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Is Luspatercept the New Standard of Care in Transfusion-Dependent Low-Risk Myelodysplastic Syndromes?

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H&O What is luspatercept, and how does it work for patients who have anemia associated with transfusion-dependent low-risk myelodysplastic syndromes (LR-MDS)?

GCM Luspatercept (Reblozyl, Celgene/BMS) is a monoclonal antibody that binds the ligands that activate the transforming growth factor beta (TGF-β) pathway. Because the TGF-β pathway inhibits erythropoiesis, binding the ligands promotes the formation of red cells. This mechanism of action is completely different from that of traditional erythropoiesis-stimulating agents (ESAs) such as erythropoietin, which work by activating the Epo receptor. Luspatercept also appears to work in a later stage of erythroid differentiation than does standard erythropoietin. Some people refer to luspatercept as an erythroid maturation agent because it promotes the maturation of red cell progenitors.

H&O Which studies contributed to the US Food and Drug Administration (FDA) approval of luspatercept for treating anemia in patients with LR-MDS, and what were the key outcomes of those studies?

GCM The phase 3 studies that led to the approval of the 2 indications for this drug in MDS are MEDALIST[1] and COMMANDS.[2] The MEDALIST study, which was published in the *New England Journal of Medicine* in 2020, enrolled 229 patients with very-low-risk, low-risk, or intermediate-risk MDS with ring sideroblasts. Eligible patients had been receiving regular transfusions of red cells and had disease that was refractory to or unlikely to respond to ESAs. Patients were randomly assigned in a 2:1 ratio to receive either luspatercept or placebo, administered subcutaneously every 3 weeks. We found that transfusion independence lasting 8 weeks or longer during the first 24 weeks of the trial—the primary endpoint of the study—occurred in 38% of the patients in the luspatercept group vs 13% of those in the placebo group (P<.001). Among patients who met the primary endpoint, the median duration of the longest single period of transfusion independence was 30.6 weeks in the luspatercept group and 13.6 weeks in the placebo group.

The most common any-grade adverse events associated with luspatercept were fatigue, diarrhea, asthenia, nausea, and dizziness. This study led to the FDA approval of luspatercept in April 2020 as a second-line compound in patients who met the study criteria, which is a relatively narrow indication.

Following the results of the MEDALIST trial, we designed the COMMANDS trial; interim results were published in the *Lancet* in 2023. This trial also enrolled patients with very-low-risk, low-risk, or intermediate-risk MDS who required red cell transfusions, but in this case the participants were ESA-naive. A total of 356 patients were randomly assigned in a 1:1 ratio to receive luspatercept or an ESA. The primary endpoint was red blood

cell transfusion independence for at least 12 weeks with a concurrent mean increase in the hemoglobin level of at least 1.5 g/dL during the first 24 weeks of the study. In an interim efficacy analysis of 301 patients who had completed 24 weeks of treatment or discontinued earlier, more patients in the luspatercept group than in the ESA group reached the primary endpoint (59% vs 31%, respectively), as assessed in the intention-to-treat population. The median duration of red blood cell transfusion independence was longer in the luspatercept arm than in the ESA arm, at 126 vs 77 weeks. Among patients without ring sideroblasts, however, luspatercept was not associated with a significant improvement in the median duration of red blood cell transfusion independence in comparison with an ESA.

These are especially compelling results because the inclusion and exclusion criteria are more sophisticated in COMMANDS than in MEDALIST, and the response criteria were more stringent. COMMANDS led to the FDA approval of luspatercept in August 2023 as a first-line treatment in patients with low-risk MDS, which is a wider indication. The interim results were confirmed by the full analysis of this trial, which we presented at the 2023 American Society of Hematology (ASH) Annual Meeting.[3]

Is there a way to make the response to luspatercept even greater?

H&O What are the side effects associated with luspatercept, and how are they managed?

