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Efficacy and Tolerability of Luspatercept in Patients with Lower Risk Myelodysplastic Syndrome and Anemia: A Systematic Review and Meta-Analysis of Phase III Randomized Controlled Trials

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Introduction:
Erythropoietin Stimulating Agents (ESAs) are the standard-of-care treatment for most patients with lower risk myelodysplastic syndrome (MDS) and anaemia. However, there has been unmet need for those who failed ESAs other than regular blood transfusion. Luspatercept is a recombinant fusion protein which binds TGF beta ligands resulting in reduction of erythroid maturation through reduction of SMAD2 and SMAD3 signaling. In recent years, studies have shown that luspatercept has significantly improved efficacy in patients with lower risk MDS who failed ESAs with some notable adverse events. The purpose of our meta-analysis is to determine efficacy by observing the rate of transfusion independence for 12 weeks or longer and haematological improvement in erythroid (HIE), and tolerability by rate of treatment emergent serious adverse events (SAE), treatment discontinuation (TD) and treatment interruption (TI) or dose reduction and treatment related mortality in patients with lower risk MDS treated with luspatercept.

Methods:
We systematically conducted a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through June 30 th, 2023. Phase III RCTs utilizing luspatercept in patients with lower risk MDS that mention efficacy i.e. transfusion independence 12 weeks or longer and HIE and tolerability i.e. rate of treatment discontinuation and interruption, dose reduction, treatment emergent serious adverse events, treatment related mortality were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q- statistic. Fixed effects model was applied.

Results:
2 phase III RCTs (MEDALIST and COMMANDS) including total 583 patients were eligible in our meta-analysis. MEDALIST trial compared luspatercept vs placebo and COMMANDS trial compared luspatercept vs erythropoietin stimulating agent. The randomization ratios were 2:1 in MEDALIST and 1:1 in COMMANDS trials. Transfusion independence for 12 weeks or longer was noted in 141 (47%) in study arm vs 77 (33.5%) in control arm at RR of 1.67 (95% CI: 1.35 -2.06; P <0.00001). 190 (63.3%) patients in study arm achieved HIE response compared to 88 (38.3%) in control arm at RR of 1.85 (95% CI: 1.53 -2.24; P<0.00001). TD due to TEAE was reported in 21 (6.3%) of luspatercept group vs 10 (4%) in control group with RR of 1.38 (95% CI: 0.67 -2.84; P = 0.39). The incidence for TI or dose reduction due to TEAE was similar between the two groups at 18% with RR of 1.23 (95% CI: 0.88 -1.72; P = 0.22). Treatment emergent SAEs were observed in 116 (35%) in the luspatercept group vs 83 (32.9%) in control group (RR, 1.09; 95% CI: 0.87-1.38; P=0.45). Treatment related mortality was noted in 13 (3.9%) of patients in the study group compared to 16 (6.3%) in the control group with RR of 0.65 (95% CI: 0.31 -1.33; P = 0.24).

Conclusions:
According to our meta-analysis, luspatercept significantly improved transfusion independent rate and HIE response in patients with lower risk MDS and anaemia compared to control arm. Furthermore, there was no statistically significant difference in the treatment emergent SAEs, treatment discontinuation, treatment interruption or dose reduction and treatment related mortality between the two groups.

Disclosures No relevant conflicts of interest to declare.

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