Effects of Imetelstat on the Stem Cells of Patients with Myelofibrosis

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Background

Imetelstat (GRN163L) – Geron Corporation

Myelofibrosis (MF) is one of myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), which are thought to originate at the level of a pluripotent hematopoietic stem cell (HSC). Therapies that target MF stem cells (MF-SC), therefore, represent a promising therapeutic strategy thought to originate at the level of a pluripotent hematopoietic stem cell. Imetelstat rapidly induces and maintains hematologic responses in ET patients who have failed or are intolerant to conventional therapies. Substantial molecular and clinical remissions by IWG criteria. This includes the reversal of bone marrow fibrosis and JAK2V617F-positive or homozygous colonies in the total numbers of colonies analyzed.

Experimental Design

- In vitro studies have demonstrated that Imetelstat selectively inhibits spontaneous megakaryocytic colony-forming unit (CFU-Meg) growth from the blood of patients with ET but not from healthy individuals.
- Phases I and II studies have demonstrated that Imetelstat can achieve complete clinical remissions in a subset of patients with MF.

Objectives

- How imetelstat achieves these beneficial effects on MF patients?
- Can Imetelstat selectively target MF stem and progenitor cells?

Results

Effects of Imetelstat on MPNs

Imetelstat (GRN163L) – Geron Corporation

Imetelstat Does not affect the Generation of CB CD34+ Aldehyde Dehydrogenase (ALDH) + Cells

Imetelstat Inhibits Hematopoietic Colony Formation by CB CD34+ Cells

Imetelstat Reduces the Generation of Myeloid and Erythroid Cells by CB CD34+ Cells

Imetelstat Does not Reduce the Generation of Myeloid and Erythroid Cells by CB CD34+ Cells

Imetelstat Inhibits the Proliferation of Phenotypically Defined MF HSCs/HPCs

Imetelstat Inhibits the Generation of MF CD34+ ALDH+ Cells

Imetelstat Reduces the Generation of MF CD34+ Erythroid Cells

Imetelstat Induces Apoptosis of MF but not CB CD34+ Cells

Conflict-of-Interest Disclosure

Wang, X. – Research funding, Geron Corporation

Treatment with Imetelstat Results in a Reduction in JAK2V617F+ Hematopoietic Progenitor Cells

Summary

- Imetelstat at the doses studied has minimal effects on normal CB hematopoiesis. By contrast, Imetelstat is capable of selectively inhibiting the proliferation of phenotypically and functionally defined MF hematopoietic stem cells and myeloid progenitor cells through promoting their apoptosis.
- Imetelstat in some patients can preferentially deplete malignant MF HPCs. Somatostatin is a potentially promising drug for the treatment of MF which appears to affect primitive MF HSCs.

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