The CXCL12/CXCR4 Pathway As a Potential Target of Tipifarnib in Acute Myeloid Leukemia and Myelodysplastic Syndromes

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BACKGROUND
CXCL12 is a chemokine that is essential for homing of myeloid cells to the bone marrow (BM).

Tipifarnib is a potent and selective inhibitor of the enzyme farnesyltransferase (FT) that had been investigated in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). While major responses were reported some AML and MDS patients, the overall activity of tipifarnib in these indications was insufficient to support a registration, and no molecular mechanism that could explain the activity of tipifarnib in AML and MDS has been identified.
Based on initial observations in T cell lymphoma (Witzig ASH 2017), we investigated a role for CXCL12 and myeloid cell homing to BM as biomarkers of the activity of tipifarnib in AML and MDS studies.

RESULTS

1. Clinical Benefit from Tipifarnib is Associated with Bone Marrow Homing of Myeloid Cells

CXCL12 is also a chemokine for neutrophils. Patients with high CXCL12 in bone marrow or hypercellularity of the CXCL12/CXCR4 pathway (e.g., in BM aspirates) present with bone marrow homing of neutrophils that is manifested clinically by isolated neutropenia (neutrophils with normal WBC count).

2. High Bone Marrow CXCL12 Causes Bone Marrow Homing of Myeloid Cells

CXCL12 is a chemotactic agent for neutrophils. Patients with high CXCL12 in bone marrow or hypercellularity of the CXCL12/CXCR4 pathway present with bone marrow homing of neutrophils that is manifested clinically by isolated neutropenia (neutrophils with normal WBC count).

3. Clinical Benefit from Tipifarnib is Observed in AML Subjects with Bone Marrow Homing of Myeloid Blasts

Tipifarnib in 1st line, elderly, frail AML patients – CTEP20

4. Clinical Benefit from Tipifarnib is Observed in MDS Subjects with Bone Marrow Homing of Neutrophils

CXCL12 is also a chemokine for neutrophils. Patients with high CXCL12 in bone marrow or hypercellularity of the CXCL12/CXCR4 pathway present with bone marrow homing of neutrophils that is manifested clinically by isolated neutropenia (neutrophils with normal WBC count).

5. The Ratio of Expression of the Myeloid Receptors CXCR4 and CXCR2 is a Potential Biomarker for Tipifarnib in Bone Marrow Neoplasias

CONCLUSIONS

- CXCL4/CXCR2 and bone marrow homing of myeloid cells constitute potential biomarkers of the activity of tipifarnib in bone marrow neoplasias supporting the hypothesis that the CXCL12/CXCR4 pathway is a potential target of FT inhibitors
- Ongoing tipifarnib trials in MDS and CMML are investigating these hypotheses
- Research on upstream and downstream farnesylated targets in the CXCL12/CXCR4 pathway is ongoing

REFERENCES

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