Rational drug design and resistance in chronic myelogenous leukemia

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Introduction

- Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that accounts for 15% of all cases of leukemia and has an annual incidence of 1.5 cases per 100,000 individuals.
- CML is driven by the BCR-ABL chimeric gene product, a constitutively active tyrosine kinase. The fusion gene results from the reciprocal balanced translocation t(9;22)(q34;q11.2), cytogenetically detected as the Philadelphia (Ph) chromosome (Fig. 1).
- The BCR-ABL oncogene possesses constitutive kinase activity that leads to the stimulation of cell-growth pathways and reduced apoptosis of CML cells. Examples of drugs implicated on the transduction pathways affected are Ras and MAP kinases.
- The natural course of CML consists on 3 phases: chronic phase, accelerated phase and a terminal blastic phase characterized by the typical acute leukemia symptoms.
- Before the era of selective BCR-ABL tyrosine kinase inhibitors (TKIs), the median survival at diagnosis in CML was 3-7 years. TKIs have revolutionized the treatment, natural history, and prognosis of CML. They have turned it to the first cancer in which a medical treatment can return patients to a normal life expectancy.

Overcoming resistance

- The complex array of mutations observed rendered difficult to envision a single second generation TKI active against all the mutations.
- A significant number of mutations prevent the kinase domain from achieving the closed conformation necessary for drug binding.

SOLUTION: to find inhibitors that bind Abl in the open configuration or with less stringent conformational requirements.

Biochemical studies

- Dual specific: Sln/Abl kinase
- Binds BCR-ABL in both active and inactive conformations (Fig. 4).
- Active against K299 mutant.
- More than 300 fold potent than imatinib.

Figure 1: Binding mode of each of the above inhibitors. Abl/Abl, proteins are deduced in color, orange or green, and show different levels of conformational flexibility. This mutational landscape is also resistant to natural mutations.

Figure 2: Despite their efficacy and optimal safety profile, all these TKIs are ineffective to the T315I mutation.

Figure 3: T315I residue is located on the gatekeeper region of the ATP binding site. It participates in a critical hydrogen bonding interaction required for high-affinity binding of the other TKIs. The T315I mutation alters the topology of the ATP-binding pocket causing a steric clash between the side chain of the isoleucine and the hydrogen from the drug.

SOLUTION: Structural-guided experiments of an inhibitor that accommodates into the T315I side chain thanks to a carbon-carbon triple bond linkage on its structure. It’s the case of Ponatinib, a 500 fold potent than imatinib approved by FDA in 2012.

- After 15 years of clinical use of Imatinib and thanks to the other TKI available, CML has become the first cancer in which a medical treatment can return patients to a normal life expectancy.
- In spite of superior data, cure has rather disappoint. Ponatinib have shown substantial amelioration in either overall survival (OS) or progression free survival (PFS) rates over Imatinib, it continues to represent the most commonly used TKI to treat CML.
- Moreover, owing to some important risks of second generation TKIs shown in the table, it may not be worth it to take them if there is no resistance or intolerance to Imatinib.

References