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.

METHODS

CTEP20 was a phase 2, multicenter, open-label study that investigated the efficacy and safety of tipifarnib in 158 older adults with previously untreated, poor-risk AML. The majority of patients had prior MDS. Global gene expression data was generated using the Affymetrix U133A gene chip from 34 pretreatment BM samples (GSE8970) and analyzed retrospectively with respect to pretreatment hematological parameters and study outcomes.

AML301 was a phase 3 (N=457), multicenter, open-label study that evaluated the efficacy and safety of tipifarnib compared with best supportive care (BSC), including hydroxyurea, as first-line therapy in elderly patients with newly diagnosed, de novo, or secondary AML. The primary endpoint was overall survival. Median overall survival was 107 days for the tipifarnib arm and 109 days for the BSC arm. The hazard ratio (tipifarnib vs BSC) for overall survival was 1.02 (non-significant, ns).

INT28 was a multicenter phase 2 study that evaluated tipifarnib in 82 pts with poor-risk MDS

The Kaplan-Meier method was employed to estimate survival and progression free survival (PFS) and the analysis of prognostic variables.

KO-TIP-004 is an ongoing phase 2 of tipifarnib in relapsed/refractory CMML patients (Patnaik, ASH 2017)

Clinical trial information: NCT00027872, NCT00093990, NCT00050154, NCT02807272

REFERENCES

1. CTEP20: Lancet at al. 2007. Blood109:1387-94
2. AML301: Harousseau et al. 2009. Blood114:1166-173
3. INT28: Fenaux et al. 2007. Blood 109:4158-63

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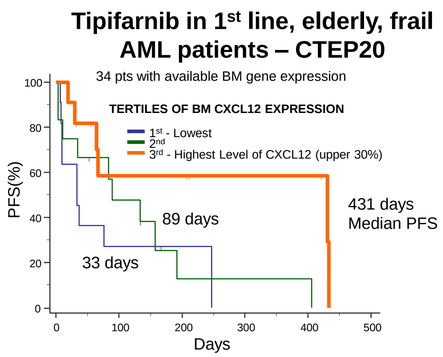
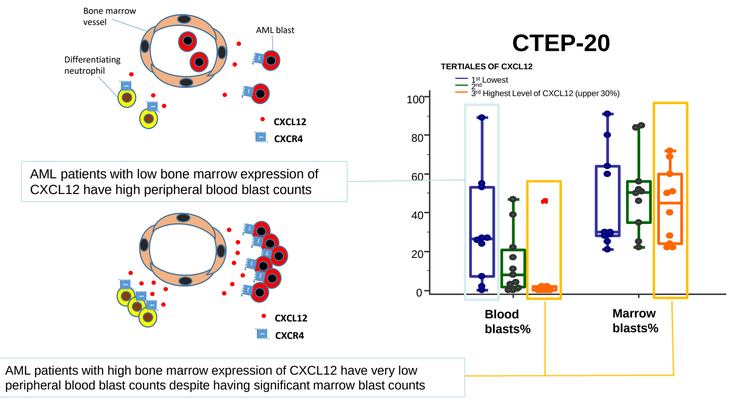
RESULTS

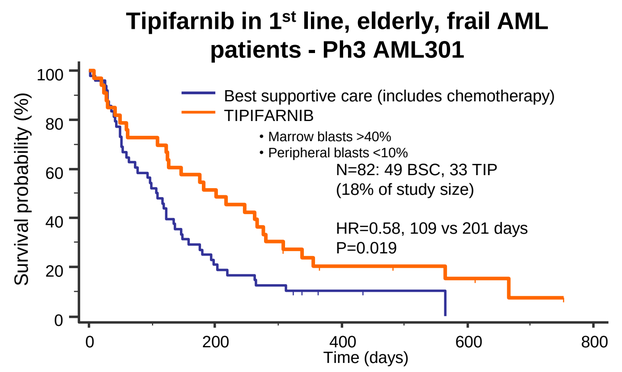
1. Clinical Benefit from Tipifarnib is Associated with Bone Marrow CXCL12



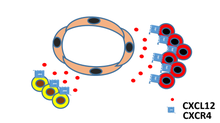
2. High Bone Marrow CXCL12 Causes Bone Marrow Homing of Myeloid Cells



