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Role of Luspatercept in the Management of Lower-Risk Myelodysplastic Syndromes

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Abstract

Treatment options are limited for patients with anemia associated with lower-risk myelodysplastic syndromes (LR-MDS). The recent approval of luspatercept for the treatment of anemia associated with very low- to intermediate-risk MDS with ring sideroblasts (RS) or with myelodysplastic/myeloproliferative neoplasm with RS and thrombocytosis has provided adult patients and practitioners with a much-needed new therapeutic option. Luspatercept is a first-in-class erythroid maturation agent that exerts its effects on later stages of erythropoiesis. In the phase III MEDALIST trial of patients with LR-MDS with RS, luspatercept (starting dose 1 mg/kg) demonstrated substantial clinical benefit (38% of patients treated with luspatercept vs. 13% of those treated with placebo [$p < .001$] achieved transfusion independence for ≥ 8 weeks during the first 24 weeks of treatment) and a favorable safety profile. The most common adverse events (AEs), including fatigue, asthenia, dizziness, and diarrhea, were more frequent during the first 4 treatment cycles and subsequently declined. This review provides a comprehensive overview of luspatercept treatment administration, including the mechanism of action, efficacy and safety data, management of dosing, and AEs associated with luspatercept treatment of patients with LR-MDS.

Myelodysplastic syndromes (MDS) are a group of malignant stem cell disorders characterized by clonal hematopoiesis, cytopenias (anemia, neutropenia, and/or thrombocytopenia), and progression to acute myeloid leukemia in approximately 20% of cases (Falantes et al., 2018; Pereira et al., 2011). Approximately two thirds of patients are initially diagnosed with lower-risk myelodysplastic syndromes (LR-MDS) per the Revised International Prognostic Scoring System (IPSS-R), which includes Very low-, Low-, and Intermediate-risk disease (Carraway & Saygin, 2020; Steensma, 2018).

Almost 90% of patients with LR-MDS present with anemia,

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which has limited treatment options (Carraway & Saygin, 2020). Erythropoiesis-stimulating agents (ESAs) are the typical first-line therapy; however, primary resistance and loss of response to ESAs are common (Germing et al., 2019; Park et al., 2017). Fenaux and colleagues (2018) reported that 31.8% of patients with LR-MDS who responded to ESAs had erythropoietin (EPO) levels < 200 mU/mL (Fenaux et al., 2018), supporting a previous predictive model using EPO levels < 500 mU/mL (Hellström-Lindberg et al., 2003). Anemia is also managed with red blood cell transfusions (RBCTs), which are associated with significant risks, including iron overload and blood-borne disease transmission. The limited treatments for anemia combined with time-consuming transfusion visits significantly impact patients' quality of life (QoL; Gattermann, 2017; Oliva et al., 2012).

In 2020, luspatercept (Reblozyl) was approved by the US Food and Drug Administration for the treatment of anemia in adults with IPSS-R Very low- to Intermediate-risk MDS with ring sideroblasts (RS), and patients with MDS/myeloproliferative neoplasms with RS and thrombocytosis who have failed ESA therapy and require ≥ 2 RBC units/8 weeks (FDA, 2020). The European Medicines Agency issued parallel approval for the treatment of transfusion-dependent anemia due to IPSS-R Very low- to Intermediate-risk MDS with RS in adult patients who had an inadequate response to or are ineligible for EPO-based therapy (EMA, 2020). Luspatercept is not a substitute for RBCTs in patients who require immediate amelioration of anemia.

MECHANISM OF ACTION

Luspatercept, a first-in-class erythroid maturation agent, is a recombinant fusion protein consisting of a modified extracellular domain of activin receptor IIB (ActRIIB) fused to the Fc domain of human IgG1. Luspatercept prevents binding of select endogenous transforming growth factor beta superfamily ligands to ActRIIB, thus reducing Smad2/3 signaling and improving erythroid precursor maturation (Attie et al., 2014; Bristol Myers Squibb, 2021). Luspatercept, therefore, improves erythropoiesis by promoting erythroid maturation through late-stage erythroid precursor differentiation (Celgene Corporation, 2021; Suragani et al., 2014).

CLINICAL TRIALS

The double-blind, placebo-controlled phase III MEDALIST trial (NCT02631070) recruited 229 patients with IPSS-R Very low-, Low-, or Intermediate-risk MDS-RS (≥ 15% RS or ≥ 5% if patients were *SF3B1*-mutation positive with < 5% bone marrow blasts) who were receiving regular RBCTs (≥ 2 units/8 weeks during the 16 weeks pre-randomization) and were refractory to or unlikely to respond to ESAs (endogenous EPO > 200 U/L). Patients were randomly assigned to receive luspatercept (n = 153) or placebo (n = 76). The primary endpoint was RBC transfusion independence (RBC-TI) ≥ 8 weeks during weeks 1 to 24; the key secondary endpoint was RBC-TI ≥ 12 weeks during weeks 1 to 24 and 1 to 48 (Fenaux et al., 2020). Nearly all (95%) patients had previously received ESAs and 57% of patients had baseline RBCT burden < 6 units/8 weeks.

