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Next-generation therapy for lower-risk MDS

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Myelodysplastic syndromes (MDS) are malignant myeloid neoplasms characterized by ineffective clonal hematopoiesis leading to peripheral blood cytopenia and a variable risk of transformation to acute myeloid leukemia. In lower-risk (LR) MDS, as defined by prognostic scoring systems recently updated with the addition of a mutation profile, therapeutic options aim to reduce cytopenia, mainly anemia. Although options for reducing the transfusion burden have recently been improved, erythropoiesis-stimulating agents (ESAs), lenalidomide, hypomethylating agents, and, more recently, luspatercept have shown efficacy in rarely more than 50% of patients with a duration of response often far inferior to the patient's life expectancy. Nevertheless, several new therapies are currently under investigation aiming at improving cytopenia in patients with LR-MDS, mostly by targeting different biological pathways. Targeting ligands of the transforming growth factor β pathway has led to the approval of luspatercept in LR-MDS with ring sideroblasts or *SF3B1* mutation, potentially replacing first-line ESAs in this population. Here, we also discuss the evolving standard of care for the treatment of LR-MDS and explore some of the most promising next-generation agents under investigation.

LEARNING OBJECTIVES

- Learn about the role of molecular-driven biology in next-generation therapies for myelodysplastic syndromes
- Review therapies for lower-risk myelodysplastic syndromes that are currently in development
- Understand how pathologic inflammatory pathways in myelodysplastic syndromes can be targeted by novel therapies

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal malignant myeloid malignancies characterized by ineffective hematopoiesis, leading to peripheral blood cytopenia, and a variable risk of transformation to acute myelogenous leukemia.[1] As 80% of patients with MDS are over 60 years of age, existing scoring systems based on cytopenia, bone marrow blast percentage, and somatic oncogenetic events are used to identify the risk of MDS progression in order to define therapeutic goals in this elderly and sometimes frail population.[2] About two-thirds of patients with MDS will present with lower-risk (LR) disease at diagnosis.[3] Even if hematopoietic stem cell transplantation (HSCT) is the only curative option, most patients with MDS are ineligible because of age or comorbidities, and the main approach for patients with LR-MDS still aims at improving cytopenia (mainly anemia) and its complications.

For many years, the therapeutic strategy for these patients was very limited, relying solely on transfusion, HSCT, and erythropoiesis-stimulating agents (ESAs). Given the recent progress made in the understanding of the pathophysiology of LR-MDS and the results of clinical trials recently published, we could now propose an updated algorithm for the management of these patients, shown in Figure 1. Through a few practical examples, we will discuss these different new therapeutic options.

CLINICAL CASE 1

A 79-year-old man with a history of type 2 diabetes and hypertension was referred to the hematology department after a routine blood test revealed anemia. The complete blood count showed hemoglobin (Hb) of 6.5 g/dL, mean corpuscular volume of 85 fL, a white blood cell count of 4.3×10^9/L, an absolute neutrophil count of 2.7×10^9/L, and platelet count of 152×10^9/L. B12, folate, and iron levels were normal, and erythropoietin was 110 U/L. A bone marrow (BM) aspirate showed marked dysplastic changes in 25% of erythroid cells, 3% of blasts, and 15% of ring sideroblasts, and next-generation sequencing (NGS) revealed an isolated *SF3B1* mutation with 25% variant allele frequency (VAF). Cytogenetics were normal. The patient received a

