Combination Treatment with Imetelstat, a Telomerase Inhibitor, and Ruxolitinib Depletes Myelofibrosis Hematopoietic Stem Cells and Progenitor Cells

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Abstract

Imetelstat

- Has potential disease-modifying activity in patients with myelofibrosis (Tefferi N Engl J Med 2015; Mascarenhas Blood 2018). This has been attributed to the ability of Ime to selectively deplete MF hematopoietic stem cells (HSC)/progenitor cells (HPC) (Wang Blood Adv 2018). As reported, the primary toxicities of Ime are cytopenias, however, they appear to be reversible, and most importantly, manageable without meaningful clinical consequences (Mascarenhas Blood 2018, Fenaux EHA 2019). Ruxolitinib (Rux) is the first and only JAK 1/2 inhibitor approved for use in patients with intermediate- or high-risk MF. Based on different mechanisms of action for Ime and Rux, we hypothesize that Ime in combination with Rux might create a regimen that would be more efficacious than single agent alone in depleting MF HSCs/CFCs. Using in vitro HPC assays and in vivo HSC assays, we evaluated the therapeutic potential of Rux and Ime. Similar results were also observed in depleting MF long-term HSCs in mice receiving splenic CD34+ cells from an additional patient. However, this same sequential drug schema did not affect normal HSC function. Collectively, these data indicate that alterations of the administration of imetelstat and ruxolitinib affect the efficacy of this drug combination in depleting MF HPCs/CFCs. We propose that cycles of Rux followed by Ime represents a potentially effective therapeutic strategy that is capable of depleting MF HPCs/CFCs with an acceptable toxicity profile.

Ruxolitinib

- Is a small molecule inhibitor of JAK1/2
- Is first FDA approved drug for the treatment of intermediate- or high-risk MF
- Only affects a subpopulation of MF HPCs, while sparing normal HSCs (Wang X, et al. Blood. 2014; 124:2987-95)
- May worsen anemia or lead to reversible thrombocytopenia

In Vitro Drug Treatment Strategy

Inhibitory Activity against MF HSCs/HPCs

Sequential Treatment with Ruxolitinib Followed by Imetelstat Has An Additive Inhibitory Activity against MF HSCs/HPCs

In Vitro Inhibitory Activity

- S1): 685; Fenaux P, et al. EHA 2019
- Fenaux P; et al. EHA 2019

 sequential drug treatment of CD34+ cells from 2 JAK2V617F+ patients resulted in greater reductions in both the percentage and absolute numbers of JAK2V617F+ myeloid progenitors than that achieved with Ime alone or combined with Ruxolitinib (Rux)

Experimental Design of In Vitro Assay

- Due to imetelstat and ruxolitinib having different mechanisms of action, we hypothesize that a combination of these two drugs might effectively deplete MF HSCs/HPCs

Combination Treatment with Ruxolitinib and Imetelstat Does Not Have Additive Inhibitory Effect on Normal HSCs/HPCs

Ruxolitinib is the first and only JAK 1/2 inhibitor approved for use in patients with intermediate- or high-risk MF who have relapsed on or are refractory to JAK inhibitor therapy, including those who are triple negative (Mascarenhas Blood 2018, Fenaux P, et al. EHA 2019). Ruxolitinib (Rux) is the first and only JAK 1/2 inhibitor approved for use in patients with intermediate- or high-risk MF who have relapsed on or are refractory to JAK inhibitor therapy, including those who are triple negative (Mascarenhas Blood 2018, Fenaux P, et al. EHA 2019). Ruxolitinib (Rux) is the first and only JAK 1/2 inhibitor approved for use in patients with intermediate- or high-risk MF who have relapsed on or are refractory to JAK inhibitor therapy, including those who are triple negative (Mascarenhas Blood 2018, Fenaux P, et al. EHA 2019). Ruxolitinib (Rux) is the first and only JAK 1/2 inhibitor approved for use in patients with intermediate- or high-risk MF who have relapsed on or are refractory to JAK inhibitor therapy, including those who are triple negative (Mascarenhas Blood 2018, Fenaux P, et al. EHA 2019).

Results

Sequential Treatment with Ruxolitinib Followed by Imetelstat Has An Additive Effect on Depleting MF Stem Cells

- No significant reductions in the numbers of MF Lin-CD34+ cells (relative to vehicle alone: Rux alone, p=0.05; vs Ime alone, p=0.059; vs Rux+Ime, p=0.052) and assayable HPCs [E-CFU-GM+BFU-E+CFU-GEMM] (p=0.04)]
- While the simultaneous treatment with Rux+Ime did not significantly reduce MF Lin-CD34+ cells and assayable HPCs. By contrast, none of these treatment combinations affected the behavior of normal HSC/CFCs. The genotyping of individual colonies showed that sequential drug treatment of CD34+ cells from 2 JAK2V617F+ patients resulted in greater reductions in both the percentage and absolute numbers of JAK2V617F+ myeloid progenitors than that achieved with Ime alone or combined with Ruxolitinib (Rux).

Hypothesis

- Potential extends overall survival of patients with intermediate-2 or high-risk MF who have relapsed on or are refractory to JAK inhibitor therapy, including those who are triple negative (Mascarenhas Blood 2018, Fenaux P, et al. EHA 2019).
- Leads to cytopenias, however, they appeared to be reversible, and most importantly, manageable without meaningful clinical consequences (Mascarenhas Blood 2018, Fenaux P, et al. EHA 2019).

Summary

- Sequential treatment with ruxolitinib followed by imetelstat has an additive inhibitory activity against MF malignant HSCs/HPCs. By contrast, neither simultaneous nor sequential combination treatment with ruxolitinib and imetelstat affects the behavior of normal HSCs.
- Sequential treatment with ruxolitinib followed by imetelstat has an additive effect in depleting MF long-term HSCs assayed using a patient-derived xenograft MF model. However, this same sequential drug schema did not affect normal HSC function.
- Our data indicate that alterations of the administration of imetelstat and ruxolitinib affect the efficacy of this drug combination in depleting MF HPCs/CFCs.
- These data suggest that ruxolitinib followed by imetelstat represents a potentially effective therapeutic strategy that is capable of depleting MF HPCs/CFCs with an acceptable toxicity profile.

Conflict-of-Interest Disclosure

This work was supported by Geron Corporation and Janssen Research & Development LLC.