The trial met the primary endpoint (38% luspatercept vs. 13% placebo; p < .001), and significantly more patients treated with luspatercept vs. placebo achieved RBC-TI ≥ 12 weeks during weeks 1 to 24 and weeks 1 to 48 (28% vs. 8% and 33% vs. 12%, respectively; both p < .001). Furthermore, 40% of patients with baseline serum EPO levels of 200 to 500 U/L who received luspatercept experienced a decrease in RBCTs (Fenaux et al., 2020) in contrast to previously observed decreasing responses to ESAs in patients with EPO > 500 IU/L (Park et al., 2020).

ADVERSE EVENTS

Fatigue, asthenia, diarrhea, nausea, dizziness, and back pain were more common with luspatercept vs. placebo in the MEDALIST trial. Fatigue was the most common (27%, any grade) adverse event (AE) reported by patients in the luspatercept arm; 5% of patients had grade 3 fatigue and one case led to a dose reduction (Table 1). Asthenia occurred in 20% of patients treated with luspatercept; 3% had grade 3 asthenia and one case led to a dose reduction (Table 1). The most frequent incidences of both AEs occurred during treatment cycles 1 to 4 and subsequently decreased (Fenaux et al., 2020).

Diarrhea (22%), nausea (20%), and dizziness (20%) were most frequent during cycles 1 to 4. All incidents of diarrhea and dizziness were grade 1 to 2, while one nausea case reached grade 3; no dose

Table 1. Common AEs With Luspatercept in the MEDALIST Trial

	Luspatercept (*n* = 153)		Placebo (*n* = 76)	
AE, *n* (%)[a]	**Any grade**	**Grade 3**	**Any grade**	**Grade 3**
Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
Diarrhea	34 (22)	0	7 (9)	0
Asthenia	31 (20)	4 (3)	9 (12)	0
Nausea[b]	31 (20)	1 (1)	6 (8)	0
Dizziness	30 (20)	0	4 (5)	0
Back pain[c]	29 (19)	3 (2)	5 (7)	0

Note. Information from Fenaux et al. (2020). AE = adverse event.
[a]AEs were not adjusted for treatment exposure.
[b]Serious AE occurred in 1 patient receiving luspatercept.
[c]Serious AE occurred in 3 patients receiving luspatercept.

adjustments were required. Back pain occurred in 19% of patients receiving luspatercept; three cases were grade 3 (Table 1) and one led to a dose reduction. The occurrence of reported back pain during cycles 1 to 4 (9%) decreased slightly during cycles 5 to 8 (6%) (Fenaux et al., 2020). Incidences of grade 3 to 4 hypertension were similar between the luspatercept and placebo arms (3%–4%).

DOSING AND ADMINISTRATION

Care should be taken to store and reconstitute luspatercept according to the package insert instructions (Bristol Myers Squibb, 2021). Luspatercept is administered via subcutaneous injection into the upper arm, thigh and/or abdomen at a starting dose of 1 mg/kg every 3 weeks and a maximum volume of 1.2 mL/injection site.

Dose adjustments based on insufficient response and continued transfusion dependence are detailed (Table 2). Dose adjustments should not occur more frequently than every 6 weeks and should not exceed 1.75 mg/kg. Modifications should be made according to pretreatment hemoglobin levels, with treatment interruption if levels are ≥ 11.5 g/dL or hemoglobin increases > 2 g/dL within 3 weeks without RBCTs (Table 2). If a patient misses a dose or delays a visit, luspatercept should be administered as soon as possible at the same dose as previously received; the next dose should be scheduled with at least 3 weeks in between doses (Bristol Myers Squibb, 2021).

Luspatercept treatment should be paused if a grade 3 to 4 AE occurs and restarted at the next lower dose level when the AE resolves to ≤ grade 1. Treatment should be discontinued if a grade 3 to 4 hypersensitivity reaction occurs (Table 2; Bristol Myers Squibb, 2021).

CLINICAL PRACTICE IMPLICATIONS

Patients who respond to luspatercept are likely to require fewer clinic visits as RBCT burden decreases. However, hemoglobin levels should be checked prior to each luspatercept administration; if an RBCT occurs before dosing, the pre-transfusion hemoglobin level should be used for dose evaluation. Patients treated with luspatercept should undergo routine monitoring for complications, particularly during the first 4 therapy cycles. To reduce treatment discontinuations, conversations with patients are crucial before treatment begins to set the expectation of transient decreases in QoL in favor of long-term benefits.