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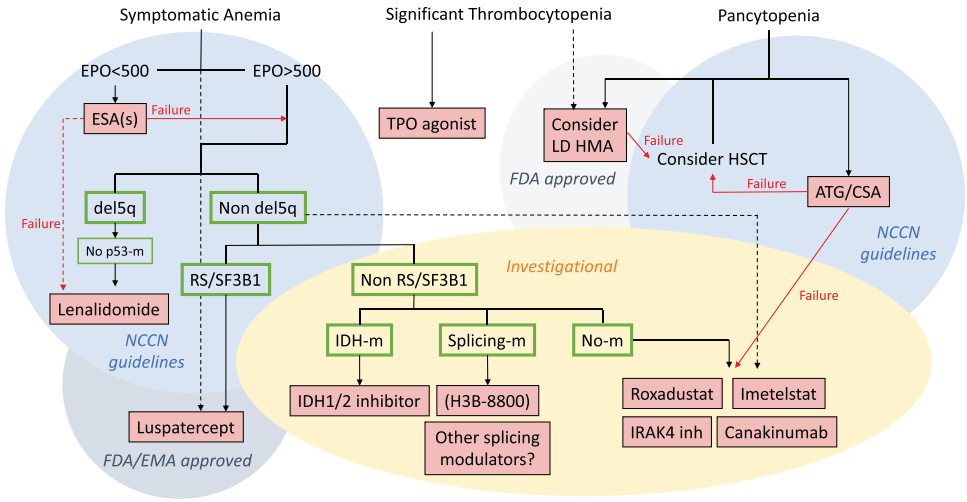

Figure 1. Treatment algorithm for lower-risk MDS—IPSS-R ≤3.5. CSA, cyclosporine; EMA, European Medicines Agency; FDA, Food and Drug Administration; m, mutated; NCCN, National Comprehensive Cancer Network; TPO, thrombopoietin.[19]

transfusion for anemia at diagnosis and ESA, epoetin (EPO)–α 450 IU/kg/wk. His Hb increased to 11.5 g/dL by the second month of EPO, and he became transfusion independent (TI). Two years later, he relapsed while still on EPO with isolated anemia and received a transfusion again. The repeated aspiration of the BM was similar to the one performed at diagnosis. Subcutaneous luspatercept (starting dose 1 mg/kg every 3 weeks) with transfusion support was started, and he reached transfusion independency by the fifth dose of luspatercept.

For all patients with MDS, existing scoring systems define multiple risk categories, but these are reduced to what is used clinically—lower- and higher-risk MDS—to guide treatment options. Even if most of the available drugs for MDS was approved according to the classical International Prognostic Scoring System (IPSS) classification published in 1998, the International Working Group (IWG) for prognosis in MDS was revised in 2012 (IPSS-R) and even more recently in 2022 (IPSS-M), taking into consideration somatic gene mutations,[2] representing a valuable tool for individual risk assessment and treatment decisions.[4]

In lower-risk MDS, defined by IPSS-R ≤3.5 or IPSS-M (moderate low, low, and very low), available therapeutic options are mainly limited to supportive care with transfusions, ESAs, lenalidomide, hypomethylating agents (HMAs, azacitidine or decitabine), and, more recently, luspatercept (Luspa) (Table 1).

Anemia is the most common cytopenia in LR-MDS and is present in almost 90% of the cases. Symptoms related to anemia deeply impact the quality of life of these patients but can also lead to worsening of cardiopulmonary function or cognitive decline. Anemia management was first based on red blood cell (RBC) transfusion, but RBC transfusion dependency (TD) is associated with decreased quality of life and iron overload. ESA was the first-line agent used for the treatment of anemia in patients with LR-MDS, being more effective among patients with serum erythropoietin (sEPO) levels ≤500 U/L and limited transfusion burden, leading to an overall response rate of 30% to 45% and an 18- to 24-month median duration of response.[5] Thus, in the recent years, many efforts have been made to improve the response rate of these patients as a first- or second-line therapy.

Targeting the transforming growth factor β pathway

SF3B1-mutated MDS are a distinct MDS subtype, as initially proposed by the IWG for the prognosis of MDS[14] and now fully defined in the recent World Health Organization 2022 classification of MDS,[1] largely overlapping MDS with ring sideroblasts (MDS-RS or with *SF3B1* mutation).

