The clinical significance of Kinetic Selectivity on ABL1 inhibitors.

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Introduction

The prognosis of chronic myeloid leukemia (CML) has changed during the past decades from a disease with an overall survival of only 5 years to one in which patients can enjoy a near normal life-expectancy.

Currently, there are five TKIs available for CML treatment in clinical practice. Imatinib and the second-generation TKIs nilotinib, dasatinib, and bosutinib are approved in newly diagnosed CML patients whereas ponatinib is a third-generation TKI approved for second line treatment or in patients harboring the BCR-ABL1T315I mutant. Recent data suggests that dasatinib and nilotinib may be more effective than imatinib as a front-line therapy. These TKIs have been demonstrated to decrease the risk of disease progression in patients groups at intermediate or high-risk compared to imatinib. Moreover, a recent retrospective study has shown higher treatment free remission rates (TFR) in patients treated with these TKIs. Consequently, dasatinib and nilotinib could potentially increase the number of patients that are able to discontinue treatment without loss of response. Lastly, nilotinib is the only TKI approved for the TFR label.

Cardiac adverse events have been reported with dasatinib, nilotinib and ponatinib, with the rates of left ventricular dysfunction highest with dasatinib. However, serious cardiac events associated with imatinib and bosutinib therapies are rare.

There is emerging data to suggest that imatinib therapy may result in decreased growth in children. In paediatric cases that are resistant or intolerant to imatinib and where allogeneic transplants are not possible, dasatinib is recommended as a second-line therapy. There are currently no reports suggesting that dasatinib may also have effects on growth in paediatric patients.

The objective was to evaluate if binding kinetics instead of affinity values may explain the differences in efficacy and toxicity of these TKIs.

KINETICfinder® assays

Enzymlogic's proprietary and optimized TR-FRET assay, KINETICfinder®, is an accurate, robust and reproducible HTS kinetic platform with a broad dynamic range.

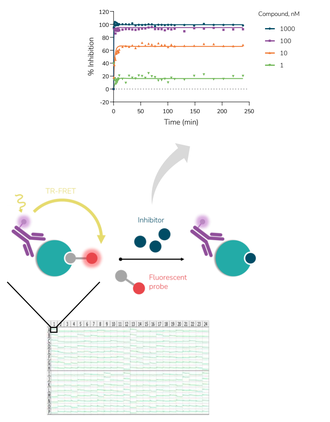

Fig 1. KINETICfinder method.

FEATURES

- HTS format: 80 compounds per plate.
- K_d, k_{on}, k_{off} and residence time in one assay.
- Rapid turnaround time.
- High sensitivity.
- No limitations linked with SPR.
- More robust, reproducible and precise than SPR and standard TR-FRET assays.
- Validated across diverse target classes.

APPLICATIONS

- Parallel SAR and SKR studies.
- Kinetic selectivity.
- Optimization of the therapeutic window.

Results

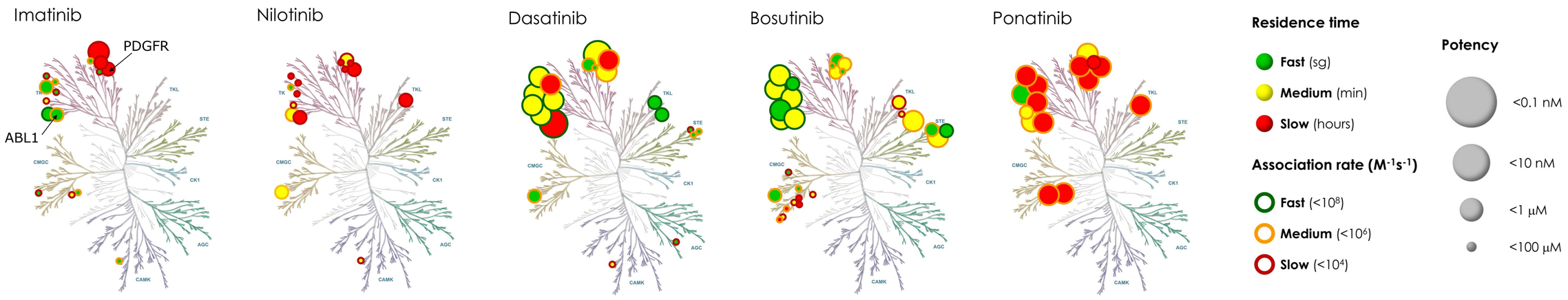

Fig 2. The kinase interaction maps represent the K_d, residence time and k_{on} of the five TKIs available for CML profiled across the kinome using KINETICfinder®.

Effect of Kinetic Selectivity of ABL1 inhibitors on clinical efficacy

The higher clinical effectiveness of dasatinib (0.01 nM) and nilotinib (15 nM) compared with imatinib (27 nM) and bosutinib (0.12 nM) cannot be explained when the in vitro inhibitory profile of these compounds towards ABL1 is exclusively based in their affinity constants.

However, when residence time is also taken into account, these TKIs can be classified in two well-differentiated groups. A first group comprised of the fast dissociating inhibitors imatinib (48 seconds) and bosutinib (23 minutes) and a second group containing the slow dissociating inhibitors nilotinib (4 hours) and dasatinib (5 hours). Therefore, residence time and not affinity might be the key differentiating factor in clinical efficacy between these TKIs.

Effect of Kinetic Selectivity of ABL1 inhibitors on clinical toxicities

Cardiovascular toxicities

A link between ABL1 inhibition and cardiac events has been demonstrated in cardiomyocytes. ABL1 is a key mediator of normal cardiac function and is expressed in the cardiac tissue. Again, residence time instead of the strength of on-target affinity correlated better with the cardiotoxicity profile seen in clinical settings of imatinib (seconds), bosutinib (minutes), nilotinib (hours), dasatinib (hours) and ponatinib (hours).

Decreased growth in children

PDGFR is an important regulator of chondrocyte proliferation and activity. Imatinib and dasatinib treatments may have direct effects on chondrocyte proliferation and activity through inhibition of PDGFRb. Whereas dasatinib (1.6 nM) displays higher potency against PDGFRb than imatinib (66 nM), it dissociates more rapidly, 48 minutes and 2.5 hours respectively. These differences in residence time might better explain the effect on growth in children reported with imatinib.

Discussion & Significance

- Creating kinetic selectivity profiles with KINETICfinder® can be a powerful tool to improve decision-making, leading to a better selection of compounds that may show different clinical responses or greater efficacy, safety and duration of action.
- We have found that compounds with similar affinity towards multiple kinases can exhibit dramatically different binding kinetics.
- Our results show that designing drugs with the desirable selectivity profiles requires not only an appropriate tuning of binding selectivity but also the modulation of kinetic selectivity.

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