Abstract

BCR/ABL is a constitutively active tyrosine kinase that has been shown to be at the heart of the development of chronic myeloid leukemia (CML) and about 30% of acute lymphoblastic leukemia (ALL). With the recent advent of tyrosine kinase inhibitors (TKIs), exemplified by Imatinib, Nilotinib, Dasatinib and Bosutinib, patients with Ph+ CML or ALL are candidates for the therapy with these agents. From the available TKIs, Imatinib is considered as front-line therapy for CML patients in chronic phase, while for Ph+ ALL patients, 2nd generation TKIs (nilotinib, dasatinib, bosutinib) might be considered as more effective therapeutic option. Since the treatment with TKIs is a long-term affair, a substantial proportion of patients acquire some sort of mutation in kinase domain of BCR-ABL, which could be a reason of treatment failure.

To date, over ninety BCR/ABL kinase domain mutations have been identified, affecting over 50 amino acids. Recurrent BCR/ABL kinase domain mutations have already been in vitro tested to approximate for their in vivo behavior.

Our goal is to invent in vitro technique that would allow testing TKI sensitivity of novel BCR/ABL kinase domain mutations, identified at very low MRD levels. The technique makes use of site-directed mutagenesis to create the novel BCR/ABL kinase domain variants in vitro, preparation and selection of stable clones of Ba/F3 cells transduced with retroviral constructs harboring the transgene and tests of their in vitro response to a panel of TKIs.

Timely information on the BCR/ABL kinase domain mutational status and its biological relevance might prove valuable for the clinical hematologist in their clinical decision making in respect to the treatment modulation and adjustment. Thus, we believe that this approach is just another step on the way to personalized, patient-tailored medicine, which in the future should be the ultimate goal for the molecular medicine.