Luspa is a recombinant fusion protein derived from human activin receptor type IIb linked to a portion of immunoglobulin G. Transforming growth factor β (TGF-β) signaling is mediated by a regulatory circuit of inhibitory and activating SMAD proteins that can inhibit the proliferation of hematopoietic stem cells (HSCs) while increasing erythroid differentiation, altogether leading to dysplastic erythropoiesis and reduced erythroid output with anemia phenotypes.[15]

The MEDALIST trial was a phase 3, randomized, double-blind, placebo-controlled study, assessing the efficacy of Luspa vs placebo in LR patients with MDS-RS refractory/intolerant or ineligible for ESA (EPO level >200 U/L) and RBC-TD.[12] In total, 153 patients received Luspa at the starting dose of 1 mg/kg subcutaneously every 21 days, while 71 patients received a placebo. According to the longer-term analysis of this study[16] and applying the new IWG 2019 response criteria,[17] the primary end point of RBC-TI ≥8 weeks was achieved in 69 (45.1%) patients in the Luspa arm vs 12 (15.8%) in the placebo arm (P<.0001); RBC-TI ≥16 weeks was achieved in 43 (28.1%) in the Luspa arm and 5 (6.6%) in the placebo arm (P=.0001).[16] One limitation of this study is that there were potential differences in the criteria for response assessment between this trial and previous studies. Importantly, the drug was well tolerated, and there was no evidence for disease progression on therapy.

There are several other clinical trials evaluating Luspa in non–MDS-RS as well as in combination with other agents, as a first- or second-line therapy. The interim efficacy analysis of the COMMANDS study, comparing in a frontline randomized trial Luspa to ESA (NCT: 03682536) in 301 TD non-del5q ESA-naive patients

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Table 1. Available therapies in LR-MDS

Agent	Mechanism of action	Population	Identifier/Trial Name	Phase	Status	Ref.
Epoietin alfa	ESA	LR-MDS with anemia	NCT01381809 EPOANE3021	3	EMA approved	5
Darbepoietin alfa	ESA	LR-MDS with anemia	NCT00095264	2	Off-label	6
Lenalidomide	Immune regulatory agent	LR-MDS del5(q)	NCT00179621	3	FDA/EMA approved	7
		LR-MDS without del(5q)	NCT01029262	3	Off-label	8
Azacitidine	HMA	MDS with pancytopenia	NCT01720225	2/3	FDA approved	9
Decitabine	HMA	MDS with pancytopenia	NCT01720225	2/3	FDA approved	9
Eltrombopag	TPO mimetic	MDS without excess blasts, with thrombocytopenia or pancytopenia	NCT02928419 EQoL-MDS	2	Off-label	10
ATG/CSA	Immunosuppressive	LR-MDS with pancytopenia	Retrospective study	NA	Off-label	11
Luspatercept	TGF-β inhibitor	MDS-RS or with *SF3B1* mutation	NCT02631070MEDALIST	3	FDA/EMA approved	12
		LR-MDS with anemia	NCT:03682536 COMMANDS	3	Off-label	13

CSA, cyclosporine A; EMA, European Medicines Agency; HMA, hypomethylating agent; NA, not applicable; TPO, thrombopoietin.

with MDS-LR, was recently published.[13] TI for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL was achieved in 86 (59%) patients in the Luspa group compared to 48 patients (31%) in the EPO group (P<.0001) with a significantly better duration of response with Luspa (P=.005). Most patients enrolled in this study had RS-MDS, and it should be noted that the responses observed in patients without RS did not differ between the Luspa and ESA arms. Despite some manageable suspected Luspa-related events (fatigue, asthenia, nausea, dyspnea, hypertension, and headache), these results suggest that treating transfusion-dependent patients with LR-MDS with Luspa as a first-line therapy might be beneficial, at least among patients with RS.

Moreover, other new drugs targeting the TGF-β pathway are under investigation (Table 2), including KER-050, a therapeutic protein designed to increase not only red blood cells but also platelets by inhibiting the signaling of a subset of the TGF-β family of proteins to promote hematopoiesis (phase 2, NCT04419649).

CLINICAL CASE 1 (continued)

After 6 months, the patient lost his response to Luspa, and NGS revealed the acquisition of an *IDH1* mutation with 15% VAF, while the patient still had LR-MDS.

Over the past decade, genomic technologies have led to a better understanding of the genetic events underlying the onset and progression of MDS and how they functionally contribute to specific aspects of the disease pathophysiology. These studies have revealed that MDS is driven by a multistep acquisition of genetic alterations that affect a recurrent set of genes, which promote the self-renewal of mutant HSCs and lead to their clonal expansion over their normal counterparts.[18] New agents targeting altered signaling pathways that induce mutant HSC clonal advantage of specific genetic alterations in MDS are currently under investigation, and the trend toward a more individualized, molecularly driven approach to patient care is likely going to increase. (Figure 1 and Table 2).

