Mobilization mechanisms of human primary precursor-B-ALL cells in an in vivo model system by the CXCR4-Antagonist AMD3100 and by Catecholamines


Abstract

Introduction:

Leukemia stem cells (LSC), similar to their normal counterparts (HSC), are well protected by adhesion to their niche in the bone marrow. Mobilization of LSC to the circulation might render them vulnerable to anti-leukemia therapy. The aim of this study was to explore mechanisms of leukemia mobilization from the BM with mobilizing agents like AMD3100 (AMD) in a pre-clinical immune deficient mouse model.

Methods:

Immunodeficient mice were engrafted with the childhood pre-B-ALL leukemic cell line G2 and with primary childhood precursor-B-ALL cells from 4 patients with up to 100% of transplanted mice being engrafted. Engraftment was without prior irradiation, thereby leading to a more physiological model of human leukemias.

Results:

Treatment with AMD lead to a significant mobilization of all transplanted leukemias with a mobilization level of between 3 - 8 times above baseline. Next, we examined the role of SDF-1 release by AMD. It could already be shown, that AMD3100 releases SDF-1 in healthy mice from the bone marrow to the peripheral blood, resulting in progenitor cell mobilization (Dar et al. Leukemia 2011). In the experiments reported here, inhibition of SDF-1 action with neutralizing CXCR4 antibodies abrogated AMD-induced leukemia mobilization. Recently we also demonstrated catecholamine receptor expression on hematopoietic stem and progenitor cells and of mobilization of these cells by catecholamines (Spiegel et al. Nat. Immunol. 2007). We showed now that the G2 cell line and all 4 examined precursor-B-ALL samples express the catecholamine receptors D3, D5 and beta-2. Treatment with high doses of epinephrine alone led to leukemia mobilization in vivo similar to AMD treatment. Lower doses of norepinephrine in combination with AMD increased leukemia mobilization up to 20 times above baseline.

Conclusions:

We could demonstrate the applicability of an in vivo xenotransplantation system of primary human precursor-B-ALL cells for research into leukemia cell mobilization. These leukemic cells can be mobilized efficiently by the CXCR4 antagonist AMD3100 and synergistically by catecholamines. The AMD-induced mobilization mechanism is most likely via secretion of SDF-1. This mobilization approach could be potentially used for future mobilization protocols of leukemia in combination with established chemotherapy to improve eradication of minimal residual disease of leukemia.