Although the exact cause of luspatercept-associated fatigue is unknown, fatigue commonly occurs with treatment, and the impact and duration will vary and may be short-lived. Fatigue should be assigned a severity score (0 to 10) based on evaluation (Butt et al., 2008; NCCN, 2022a). The patient's focused history should be reviewed to determine underlying contributing factors, such as pain, emotional distress, anemia, sleep disturbances, and drug interactions (NCCN, 2022a). Fatigue may be managed by addressing underlying factors and educating patients and family/caregivers on fatigue patterns and helpful behavioral changes. Importantly, the practitioner should convey that treatment-related fatigue is not necessar-

Table 2. Luspatercept Dosing Recommendations for Treatment of Anemia in Patients With LR-MDS With RS

Luspatercept dose increase recommendations[a]	
Starting dose	1 mg/kg every 3 weeks
No RBC-TI after ≥ 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	Dose increase to 1.33 mg/kg every 3 weeks
No RBC-TI after ≥ 2 consecutive doses (6 weeks) at 1.33 mg/kg	Dose increase to 1.75 mg/kg every 3 weeks
No reduction in RBCT burden after ≥ 3 consecutive doses (9 weeks) at 1.75 mg/kg	Discontinue treatment
Dose decrease recommendations for predose hemoglobin levels or rapid hemoglobin increase	
Predose hemoglobin ≥ 11.5 g/dL in the absence of RBCTs	Pause treatment until hemoglobin is ≤ 11 g/dL
Increase in hemoglobin > 2 g/dL within 3 weeks in the absence of transfusions and current dose is:	
1.75 mg/kg	Reduce dose to 1.33 mg/kg
1.33 mg/kg	Reduce dose to 1.00 mg/kg
1.00 mg/kg	Reduce dose to 0.80 mg/kg
0.80 mg/kg	Reduce dose to 0.60 mg/kg
0.60 mg/kg	Discontinue treatment

Note. Adapted from Bristol Myers Squibb (2021). LR-MDS = lower-risk myelodysplastic syndromes; RBC = red blood cell; RBCT = RBC transfusion; RBC-TI = RBC transfusion independence; RS = ring sideroblasts.
[a]Do not increase the dose if the patient experiences grade 3–4 hypersensitivity reactions (in which case discontinue treatment) or other grade 3–4 adverse reactions (in which case interrupt treatment and restart treatment at the next lower dose level per dose reductions above when the adverse reaction resolves to ≤ grade 1; discontinue treatment if the dose delay is > 12 consecutive weeks).

ily indicative of disease progression or that treatment is not working (NCCN, 2022a).

For patients experiencing diarrhea, management recommendations include hydration, electrolyte replacement, and antidiarrheal medications such as diphenoxylate/atropine, loperamide, or anticholinergic agents. Treatment for persistent nausea and vomiting involves targeted titration of dopamine-receptor antagonists, followed by consideration of corticosteroids, 5-HT3 receptor antagonists, antipsychotics, anticholinergic agents, antihistamines, oral cannabinoids, or mirtazapine (NCCN, 2022b). Dizziness should be managed with improved hydration and behavioral changes focused on careful movement and posture adjustment (Cancer.Net, 2018).

For patients experiencing pain, a comprehensive assessment should be initiated to diagnose the etiology and pathophysiology of the pain (NCCN, 2022c). The patient's pain management goals and expectations should be determined and discussed with their family/caregivers. Treatment must be individualized to clinical circumstances and patient wishes, aiming to maximize function and QoL. Pharmacologic analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, may be offered alongside psychosocial support and education (NCCN, 2022c). Patients treated with NSAIDs should be monitored for stomach bleeding in association with thrombocytopenia and renal effects; both NSAIDs and acetaminophen can mask fever in individuals with severe neutropenia (FDA, 2016, Stephens, 2020).

SUMMARY

In the MEDALIST trial, 38% of patients with LR-MDS with RS in the luspatercept arm who had been receiving regular RBCTs and whose disease was refractory to or unlikely to respond to ESA achieved RBC-TI ≥ 8 weeks during weeks 1 to 24, and 28% achieved RBC-TI ≥ 12 weeks during weeks 1 to 24 (Fenaux et al., 2020). These data suggest luspatercept treatment may improve patients' QoL by reducing their transfusion burden, number of hospital visits, and short-term and long-term transfusion morbidity. Although luspatercept generally has a favorable safety profile, early discussion and monitoring of AEs, especially fatigue, should be undertaken, particularly during the initial 4 treatment cycles.

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