Somatic mutation-driven therapies: Isocitrate dehydrogenase and spliceosome inhibitors

Isocitrate dehydrogenase (*IDH*) mutations are gain-of-function mutations, leading to an hypermethylated phenotype, disrupting TET2 function, and leading to an impaired hematopoietic differentiation. *IDH1* or *IDH2* mutations are detected in about 10% of patients with MDS. Following US Food and Drug Administration approval in acute myelogenous leukemia, IDH1/2 inhibitors ivosidenib, olutasidenib, and enasidenib (ENA) are currently developed in higher-risk patients with MDS, but some clinical trials also evaluate their efficacy in LR-MDS (Table 2).[20,21] Of note, in a preclinical study, ENA was shown to increase the erythroid differentiation of the hematopoietic stem and progenitor cells without myeloid differentiation, suggesting an erythroid-specific differentiation effect independent of its effect on mutant and wild-type *IDH2*.[22] Based on this preclinical rationale, ENA is under investigation in anemic patients with LR-MDS without *IDH2* mutation (NCT05282459).

MDS cells with splicing factor mutations rely on the wild-type allele for splicing, and the preferential inhibition of the wild-type allele results in lethality of the cells. H3B-8800 is an oral small-molecule splicing modulator, preferentially targeting the sF3b complex, and in preclinical models, including xenograft leukemia models with or without core spliceosome mutations, it has broad antitumor activity.[23] This drug was evaluated in a phase 1, open-label, first-in-human study in patients with myeloid malignancies (n=84) and splicing factor mutations (NCT02841540).[24] Unfortunately, no complete or partial responses meeting IWG criteria were observed; however, RBC transfusion-free intervals >56 days were observed in 9 patients who were transfusion dependent at study entry (15%). Given the high frequency of splicing mutations in MDS, additional splicing inhibitors are also undergoing preclinical assessments.

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Table 2. Emerging therapy in LR-MDS

Agent	Mechanism of action	Phase	Population	Identifier	Ref.
Ivosidenib	IDH1 inhibitor	2	Treatment-naive HR-MDS R/R (HMA) HR-MDS R/R (ESA) LR-MDS with anemia All with IDH1m	NCT03503409	20
Enasidenib	IDH2 inhibitor	2	Treatment-naive HR-MDS R/R (HMA) HR-MDS R/R (ESA) LR-MDS with anemia All with IDH2m	NCT03744390	21
		2, with AZA	MDS, excess blats, AML, CMML with IDH2m	NCT03383575	
Olutasidenib (FT-2102)	IDH1 inhibitor	2, with/without AZA/L-DAC	SMD and AML with IDH1m	NCT02719574	
H3B-8800	Splicing modulator	1	SMD, AML, CMML	NCT02841540	24
Roxadustat	HIF inhibitor	3	LR-MDS with anemia, low transfusion burden	NCT03263091	29
		2/3	LR-MDS with anemia	NCT03263091	
Imetelstat	Telomerase inhibitor	2/3	R/R (ESA) LR-MDS	NCT02598661	25
KER-050	TGF-β inhibitor	2	R/R (ESA) LR-MDS	NCT04419649	
Canakinumab	Il-1β inhibitor	1/2, with darbepoietin	R/R (ESA) LR-MDS	NCT04798339	
		2	R/R (ESA) LR-MDS	NCT05237713	
		2	R/R (ESA/HMA) LR-MDS/CMML	NCT04239157	
Emavusertib (CA-4948)	IRAK4 inhibitor	2	Treatment-naive and R/R (ESA) LR-MDS	NCT05178342	
BMS-986253	IL-8 inhibitor	1/2, with/without DEC/cedazuridine	R/R (HMA) HR-MDS R/R (ESA/LEN/Luspa) LR-MDS	NCT05148234	
SX-682	CXCR1 and CXCR2 inhibitor	1	R/R (ESA/LEN) LR-MDS	NCT04245397	
Tomaralimab	TLR2 inhibitor	1/2	R/R (ESA/LEN) LR-MDS	NCT02363491	

AML, acute myelogenous leukemia; AZA, azacitidine; CMML, chronic myelomonocytic leukemia; DEC, decitabine; HIF, hypoxia-inducible factor; L-DAC, low-dose aracytine; LEN, lenalidomide; MDS, myelodysplastic syndrome; R/R, relapse/refractory.

