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Home / December 6, 2014; Blood: 124 (21)

The Vascular Niche Is Involved in Regulating Leukemic Stem Cells in Murine Chronic Myelogenous Leukemia

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Abstract

Chronic myelogenous leukemia (CML) is effectively controlled by tyrosine kinase inhibitors (TKIs) such as imatinib mesylate, leading to a hematologic remission in >90% of patients. However, the majority of patients relapse once TKI therapy is discontinued, suggesting that CML leukemia stem cells (LSC) are not eradicated. We recently showed that modulation of the osteoblastic niche can lead to reduction of LSC in CML (Krause et al., Nat. Med. 2013;19:1513), but the role of the vascular hematopoietic stem cell niche in CML has not been well defined.

E-selectin is expressed on bone marrow (BM) endothelium within the vascular niche, whereas loss of E-selectin expression or treatment with GMI-1271, an E-selectin small molecule antagonist, enhances HSC quiescence and self-renewal (Winkler et al., Nat. Med. 2012;18:1651). E-selectin also plays a critical role in the homing and engraftment of CML LSCs (Krause et al., Blood 2014;123:1361) through E-selectin ligands expressed on the LSCs, including CD44 (Krause et al., Nat. Med. 2006;12:1175). We, therefore, hypothesized that E-selectin blockade with GMI-1271 may overcome niche-mediated resistance to TKIs and eradicate CML LSC.

Using the well-described murine retroviral transduction/transplantation model of CML we showed that the white blood cell count (WBC) of mice with BCR-ABL1-induced CML-like leukemia was significantly reduced by treatment with imatinib plus GMI-1271 (or imatinib alone) and there was a trend towards WBC reduction by treatment with GMI-1271 alone ($P=0.07$). The percentage of GFP⁺ Mac-1⁺ cells in peripheral blood on day 16 post-transplant was decreased by imatinib or GMI-1271 alone or by combined treatment with imatinib and GMI-1271. Spleen weights were significantly reduced by combined treatment with imatinib plus GMI 1271. Furthermore,

December 06, 2014 [Table of Contents](#)

[← Previous](#)

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the BM GFP⁺ (*BCR-ABL1*⁺) Lin⁻ c-Kit⁺ Sca-1⁺ population, which contains the LSCs in this model, was significantly reduced in animals treated with GMI-1271 compared to vehicle controls. As expected, treatment with imatinib alone had no effect on BM LSC frequency, and there was no added benefit in the reduction of LSC when imatinib and GMI-1271 were combined. In addition, the survival of mice treated with imatinib plus GMI-1271 was significantly prolonged compared to vehicle-treated animals, with ~20% of mice treated with GMI-1271 alone or the combination of imatinib and GMI-1271 exhibiting long-term low-burden disease despite discontinuation of treatment on day 28 post-transplant. In these primary recipients neither *BCR-ABL1*⁺ myeloid cells nor *BCR-ABL1*⁺ LSC were mobilized to peripheral organs. However, fewer *BCR-ABL1*⁺ LSC were found in the spleen of mice treated with GMI-1271 compared to imatinib-treated mice. There was a significant reduction in the frequency of cycling *BCR-ABL1*⁺ LSC in mice treated with GMI-1271 and imatinib.

To assess directly the effect of E-selectin inhibition on LSC frequency and function, we transplanted BM from primary leukemic mice treated with vehicle, imatinib, GMI-1271 or the combination of imatinib and GMI-1271 into irradiated secondary recipient mice. There was a significant reduction of WBC and a trend towards reduction of *BCR-ABL1*⁺ myeloid cells in secondary recipients of BM from donors treated with GMI-1271 alone or in combination with imatinib, but not by imatinib alone.

These data suggest that modulation of the vascular niche and, specifically, inhibition of E-selectin may be a possible strategy to target LSC in CML, possibly via a reduction in S-G2/M as cells arrest prior to apoptosis, even when imatinib is discontinued. Further studies on the effects of GMI-1271 on homing of LSC and the more exact mechanism of LSC reduction by GMI-1271 are being performed.

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Krause: *Glycomimetics, Inc.*: Research Funding.

- * Asterisk with author names denotes non-ASH members.

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