TKIs (Tyrosine Kinase Inhibitors) Mechanism of action and toxicity in CML Patients

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Introduction

- In people with chronic myeloid leukemia, A section of chromosome 9 switches places with a section of chromosome 22, creating an extra-short chromosome 22 and an extra-long chromosome 9.

- **The extra-short chromosome 22 (Philadelphia chromosome)** named for the city where it was discovered. The Philadelphia chromosome is present in the blood cells of 90 percent of people with chronic myeloid leukemia .

- **The Philadelphia chromosome** creates a new gene (**The BCR-ABL) , the** gene contains instructions that tell the abnormal blood cell to produce too much of **tyrosine kinase.**

- Tyrosine kinase promotes cancer by allowing certain blood cells to grow out of control. **Targeted drugs that block the action of tyrosine kinase .**

Mechanism of Action (TKIs)

In general Tyrosine kinases are enzymes responsible for the activation of proteins by adding a phosphate group from ATP to one or more protein amino acid (phosphorylation).

TKIs block ATP binding site

Mechanism of Action (TKIs)

Tyrosine kinase can be classified to :

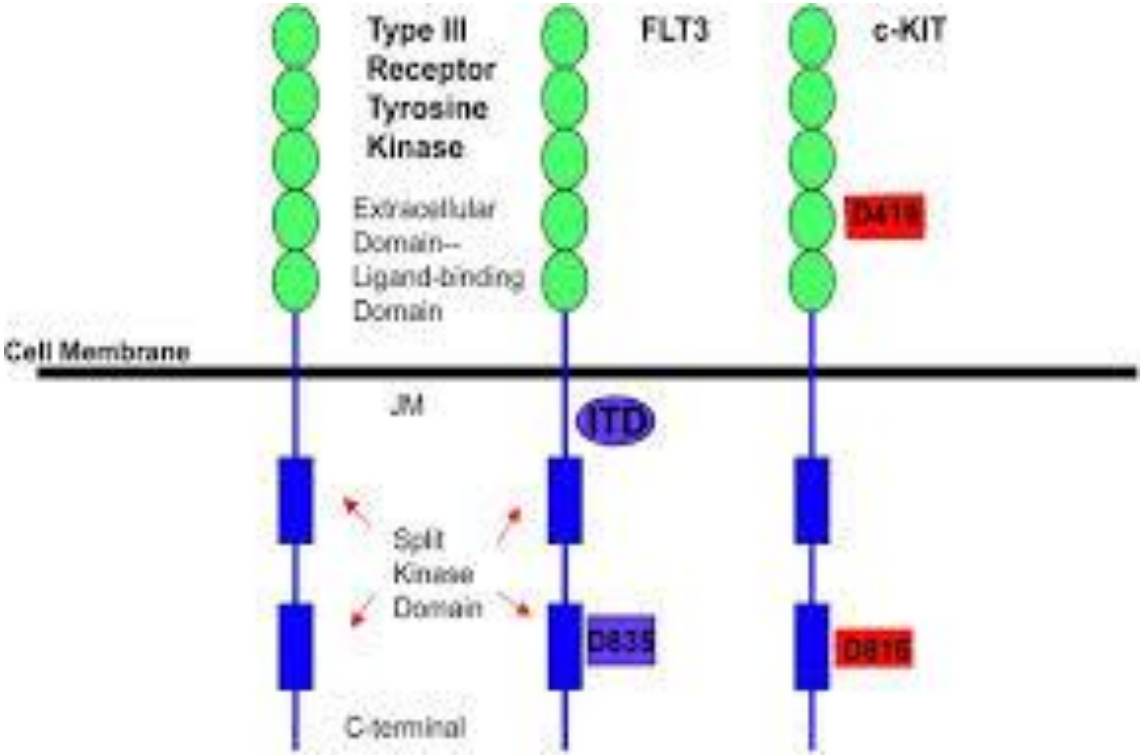
- Receptor Tyrosine Kinase (with transmembrane domains). :
  eg : EGFR , PDGFR

- Non receptor Tyrosine Kinase (cytoplasmic without domains):
  eg : SRC , ABL

RGFR : Epidermal growth factor receptor.

PDGFR : Platelet derived growth factor receptor

Receptor Tyrosine Kinase



Mechanism of Action
(Imatinib)

- Imatinib is a protein-tyrosine kinase inhibitor that potently inhibit the activity of the BCR-ABL Tyrosine kinase (TK) , as well as several receptor tyrosine kinase :

  * **KIT** , the receptor for stem cell factor **(SCF) .**
  * The discoidin domain receptors **(DDR1)** and **(DDR2)**,
  * The colony stimulating factor receptor **(CSF-1R)** .
  * Platelet-derived growth factor receptors alpha and beta **(PDGFR-alpha and PDGFR beta)**.

- **Imatinib selectively inhibits** proliferation and induces apoptosis in BCR- ABL positive cell lines .