Targeting telomerase activity

As in vitro studies have shown increased telomerase activity compared with controls in MDS cells and that the expression of human telomerase reverse may drive the neoplastic clonal cell expansion, imetelstat, a novel telomerase inhibitor, has been developed in MDS. This is a potent, first-in-class, competitive inhibitor of telomerase enzymatic activity that specifically targets the RNA template of human telomerase. In a phase 2 study that included 57 patients with heavily TD LR-MDS (61% MDS-RS), imetelstat induced durable TI in 37% (8-week TI), with a median TI duration of 65 weeks.[25] Nevertheless, profound myelosuppression was the main side effect of this drug. Results of the phase 3 double-blind placebo-controlled iMerge trial evaluating imetelstat in RBC-TD, ESA-relapsed/refractory LR-MDS were presented at American Society of Clinical Oncology and EHA in 2023.[26] The primary end point was met, 47 patients (39.8%) vs. 9 patients (15.0%) (P<.001) achieving 8-week TI, with a significantly longer duration of TI with imetelstat compared to placebo (51.6 vs 13.3 weeks, P<.01). TI rate was also significantly higher with imetelstat vs placebo across subgroups, including patients without RS. No new safety signals were identified and similar rates of grade ≥3 bleeding and infections were observed on imetelstat and placebo. These results support imetelstat's benefit to a heavily TD LR-MDS patient population, and it is very likely that this drug will join the therapeutic armamentarium of LR-MDS in the coming years.

Targeting the hypoxia-inducible factor pathway

The hypoxia-inducible factor pathway has been implicated in the regulation of hematopoiesis. Roxadustat is an oral hypoxia-inducible factor–prolyl hydroxylase inhibitor. It has been shown to increase hemoglobin and EPO levels as well as reduce hepcidin in patients with chronic kidney disease in phase 3 trials.[27,28] In MDS, roxadustat has been studied in a phase 3, double-blind, placebo-controlled study (MATTERHORN) evaluating the efficacy of roxadustat to treat low transfusion burden anemia in LR-MDS (NCT03263091). Interim results of 24 enrolled patients have shown 8-week and 20-week RBC-TI of 38% and 17%, respectively, with efficacy across MDS subtypes and baseline EPO levels.[29] However, a press release recently reported that the MATTERHORN study did not met its primary efficacy end point (47.5% for roxadustat compared to 33.3% for placebo; P=.217).[30] Another phase 2/3 trial is currently evaluating roxadustat in patients with LR-MDS with anemia (not only low transfusion burden anemia) in China (NCT03263091). While these results are disappointing, it remains important to continue the investigation of low-toxicity oral treatments that can improve quality of life in these patients.

CLINICAL CASE 2

A 65-year-old woman was admitted to our hospital for fatigue, dyspnea, and pancytopenia (Hb, 6.3 g/dL; absolute neutrophil

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count, 0.8×10⁹/L; platelets, 23×10⁹/L). A BM biopsy specimen showed a hypocellular marrow with dysgranulopoiesis and erythroid dysplasia and a normal reticulin staining pattern. Karyotype was normal. NGS panel analysis identified an isolated *TET2* (VAF 12%) somatic mutation. She received anti–thymocyte globulin (ATG) plus oral cyclosporine with transfusion support and reached complete remission within 8 weeks following treatment. Sixteen months later, she relapsed with mild pancytopenia, BM was still hypocellular, karyotype was normal, but there was clonal evolution with the acquisition of another *TET2* (VAF 5%) in addition to the prior one (VAF 15%) and an additional *EZH2* mutation (VAF 13%). She was recused for HSCT due to comorbidities and subsequently received HMA therapy without response.