GCM Luspatercept is generally very well tolerated, with no mortality or severe toxicities seen in COMMANDS. Indeed, when we presented the full analysis of COMMANDS at the 2023 ASH Annual Meeting and we adjusted for exposure to the agent, the toxicity profile was similar to that of the ESA.[3] The duration of therapy in the COMMANDS trial was nearly twice as long with luspatercept as with the ESA, at 51.3 vs 37.0 weeks, respectively, so there was more time for toxicities to develop with luspatercept. In practice, these patients will remain on therapy for a long time, whether they are using luspatercept or an ESA.

H&O Can you discuss the updates on luspatercept that were presented at the 2024 European Hematology Association Congress?

GCM Several posters provided updated analyses of the COMMANDS study. One poster showed that baseline mutation burden, variant allele frequency, and Molecular International Prognostic Scoring System risk category affected the response rates and duration of response in patients treated with an ESA, but not in those treated with luspatercept.[4] Another poster showed that luspatercept improved overall hematopoiesis and decreased inflammatory biomarkers at the same time that it had positive effects on erythropoiesis.[5] A third poster found that erythroid hematologic improvement occurred in a greater proportion of patients treated with luspatercept than of patients treated with an ESA.[6] A fourth poster found that luspatercept was better than an ESA at improving hemoglobin levels, reducing the transfusion burden, and reducing the number of red blood cell units transfused.[7]

H&O What upcoming studies or clinical trials are investigating the efficacy of luspatercept in LR-MDS?

GCM The phase 3 ELEMENT-MDS study is currently testing luspatercept in transfusion-independent patients (NCT05949684). It will be very interesting to see how patients who have a lesser transfusion burden fare with luspatercept. In addition, several studies in Europe are looking at higher doses of luspatercept in MDS.

H&O What is ahead for luspatercept?

GCM Luspatercept is gradually becoming the standard of care in the United States for the first- and second-line treatment of anemia in low-risk MDS, and it is starting to be approved in other countries around the world. It is exciting to see new compounds become available for these patients. Is there a way to make the response to luspatercept even greater? Researchers are discussing the possibilities of different dose schedules and new combinations. With time, I expect luspatercept to become the standard of care for a significant fraction of patients with low-risk MDS and anemia.

Disclosures

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1. 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.

2. 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.

3. Garcia-Manero G, Platzbecker U, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent (ESA)-naive patients (Pts) with transfusion-dependent (TD) lower-risk myelodysplastic syndromes (LR-MDS): full analysis of the COMMANDS trial [ASH abstract 193]. *Blood*. 2023;142(1)(suppl).

4. Komrokji RS, Hayati S, Ugidos M, et al. Comparative analysis of clinical benefit by genomic landscape and mutational burden of luspatercept versus epoetin alfa in lower-risk myelodysplastic syndromes (MDS) in the phase 3 COMMANDS study. Poster presented at: 29th European Hematology Association Congress; June 13-16; Madrid, Spain. Abstract P749.

5. Hayati S, Uwe Platzbecker U, Aluri S, et al. Luspatercept improves hematopoiesis in lower-risk myelodysplastic syndromes (MDS): comparative biomarker analysis of ring sideroblast-positive and -negative subgroups from the phase 3 COMMANDS study. Poster presented at: 29th European Hematology Association Congress; June 13-16; Madrid, Spain. Abstract P763.

6. Garcia-Manero G, Della Porta MG, Santini V, et al. Multilineage and safety results from the COMMANDS trial in transfusion-dependent, erythropoiesis-stimulating agent-naive patients with very low-, low-, or intermediate-risk myelodysplastic syndromes. Poster presented at: 29th European Hematology Association Congress; June 13-16; Madrid, Spain. Abstract P780.

7. Santini V, Zeidan AM, Platzbecker U, et al. Clinical benefit of luspatercept in transfusion-dependent, erythropoiesis-stimulating agent-naive patients with very low-, low- or intermediate-risk myelodysplastic syndromes in the COMMANDS trial. Poster presented at: 29th European Hematology Association Congress; June 13-16; Madrid, Spain. Abstract P785.