Inhibition of bcr-abl gene expression by small interfering RNA sensitizes for imatinib mesylate (STI571).

Abstract:
Bcr-Abl proteins are effective inducers of the leukemic phenotype in chronic myeloid leukemia (CML) and distinct variants of acute lymphoblastic leukemia (ALL). Targeting bcr-abl by treatment with the selective tyrosine kinase inhibitor imatinib has proved to be highly efficient for controlling leukemic growth. However, it is unclear whether imatinib is sufficient to eradicate the disease because of primary or secondary resistance of leukemic cells. Therefore, targeting Bcr-Abl with an alternative approach is of great interest. We demonstrate that RNA interference (RNAi) with a breakpoint-specific short-interfering RNA (siRNA) is capable of decreasing Bcr-Abl protein expression and of antagonizing Bcr-Abl-induced biochemical activities. RNAi selectively inhibited Bcr-Abl-dependent cell growth. Furthermore, bcr-abl-homologous siRNA increased sensitivity to imatinib in Bcr-Abl-overexpressing cells and in a cell line expressing the imatinib-resistant Bcr-Abl kinase domain mutation His396Pro, thereby antagonizing 2 of the major mechanisms of resistance to imatinib.