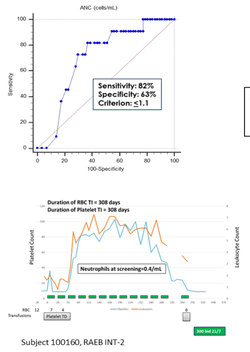
3. Clinical Benefit from Tipifarnib is Observed in AML Subjects with Bone Marrow Homing of Myeloid Blasts

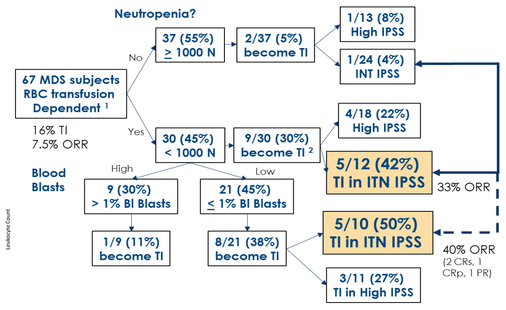


4. Clinical Benefit from Tipifarnib is Observed in MDS Subjects with Bone Marrow Homing of Neutrophils



CXCL12 is also a chemotactic agent for neutrophils. Patients with high CXCL12 in bone marrow or hyperactivity of the CXCL12/CXCR4 pathway (e.g. WHIM syndrome) present with bone marrow homing of neutrophils that is manifested clinically by isolated neutropenia (neutropenia with normal WBC counts)

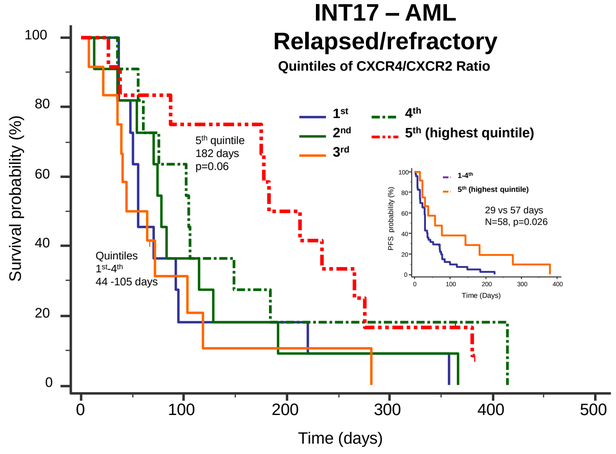


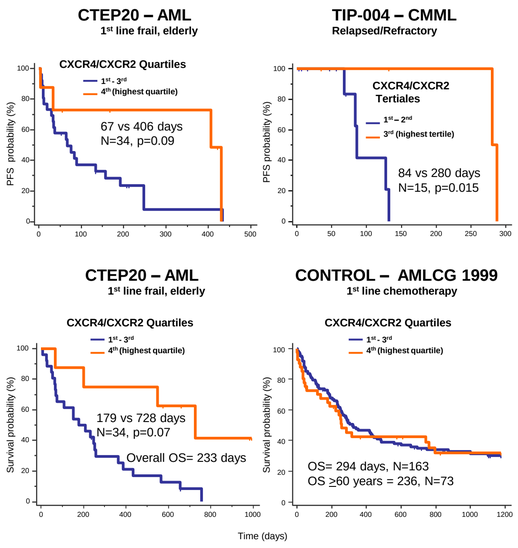


1. Transfusion dependence was defined as 1 or several RBC transfusion units recorded from screening to cycle1 Day 1 in the study report
2. Duration: 168, 56, 55, 245, 666, 446, 223, 308, and139 days

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

CXCL12 is produced by bone marrow vascular/mesenchymal cells. The CXCL12 receptor CXCR4 and its antagonistic receptor CXCR2 are present in the surface of myeloid cells. Analysis of CXCR4 and CXCR2 expression in bone marrow aspirates of mononuclear cells revealed an association between the ratio of CXCR4 to CXCR2 and the clinical activity of tipifarnib that was consistent across endpoints, clinical settings and indications





CONCLUSIONS

- **CXCR4/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**