FMS-like tyrosine kinase 3-internal tandem duplication tyrosine kinase inhibitors display a nonoverlapping profile of resistance mutations in vitro.

Abstract:

FMS-like tyrosine kinase 3 (FLT3) inhibitors have shown activity in the treatment of acute myelogenous leukemia (AML). Secondary mutations in target kinases can cause clinical resistance to therapeutic kinase inhibition. We have previously shown that sensitivity toward tyrosine kinase inhibitors varies between different activating FLT3 mutations. We therefore intended to determine whether different FLT3 inhibitors would produce distinct profiles of secondary, FLT3 resistance mutations. Using a cell-based screening approach, we generated FLT3-internal tandem duplication (ITD)-expressing cell lines resistant to the FLT3 inhibitors SU5614, PKC412, and sorafenib. Interestingly, the profile of resistance mutations emerging with SU5614 was limited to exchanges in the second part of the kinase domain (TK2) with exchanges of D835 predominating. In contrast, PKC412 exclusively produced mutations within tyrosine kinase domain 1 (TK1) at position N676. A mutation at N676 recently has been reported in a case of PKC412-resistant AML. TK1 mutations exhibited a differential response to SU5614, sorafenib, and sunitinib but strongly impaired response to PKC412. TK2 exchanges identified with SU5614 were sensitive to PKC412, sunitinib, or sorafenib, with the exception of Y842D, which caused a strong resistance to sorafenib. Of note, sorafenib also produced a highly distinct profile of
resistance mutations with no overlap to SU5614 or PKC412, including F691L in TK1 and exchanges
at position Y842 of TK2. Thus, different FLT3 kinase inhibitors generate distinct, nonoverlapping
resistance profiles. This is in contrast to Bcr-Abl kinase inhibitors such as imatinib, nilotinib, and
dasatinib, which display overlapping resistance profiles. Therefore, combinations of FLT3 inhibitors
may be useful to prevent FLT3 resistance mutations in the setting of FLT3-ITD-positive AML.

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