Materials and Methods

PDX model:

The Dual E-selectin/CXCR4 Antagonist GMI-1359 Exerts Anti-leukemia Efficacy Against FLT3-ITD-mutated Acute Myeloid Leukemia in A Patient-derived Xenograft Murine Model

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Background

Acute myeloid leukemia (AML) is a molecularly heterogeneous disease with poor clinical outcome. Targeted therapy of FMS-like tyrosine kinase-3 (FLT3)-mutated AML patients using small molecular inhibitors including sorafenib showed clinical success in reducing leukemia blasts in peripheral blood. However, they have limited effect on leukemic stem cells in the bone marrow (BM) microenvironment (1, 2). The BM is presumed to be the reservoir for leukemia stem cells (LSCs) that persist during targeted therapy and mediate disease relapse. The interaction of leukemic blasts with the BM microenvironment is mediated by receptor-ligand axes such as CXCR4/SDF-1, E-selectin/HECA-452, and cell-cell contact have also been associated with drug resistance in FLT3 mutated AML (3-5). We recently reported that targeting CXCR4/E-selectin with the dual inhibitor GMI-1359 (GlycoMimetics, Inc., Rockville, MD) showed efficient mobilization of leukemia cells in to the circulation, and significant prolonged survival of mice in a FLT3-ITD mutant AML cells-xenografted murine model (6, 7). In the present study, we further evaluated the anti-leukemia effects of GMI-1359 in a patient-derived xenograft (PDX) murine model. We demonstrated that GMI-1359 enhances normal hematopoiesis in the BM in addition to its anti-leukemia effects, either alone or combined with sorafenib treatment.

References


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