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Despite inhibitory effects on normal hematopoiesis in vitro, imatinib and nilotinib do not prevent engraftment of human CD34+ HSCs in immunodeficient NSG mice

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Background
The BCR-ABL tyrosine kinase inhibitor imatinib has previously been shown to also inhibit the tyrosine kinase c-kit, the stem cell factor receptor. Nilotinib is 30 times more potent than imatinib to inhibit BCR-ABL in vitro, but very few information is available on its inhibitory effects on c-kit, and thus on normal hematopoiesis.

Aims
To compare, in vitro and in vivo, the inhibitory effects of imatinib and nilotinib on proliferation, differentiation and engraftment capacity of human cord blood CD34+ HSCs.

Results
CFC assays showed that both imatinib and nilotinib have a significant inhibitory effect on the number of early progenitors from 3 healthy donors incubated during 14 days with or without TKIs at physiological concentrations (1 and 5 µM). Despite this inhibitory effect on CFCs, LTC-IC frequencies were not affected by a 5-week incubation with TKIs (n=3). Since decrease of CFCs in presence of TKIs could be explained by inhibition of entry into cell cycle, we investigated the proliferation of CD34+ cells cultured for 48h with TKIs. Our data demonstrate a significant decrease of HSC proliferation with imatinib 1 µM (73.2±4.5%; n=3; p=0.003) or nilotinib 1 µM (68.4±11.4%; n=3; p=0.026). Finally, we compared the impact of imatinib and nilotinib on engraftment in a xenotransplantation model. Twenty-five NSG mice, sublethally irradiated and inoculated intravenously with 6.105 human CD34+ HSCs, were treated orally with a placebo, imatinib 150 mg/kg/day or nilotinib 75 mg/kg/day for 42 days. Bone marrow chimerism was analyzed by flow cytometry. No significant differences were seen between mice treated with imatinib (47.7±5.3%; n=8; p=0.4130) or placebo (52.5±2.7%; n=9), while engraftment of human HSCs was slightly decreased (40.6±4.4%; n=8; p=0.0314) in mice treated with nilotinib.

Conclusion
Although TKIs inhibit hematopoiesis in vitro, they do not prevent engraftment in NSG mice even if chimerism was slightly lower in mice given nilotinib.