In eligible patients with severe hypoplastic MDS, HSCT should be considered as soon as possible. For those who are not candidates, and for some patients in whom the clinical picture can parallel bone marrow failure phenotype with pancytopenia and hypocellular marrow, anti–T-cell immunosuppressive therapy or HMA therapy is often considered (Figure 1).

In a large retrospective analysis of 207 patients with MDS treated with immunosuppressive therapy, horse ATG plus cyclosporine was more effective than rabbit ATG, and the highest rate of RBC-TI was achieved among patients with hypocellular BM.[11] Moreover, eltrombopag, a thrombopoietin agonist might be also effective as a single agent in patients with LR-MDS with a predominating thrombocytopenia,[10] but thrombopoietin agonist should be avoided in patients with excess blasts, and this drug is not approved in this indication (Table 1).

Low-dose HMA-based regimen

Although in Europe, HMA use is restricted to patients with higher-risk MDS, low-dose HMA (5-day regimen) is commonly used in the United States for patients with LR-MDS with multilineage cytopenia or as second-line therapy. The 5-year follow-up of attenuated dosing schedules of lower-dose HMA (azacitidine or decitabine, daily×3 days in every 28-day cycle) in patients with LR-MDS was recently published.[9] Among the 113 evaluable patients, the overall response rate was 60% with 36% achieving complete response and 18% hematological improvement, with no survival difference between those who received azacitidine or decitabine (median overall survival of 33 months). These results suggest the use of lower-dose HMA in this frail population. Indeed, the 3-day regimen is currently evaluated in a phase 2 randomized study comparing azacitidine and decitabine when given on a shorter than standard dosing schedule in patients with TD LR-MDS (NCT02269280).

Targeting inflammatory signaling

Emerging data demonstrate that inflammation can lead to a selective outgrowth of aberrant stem cells while inhibiting healthy hematopoiesis, resulting in worsening of cytopenia in MDS.[31] Moreover, clonal hematopoiesis mutations, especially in the *TET2* gene, can by themselves lead to a proinflammatory state by making macrophages more proliferative and secretory.[32]

For this reason, several agents are under investigation targeting immune/inflammatory pathways (Table 2). One critical target is IRAK4, which hyperactivates NF-κB. IRAK4 can be found in longer and shorter isoforms, and *U2AF1* and *SF3B1* mutations can lead to altered exon inclusion, leading to preferential production of a longer isoform (IRAK4-L). This longer isoform results in a maximal activation of innate immune signaling pathways.[33] Preclinical studies have shown that inhibition of IRAK4-L by pharmacologic and genetic means can suppress leukemic proliferation, and clinical trials are now evaluating the efficacy of IRAK4 inhibitors (CA-4948, emavusertib) in LR-MDS (NCT05178342).

Among other pathways, a phase 2 trial of canakinumab, an interleukin 1β–blocking monoclonal antibody that is well tolerated in other inflammatory conditions, has recently opened for inclusion (NCT04239157). Interestingly, an exploratory analysis suggested that the presence of clonal hematopoiesis predicts for cardiovascular benefit with canakinumab.[34] Two other trials evaluating canakinumab in MDS are under way, including one in association with ESA (NCT 04798339, NCT 05237713).

A number of additional agents are being studied for LR-MDS targeting the concept of inflammation and innate immunity (Table 2, Figure 1).

Conclusion

The genetic and biological heterogeneity of MDS provides significant challenges in developing new clinical therapeutics, maybe due to the lack of good preclinical in vitro/in vivo model. However, emerging data in lower-risk MDS pathobiology, including the role of the TGF-β pathway, telomerase inhibition, and inflammation, have led to a recent increase in next-generation therapies for these patients. In particular, recent reports from luspatercept and imetelstat trials suggest an alternative to the current standard-of-care treatment for anemia in patients with lower-risk myelodysplastic syndromes with or without ring sideroblasts who require RBC transfusions.

Conflict-of-interest disclosure

Marie Sébert: honoraria: Abbvie, Servier, BMS, Gilead, Jazz Pharmaceuticals.

Off-label drug use

Marie Sébert: There is nothing to disclose.

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