The low frequency of clinical resistance to PDGFR inhibitors in myeloid neoplasms with abnormalities of PDGFRA might be related to the limited repertoire of possible PDGFRA kinase domain mutations in vitro.

Abstract:
Myeloproliferation with prominent eosinophilia is associated with rearrangements of PDGFR-A or -B. The most common rearrangement is FIP1L1-PDGFR-A (FP). The majority of patients with PDGFR-rearranged myeloproliferation respond to treatment with imatinib. In contrast to BCR-ABL-positive chronic myelogenous leukemia, only few cases of imatinib resistance and mutations of the FP kinase domain have been described so far. We hypothesized that the number of critical residues mediating imatinib resistance in FP in contrast to BCR-ABL might be limited. We performed an established systematic and comprehensive in vitro resistance screen to determine the pattern and frequency of possible TKI resistance mutations in FP. We identified 27 different FP kinase domain mutations including 25 novel variants, which attenuated response to imatinib, nilotinib or sorafenib. However, the majority of these exchanges did not confer complete inhibitor resistance. At clinically achievable drug concentrations, FP/T674I predominated with imatinib, whereas with nilotinib and sorafenib, FP/D842V and the compound mutation T674I+T874I became prevalent. Our results suggest that the PDGFR kinase domain contains a limited number of residues where exchanges
critically interfere with binding of and inhibition by available PDGFR kinase inhibitors at achievable concentrations, which might explain the low frequency of imatinib resistance in this patient population. In addition, these findings would help to select the appropriate second-line drug in cases of imatinib-resistant disease and may be translated to other neoplasms driven by activated forms of PDGFR-A or -B.