Bcr-Abl resistance screening predicts a limited spectrum of point mutations to be associated with clinical resistance to the Abl kinase inhibitor nilotinib (AMN107).

Abstract:

In advanced-phase chronic myeloid leukemia (CML), resistance to imatinib mesylate is associated with point mutations in the BCR-ABL kinase domain. A new generation of potent ABL kinase inhibitors is undergoing clinical evaluation. It is important to generate specific resistance profiles for each of these compounds, which could translate into combinatorial and sequential treatment strategies. Having characterized nilotinib (AMN107) against a large panel of imatinib mesylate-resistant Bcr-Abl mutants, we investigated which mutants might arise under nilotinib therapy using a cell-based resistance screen. In contrast to imatinib mesylate, resistance to nilotinib was associated with a limited spectrum of Bcr-Abl kinase mutations. Among these were mutations affecting the P-loop and T315I. Rarely emerging resistant colonies at a concentration of 400 nM nilotinib exclusively expressed the T315I mutation. With the exception of T315I, all of the mutations that were identified were effectively suppressed when the nilotinib concentration was increased to 2000 nM, which falls within the peak-trough range in plasma levels (3.6-1.7 microM) measured in patients treated with 400 mg twice daily. Our findings suggest that nilotinib might be superior to imatinib mesylate in terms of the development of resistance. However, our study indicates that clinical resistance to nilotinib may be
associated with the predominant emergence of T315I.