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Crizotinib overcomes microenvironment-mediated drug resistance in Ph-positive leukemia

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Introduction & Aim: Crizotinib exhibited activity against ABL tyrosine kinase. In this study, we evaluate crizotinib's ability to overcome drug resistance in Ph+ leukemia mediated by soluble factors secreted from mesenchymal stem cells (MSCs).

Materials & Methods: Condition media (CM) collected from MSCs abolished imatinib's ability to induce apoptosis in CML cells and confers drug resistance to imatinib in chronic myeloid leukemia (CML) cells. In contrast, crizotinib overcame the CM-mediated drug resistance. Cytokine array of CM collected from MSC revealed the presence of significant amounts of murine interleukin 3 (mIL-3). Moreover, exposure to CM significantly increased phosphorylated STAT levels leading to JAK2 activation. Interfering with JAK/STAT pathway, restored partial sensitivity to imatinib in CML cells exposed to CM. Interestingly, crizotinib, unlike imatinib, actively inhibited JAK2 and therefore overcome mesenchymal soluble factor-mediated drug resistance in Ph+ leukemia.

Conclusion: In conclusion, our findings indicate that soluble factors found in CM contribute to imatinib drug resistance in CML by activating the JAK/STAT pathway. Crizotinib, an ALK/Met inhibitor, which also inhibits ABL kinase activity, is also capable of inhibiting JAK2 activity and consequently overcoming mesenchymal soluble factor-mediated drug resistance in Ph+ leukemia.

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