

ESA- Still the 1st line for LR-MDS? - No perspective

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Fatigue due to anaemia is one of the most common symptoms that brings patients diagnosed with lower-risk myelodysplastic syndromes (MDS) to medical attention. As a result, the goals in treating patients with lower-risk myelodysplastic syndromes are often focused on improving cytopenias and quality of life. Erythropoiesis-stimulating agents (ESAs), such as recombinant erythropoietin, are used for transfusion-dependent anaemia, particularly in patients with low serum erythropoietin (<500 U/L) and a red blood cell transfusion requirement of less than 2 red blood cell units per month. Response to ESA-based therapy can be as high as 70%,¹ but if serum erythropoietin is higher than 500 U/L, the expected response rate is lower than 10%. In April, 2020, luspatercept—an erythroid maturation agent with a mechanism of action distinct from ESA therapy—was approved by the US Food and Drug Administration for patients with lower-risk myelodysplastic syndromes (with the presence of ring sideroblasts and or SF3B1 mutation) who were transfusion dependent with disease refractory to or unlikely to respond to ESA-based therapy. Luspatercept binds to select transforming growth factor- β superfamily ligands and decreases Smad-2/3 signalling. It is this inhibitory effect on Smad-2/3 signalling that enables late stage erythroblast differentiation.

Due to the favourable responses seen with luspatercept, a possible role for its use as initial therapy for transfusion-dependent patients with lower-risk MDS has emerged. The COMMANDS study is an open-label investigation of luspatercept versus epoetin alfa in ESA-naive patients with lower-risk MDS. The trial enrolled 356 patients and is ongoing for follow-up. In the interim analysis 301 patients were randomly assigned to receive either luspatercept (n=147) or epoetin alfa (n=154). 73% of the study population had MDS that was positive for ring sideroblasts. The primary endpoint was defined as red blood cell transfusion independence for at least 12 weeks with a concurrent increase in mean haemoglobin of at least 1.5 g/dL (weeks 1–24) and was reached in 86 (59%) of 147 patients assigned to luspatercept versus 48 (31%) of 154 patients assigned to erythropoietin alfa therapy (p<0.0001). Furthermore, the median duration of red blood cell transfusion independence lasting at least 12 weeks was longer with luspatercept than with epoetin alfa (127 vs 77 weeks). Overall, luspatercept showed an acceptable safety profile consistent with previous observations. A better response rate with luspatercept was observed in all patient's subgroups stratified according endogenous EPO levels, and the severity of transfusion dependency. In patients without ring sideroblasts the response rate of the two treatment arms was comparable, the exposure to luspatercept being associated with longer response duration

These findings show that ESA-naive patients with lower-risk myelodysplastic syndromes benefit from upfront luspatercept-based therapy, particularly those with ring sideroblast-positive status or SF3B1 mutated profiles.