Abstract: S177

Title: JAK INHIBITION AND COMBINATION THERAPY IN THE TREATMENT OF MURINE BONE MARROW FAILURE

Abstract Type: Oral Presentation

Session Title: BMF translational research

Background:

Immune aplastic anemia (AA) is characterized by marked pancytopenia due to T cell-mediated destruction of hematopoietic stem and progenitor cells (HSPCs). Janus kinase (JAK)1/2 inhibition by ruxolitinib (RUX) was effective in our pre-clinical murine model of immune bone marrow failure (BMF) (Groarke E, et al. Blood, 2022). A clinical trial using RUX in AA patients is in development based on these results. While RUX is effective in murine BMF, hematologic toxicity remains a concern.

Aims:

Evaluate 1) long-term RUX toxicity in healthy mice; 2) efficacy of other JAK inhibitors baricitinib (BAR, JAK1/2) and tofacitinib (TOF, JAK1/3) in BMF mice; 3) combined lower-dose RUX and cyclosporin (CsA) therapy in murine models.

Methods:

To assess hematoxicity of RUX, CByB6F1 mice were fed normal chow mixed with 2 mg/Kg of ruxolitinib for 4 weeks and then normal chow. Animals were evaluated at 2, 5, and 10 weeks.

To induce BMF, CByB6F1 mice were pre-irradiated with 5 Gys followed by injection of 5×10^6 lymph node (LN) cells from B6 donors. BMF mice were untreated (BMF) or were treated with BAR (10 mg/Kg gavage once daily, 5 days/week for 3 weeks), TOF (10 mg/Kg gavage twice daily, 5 days/week for 3 weeks), or a combination therapy with RUX (15 mg/Kg gavage twice daily, 5 days/week for 3 weeks) and CsA (25 mg/Kg i.p. once daily, 5 days/week for 2 weeks). All treatments started at day 3 following LN infusion. Mice were assessed at 2 weeks or kept for 8-10 weeks to monitor survival.

Results:

In the toxicity study, RUX increased neutrophils and platelets and decreased red blood cells at both 2 and 5 weeks. These blood counts returned to normal levels by 10 weeks. RUX treatment caused a 12% decline in BM cell number but increased proportions of KSL (c-kit+Sca-1+Lin-) cells, with more colony-forming units when BM was cultured in vitro. For irradiation protection in vivo, there was no significant difference between RUX-treated and control donors in their ability to rescue recipients from lethal irradiation.

In treatment studies with other JAK inhibitors, BAR or TOF monotherapy improved blood counts to variable levels, and extended survival. After BMF induction, 33% (5 of 15) of BAR-treated mice and 40% (4 of 10) of TOF-treated mice were alive at 8 weeks while 0% (0/10) BMF mice survived beyond 5 weeks.

In a combination treatment study with lower dose RUX and CsA, we observed significantly higher neutrophil and platelet counts in the RUX+CsA group than in control BMF, CsA alone, or RUX alone groups at 2 weeks. Overall survival was significantly better with RUX+CsA: 80% (8/10) mice in the combined low dose treatment group were alive while 0% (0/5) mice in the untreated BMF group, and 13% (1/8) and 38% (3/8) mice in the CsA or RUX single therapy groups were alive at 8 weeks following BMF induction (Figure 1).

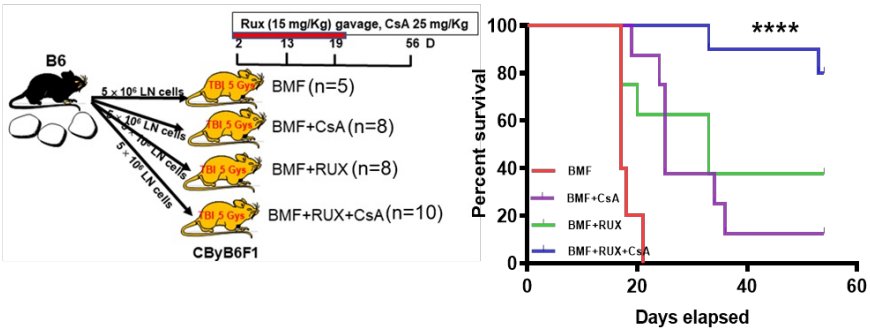

Figure 1. Survival of bone marrow failure mice treated with lower dose of ruxolitinib combined with cyclosporin.

Summary/Conclusion: RUX had little toxicity in normal mice, and minimal effect on HSPC function. JAK inhibition with BAR or TOF increased blood counts and extended survival in murine BMF, but their efficacy was inferior to standard dose RUX as reported previously. RUX is primarily a JAK1/2 inhibitor but also has weaker activity against JAK3 and TYK2, which may influence its efficacy in immune BMF. Combination of low-dose RUX and CsA resulted in both prolonged overall survival and sustained improvements in peripheral blood counts compared to either low-dose RUX or CsA alone. Low-dose RUX and CsA combination therapy in patients would potentially counter hematotoxicity and other side effects of standard dose RUX in immune BMF patients.

Keywords: Ruxolitinib, Immunosuppressive therapy, Janus Kinase inhibitor, Bone marrow failure