Ibrutinib inhibits CXCR4 signaling leading to impaired B-cell adhesion and reduced leukemic-cell survival in chronic lymphocytic leukemia

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Bruton's tyrosine kinase (BTK) and chemokine receptor CXCR4 are linked in hematologic malignancies. Administering BTK inhibitor ibrutinib in B-cell malignancies, including chronic lymphocytic leukemia (CLL), typically causes lymphocytosis followed by clonal contraction, suggesting a key role of BTK in CXCR4 signaling regulated B-cell growth, migration and adhesion. We first studied this in an aggressive CLL mouse model using transplantable TCL1-192 leukemia cells. In this model, ibrutinib caused rapid re-distribution of CLL cells from solid tissues into the circulation. Ibrutinib also blocked B-cell homing and proliferation in tissue niches. These actions are associated with dysfunctional CXCR4; ibrutinib impaired CXCR4 signaling by blocking receptor recycling and phosphorylation regulated by PLCγ2, PKCμ, PIM-1 and BTK.

Dysfunctional CXCR4 was also seen in most ibrutinib-treated CLL patients; although unlike murine experiments, surface membrane CXCR4 levels increased in patients after treatment. As the level and duration of ibrutinib-induced lymphocytosis are associated with favorable prognostic features, there was greater inhibition in phosphorylated CXCR4 levels in patients with unfavorable disease (U-CLL) versus those with favorable disease (M-CLL). U-CLL but not M-CLL patients also had significantly reduced pro-survival BCL2 protein levels after treatment. These data suggest ibrutinib-mediated greater loss of CLL cells at tissue sites in patients with poor prognosis. We therefore investigated ibrutinib-induced changes in tissue resident cells in a xenograft mouse model using primary patient cells (2 U- and 3 M-CLL). Ibrutinib again resulted in dysfunctional CXCR4 and significantly inhibited CLL B-cell growth in spleens in all the cases but to a much greater extent in U-CLL than M-CLL. These data are consistent with greater loss of tissue resident cells in U-CLL patients with more marked reduction of phosphorylated CXCR4 and BCL2 after ibrutinib treatment.

Overall, our findings suggest the key role of BTK in CXCR4-regulated malignant B-cell chemotaxis and adhesion to microenvironment. Compared to M-CLL, ibrutinib-treated U-CLL patients have greater inhibition of phosphorylated CXCR4 and pro-survival BCL2 protein that lead to enhanced cell death in situ after loss of contact with elements in the tumor microenvironment. Our data identify CXCR4 as a key regulator of BTK-mediated CLL-cell retention and elucidate previously unappreciated mechanisms for these effects.