety, time to achieve the modified hematologic improvement-erythroid response, and the duration of this response.

While it is impracticable to list all ongoing clinical trials investigating novel therapeutic options in transfusion-independent and -dependent lower-risk MDS patients, it needs to be mentioned that there is a discrepancy between the prevalence of lower-risk disease and the clinical trial landscape. While the majority of MDS patients is considered lower risk at primary diagnosis, only a small proportion of clinical trials is initiated in that population and most trials focus on higher-risk disease.[33-35]

Unmet needs in current clinical trials

Health-related QoL in patients with lower-risk MDS is affected by a wide range of factors including the physical symptoms of the disease, the side effects of treatments, emotional well-being and social and economic impacts. Compared to age- and sex-matched healthy individuals, patients with lower-risk MDS experience severe impediments with regards to pain, mobility, anxiety and depression as well as usual activities of daily living.[36] Nevertheless, improvement of health-related QoL is oftentimes neglected as an endpoint in clinical trials in favor of surrogate endpoints, such as transfusion independency. While the latter might be a suitable endpoint to measure in clinical trials, its effect on patients' well-being remains to be elucidated and might differ significantly between certain interventions. It is, therefore, necessary to integrate improvements of QoL and patient-reported outcomes as endpoints into future clinical trials.[37] Importantly, from the three aforementioned clinical phase III trials in lower-risk MDS, neither MEDALIST nor COMMANDS found a significant improvement of health-related QoL, although the trials met their primary endpoints.[38] So far, only IMerge found a significant improvement of patient-reported outcomes following the application of imetelstat.[39] This underlines that, especially in lower-risk patients, transfusion independency is a sub-

optimal endpoint, since health-related QoL should be at the center for this population.

Conclusion

Although treatment of lower-risk MDS patients focused on supportive care in the last decades, novel insights into the pathogenesis of the disease, improved risk stratification and the latest positive phase III trials have improved the therapeutic landscape for this heterogeneous population. The introduction of luspatercept and imetelstat ushered in a new era of risk-adapted treatment in lower-risk patients. Future clinical trials will address currently unmet needs, such as the role of novel agents in transfusion-independent patients and will explore innovative modes of actions to improve the natural history of lower-risk MDS.

Disclosures

AMAM has no conflicts of interest to disclose. UP has received research funding from Roche, Syros, Curis, Servier, Amgen, Novartis, Fibrogen, Takeda, Silence Therapeutics, BeiGene, Geron, Janssen Biotech, Jazz, Merck and Bristol Myers Squibb; has received honoraria from Syros, Servier, Takeda, Silence Therapeutics, Jazz, Bristol Myers Squibb and Celgene; has provided consultancy services for Syros, Curis, Servier, Amgen, Novartis, Takeda, Silence Therapeutics, AbbVie, Geron, Janssen Biotech, Jazz and Bristol Myers Squibb; is a member of the Board of Directors or advisory committees for MDS Foundation and Bristol Myers Squibb and has received both travel support and medical writing assistance from Bristol Myers Squibb.

Contributions

AMAM and UP designed and executed this project and wrote the manuscript.

References

1. Sekeres MA, Taylor J. Diagnosis and treatment of myelodysplastic syndromes: a review. JAMA. 2022;328(9):872-880.
2. Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(8):1307-1325.
3. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood. 2012;120(12):2454-2465.
4. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020;382(2):140-151.
5. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023;402(10399):373-385.
6. Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;403(10423):249-260.
7. Kubasch AS, Fenaux P, Platzbecker U. Development of luspatercept to treat ineffective erythropoiesis. Blood Adv. 2021;5(5):1565-1575.
8. Abou Zahr A, Bernabe Ramirez C, Wozney J, Prebet T, Zeidan AM. New insights into the pathogenesis of MDS and the rational therapeutic opportunities. Expert Rev Hematol. 2016;9(4):377-388.
9. Ogawa S. Genetics of MDS. Blood. 2019;133(10):1049-1059.
10. Aleshin A, Greenberg PL. Molecular pathophysiology of the myelodysplastic syndromes: insights for targeted therapy. Blood Adv. 2018;2(20):2787-2797.
11. Taylor J, Lee SC. Mutations in spliceosome genes and therapeutic opportunities in myeloid malignancies. Genes Chromosomes Cancer. 2019;58(12):889-902.
12. Heuser M, Yun H, Thol F. Epigenetics in myelodysplastic syndromes. Semin Cancer Biol. 2018;51:170-179.
13. Ghobrial IM, Detappe A, Anderson KC, Steensma DP. The bone-marrow niche in MDS and MGUS: implications for AML and MM. Nat Rev Clin Oncol. 2018;15(4):219-233.
14. Winter S, Shoaie S, Kordasti S, Platzbecker U. Integrating the "immunome" in the stratification of myelodysplastic syndromes and future clinical trial design. J Clin Oncol. 2020;38(15):1723-1735.
15. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079-2088.
16. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for myelodysplastic syndromes. NEJM Evid. 2022;1(7):EVIDoa2200008.
17. Steensma DP, Fenaux P, Van Eygen K, et al. Imetelstat achieves meaningful and durable transfusion independence in high transfusion-burden patients with lower-risk myelodysplastic syndromes in a phase II study. J Clin Oncol. 2021;39(1):48-56.
18. Weidner H, Rauner M, Trautmann F, et al. Myelodysplastic syndromes and bone loss in mice and men. Leukemia. 2017;31(4):1003-1007.
19. Oliva EN, Riva M, Niscola P, et al. Eltrombopag for low-risk myelodysplastic syndromes with thrombocytopenia: interim results of a phase II, randomized, placebo-controlled clinical trial (EQOL-MDS). J Clin Oncol. 2023;41(28):4486-4496.
20. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del5q. Blood. 2011;118(14):3765-3776.
21. López Cadenas F, Lumbreras E, González T, et al. Evaluation of lenalidomide (LEN) vs placebo in non-transfusion dependent low risk del(5q) MDS patients. Final results of Sintra-REV phase III international multicenter clinical trial. Blood. 2022;140(Supplement 1):1109-1111.
22. Díez-Campelo M, López-Cadenas F, Xicoy B, et al. Low dose

