Dasatinib and nilotinib are active in imatinib-resistant chronic myelocytic leukemia (CML) and many patients undergo sequential treatment. We aimed at modeling sequential tyrosine kinase inhibitor (TKI) resistance in vitro to compare the sequences imatinib-nilotinib-dasatinib and imatinib-dasatinib-nilotinib. We designed an in vitro model for sequential TKI resistance in CML. Replicates of imatinib-resistant cell lines were treated with dasatinib or nilotinib. Second-line resistant replicates were exposed to third-line treatment. Growth of all replicates in all three lines of treatment was associated with T315I. However, T315I occurred with low abundance and did not increase during sequential treatment. Nilotinib second-line more often gave rise to sequential resistance compared with dasatinib due to pre-existing P-loop mutations, especially at suboptimal drug concentration. In contrast, mutations predisposing to dasatinib resistance such as F317C/V and V299L did not occur before dasatinib exposure. Nilotinib third-line did not overcome imatinib-dasatinib resistance due to pre-existing T315I or P-loop/V299L or P-loop/F317 exchanges. Dasatinib third-line suppressed imatinib-nilotinib-resistant replicates with residual sensitivity. Sequential acquisition of BCR-ABL drug resistance mutations in CML might be underestimated. Resistance to sequential TKI monotherapy in vitro...
more often was associated with stepwise acquisition of drug-specific compound mutations compared with T315I. Pre-existing mutations strongly limited the activity of both third-line treatments, and the activity of nilotinib second-line in vitro critically depended on drug concentration. Clin Cancer Res; 19(11): 2962-72. ©2013 AACR.

Zeitschriftentitel / Abkürzung:
Clin Cancer Res

Jahr: 2013
Band: 19
Heft / Issue: 11
Seiten: 2962-72
Sprache: eng
Print-ISSN: 1078-0432
TUM Einrichtung:
III. Medizinische Klinik und Poliklinik

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > III. Medizinische Klinik und Poliklinik (Hämatologie / Onkologie) > 2013

entries: