Abstract: P1559

Title: COMBINATION THERAPY WITH LUSPATERCEPT AND THE FERROPORTIN INHIBITOR VAMIFEPORT IS SUPERIOR TO EITHER DRUG ALONE IN IMPROVING MDS PATHOPHYSIOLOGY

Abstract Type: Poster Presentation

Topic: Iron metabolism, deficiency and overload

Background:

Although patients with myelodysplastic syndromes (MDS) commonly develop iron overload as a consequence of ineffective erythropoiesis and chronic transfusion therapy, it has remained unclear whether and how iron excess is detrimental for MDS pathophysiology. Recently, we have shown that iron restriction by the oral ferroportin (FPN) inhibitor vamifeport improves anemia and reduces myeloid skewing, being of benefit for MDS as single treatment. Luspatercept, a recombinant fusion protein acting as TGF-β superfamily ligands trap, has recently gained FDA approval for the treatment of anemia in low-risk MDS patients. Luspatercept promotes EPO-independent maturation of late-stage erythroid cells, resulting in increased hemoglobin and red blood cells (RBCs) count. However, this drug -due to a lack of improvement in myeloid skewing and AML evolution - is considered a non-disease-modifying therapy.

Aims:

In this study we investigated the effect of a combined therapy using luspatercept and the FPN inhibitor vamifeport in a preclinical MDS mouse model, with the hypothesis that both drugs have additive effects with further benefit for the disease.

Methods:

To this end, we administered vamifeport in NUP98-HOXD13 MDS mice for 3 months (2.5mg/), combined with luspatercept for the last 2 months (5mg/kg twice a week), starting at 3 months of age.

Results:

At steady-state MDS mice develop anemia, neutropenia and lymphopenia, together with an iron overload phenotype, hallmarked by inappropriately low hepcidin levels, elevated serum iron and transferrin saturation, non-transferrin-bound iron (NTBI) formation and tissue iron deposition. Vamifeport administration in MDS mice reduced serum iron and NTBI formation and prevented tissue iron loading, either as a single or combined treatment with luspatercept. Luspatercept and vamifeport, as single-agent treatment, ameliorated anemia and the maturation of bone marrow and splenic RBCs in MDS mice. The combined therapy further improved anemia compared to the treatments with either drug alone, as suggested by the higher hemoglobin levels ($P<0.01$) and decreased early erythroid precursors, sign of more effective erythropoiesis.

Importantly, vamifeport, but not luspatercept, significantly altered myeloid skewing in MDS, revealing a major role of the iron status in myeloid expansion. Myeloid bias, monitored as percentage of CD11b+ Gr1+ myeloid cells in the bone marrow was attenuated by iron restriction in vamifeport-treated MDS mice either as single or combo treatment ($P<0.01$). Furthermore, the number of immature cKit+ myeloid blasts in the peripheral blood of MDS animals were decreased by vamifeport alone and in combination with luspatercept, but not by luspatercept alone ($P<0.01$). Overall, the combination therapy with vamifeport and luspatercept showed superior effects in improving anemia and myeloid bias as compared to single treatments.

Summary/Conclusion:

In conclusion, our results show that iron restriction by vamifeport enhances the erythroid maturation action of luspatercept, likely by improving iron utilization in erythroid cells and ameliorating their survival. Furthermore, vamifeport improves the myeloid skewing in the MDS model, suggesting disease-modifying activity as single

agent as well as combined therapy with luspatercept. Together, these data prove that combo therapies aimed at restricting iron and boosting erythroid maturation may offer additive beneficial effects in MDS and provide pre-clinical evidence for combining iron restriction and TFG-β superfamily ligand-trap approaches as more effective therapeutic strategies for the treatment of MDS.

Keywords: Myelodysplastic syndrome, Iron overload