lenalidomide versus placebo in non-transfusion dependent patients with low risk, del(5q) myelodysplastic syndromes (SintraREV): a randomised, double-blind, phase 3 trial. Lancet Haematol. 2024;11(9):e659-e670.
23. Hochman MJ, DeZern AE. Myelodysplastic syndrome and autoimmune disorders: two sides of the same coin? Lancet Haematol. 2022;9(7):e523-e534.
24. Li H, Hu F, Gale RP, Sekeres MA, Liang Y. Myelodysplastic syndromes. Nat Rev Dis Primers. 2022;8(1):74.
25. Stahl M, DeVeaux M, de Witte T, et al. The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort. Blood Adv. 2018;2(14):1765-1772.
26. Platzbecker U, Germing U, Götze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017;18(10):1338-1347.
27. Platzbecker U, Götze KS, Kiewe P, et al. Long-term efficacy and safety of luspatercept for anemia treatment in patients with lower-risk myelodysplastic syndromes: the phase II PACE-MDS study. J Clin Oncol. 2022;40(33):3800-3807.
28. Franke G-N, Lückemeier P, Platzbecker U. Allogeneic stem-cell transplantation in patients with myelodysplastic syndromes and prevention of relapse. Clin Lymphoma Myeloma Leuk. 2021;21(1):1-7.
29. Platzbecker U. Treatment of MDS. Blood. 2019;133(10):1096-1107.
30. Zeidan AM, Komrokji RS, Buckstein R, et al. The ELEMENT-MDS trial: a phase 3 randomized study evaluating luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, non-transfusion-dependent, lower-risk myelodysplastic syndromes. Blood. 2023;142(Supplement 1):6503.
31. Fattizzo B, Vercellati C, Marcello A, et al. Glycolytic activity and in vitro effect of the pyruvate kinase activator AG-946 in red blood cells from low-risk myelodysplastic syndromes patients: a proof-of-concept study. Am J Hematol. 2024;99(6):1201-1204.
32. Al-Samkari H, Fenaux P, Sekeres MA, et al. A phase 2a/2b multicenter study of AG-946 in patients with anemia due to lower-risk myelodysplastic syndromes. Blood. 2022;140(Supplement 1):4076-4078.
33. Duetz C, Cucchi DGJ, Polak TB, et al. The wider perspective: twenty years of clinical trials in myelodysplastic syndromes. Br J Haematol. 2022;196(2):329-335.
34. Merz AMA, Sébert M, Sonntag J, Kubasch AS, Platzbecker U, Adès L. Phase to phase: navigating drug combinations with hypomethylating agents in higher-risk MDS trials for optimal outcomes. Cancer Treat Rev. 2024;123:102673.
35. Merz AMA, Platzbecker U. Beyond the horizon: emerging therapeutic approaches in myelodysplastic neoplasms. Exp Hematol. 2024;130:104130.
36. 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.
37. Oliva EN, Platzbecker U, Fenaux P, et al. Targeting health-related quality of life in patients with myelodysplastic syndromes - current knowledge and lessons to be learned. Blood Rev. 2021;50:100851.
38. Oliva EN, Platzbecker U, Garcia-Manero G, et al. Health-related quality of life outcomes in patients with myelodysplastic syndromes with ring sideroblasts treated with luspatercept in the MEDALIST phase 3 trial. J Clin Med. 2021;11(1):27.
39. Sekeres MA, Diez-Campelo M, Zeidan AM, et al. Improvement of patient-reported outcomes among heavily pretreated patients with lower-risk myelodysplastic syndromes and high transfusion burden treated with imetelstat on the IMerge phase 3 trial. Blood. 2023;142(Supplement 1):6479.