Abstract

Acute myeloid leukemia (AML) is a relatively rare and fast-growing malignant disease. There are approximately 20,000 new cases each year in the United States, and the incidence rate has increased. Receptor tyrosine kinase (RTK) inhibition has been successfully used in various solid tumors and hematological malignancies. The high frequency of Fms-like Tyrosine Kinase 3 (FLT3) mutation has been detected, and therefore considered as a potential target for AML. HM43239 is an orally active, potent small molecule inhibitor of FLT3. As a FLT3 inhibitor, its activity was confirmed in vitro and in vivo preclinical data. HM43239 may overcome the resistance mutants, such as FLT3 ITD/TKD double mutants. The target validation was shown by the fact that the treatment with HM43239 resulted in inhibition of FLT3 phosphorylation and downstream signaling pathways such as phospho-STAT5. Moreover, HM43239 monotherapy induces dose-dependent regression of the tumor growth in FLT3 ITD mutant xenograft model. Here, we introduce a novel FLT3 inhibitor, HM43239 has been successfully used in various solid tumors and hematological malignancies. And therefore considered as a potential therapeutic target for AML.

In vitro Biochemical Profiles

- **Mode of Action**
  - Inhibition of FLT3 signaling in AML cell lines
  - Induction of apoptosis in FLT3-ITD expressing cells

Induction of Apoptosis

- A. Annexin-V FACS analysis
  - MV-4-11
  - MOLM-14

PD/PK Profiles

- A. PK/PD profile in MV-4-11 xenograft mice
  - Days after cell implantation
  - Percent survival

LSC Regulation

- Regulation of leukemic stem cell-like population in KG-1a
  - Non-treated
  - HM43239

In vivo Efficacy in Xenografted Mice

- Anti-tumor activity in MV-4-11 or MOLM-13 xenograft mice
  - A. MV-4-11
  - B. MOLM-13

In vivo Efficacy in Orthotopic Mice

- Anti-tumor efficacy in AML bone marrow transplantation model
  - A. MV-4-11
  - B. MOLM-13

Conclusion

- HM43239 is a small molecule inhibitor of FLT3 that has been evaluated as a novel therapeutic agent for the treatment of acute myeloid leukemia (AML).
- Not only in vitro but also in vivo anti-tumor activity of HM43239 in FLT3 ITD mutant xenograft model was well correlated.
- Compelling evidence has demonstrated that the induction of apoptosis was dose-dependently increased as well as the inhibition of FLT3 signaling pathways.
- HM43239 has a potential for regulating leukemic stem cell, and therefore might overcome intrinsic or acquired resistance.

References


Author Disclosures

All Authors: Employees in Hannmi Pharmaceutical Co., Ltd.