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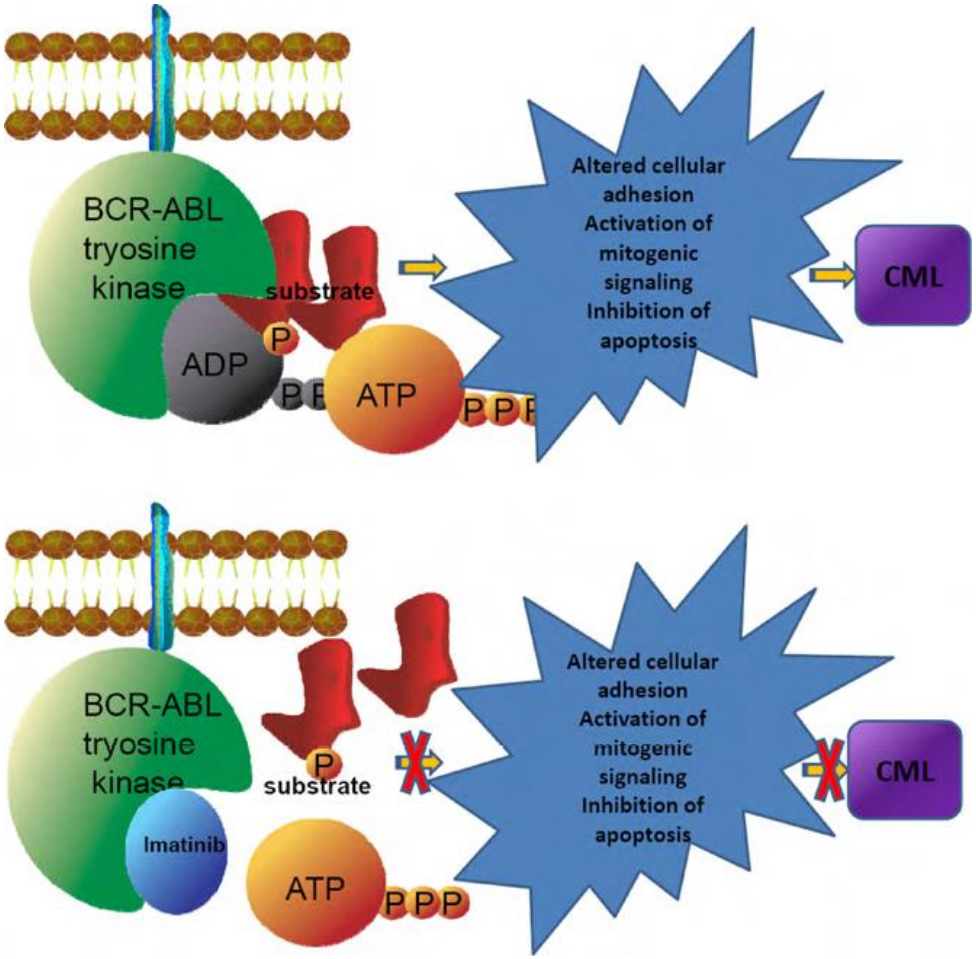
Mechanism of Action
(Imatinib)



Mechanism of Action
(Nilotinib)

- **Nilotinib is a potent and selective inhibitor of tyrosine kinase of the BCR-ABL** , It binds strongly with ATP-binding site .

- It is a potent inhibitor of wild- type BCR-ABL and maintains activity against **32/33 imatinib resistant mutant forms of BCR-ABL** .

- **Nilotinib inhibits the proliferation and induces apoptosis in BCR-A**BL in positive leukemia cells .

- Nilotinib inhibited the kinases PDGFR , c-KIT , CSF-1R, and DDR1 .

PDGFR : Platelet Derived Growth Factor Receptor .
CSF-1R : colony stimulating factor receptor .
DDR1 : discoidin domain receptors

Mechanism of Action
(Dasatinib)

- **Dasatinib : 2nd generation TKI which inhibits the following kinases:**

  - SRC non receptor TK family.
  - c-KIT .
  - EPHA2 .
  - PDGFRβ.

EPHA2 : ephrin type-A receptor 2 .
PDGFRβ : platelet-derived growth factor receptor β

TKIs Toxicity

Imatinib

- Edema and severe fluid retention have occurred. **Weigh patients regularly and management unexpected rapid weight gain by drug interruption and diuretics.**

- **Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred**. management with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter .

Imatinib

- congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. **Patients with cardiac disease or risk factors for cardiac failure should be monitored and treated .**

- Hepatotoxicity. **Assessment liver function before initiation of treatment and monthly thereafter or as clinically indicated.**

- **Myalgia , GIT events (diarrhea) , hypophosphatemia**

Imatinib

- Embryo-fetal Toxicity

can cause fetal harm when administered to a pregnant woman. Imatinib was teratogenic in rats when administered during organogenesis at doses approximately equal to the maximum human dose of 800 mg/day based on body surface area.

If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed about of the potential hazard to a fetus

Nilotinib

- **Myelosuppression**

Treatment with Nilotinib can cause Grade 3/4 thrombocytopenia, neutropenia and anemia. complete blood counts should be performed every 2 weeks for the first 2 months and then monthly thereafter, or as clinically indicated**. Myelosuppression was generally reversible and usually managed by withholding Nilotinib temporarily or dose reduction .**

- **QT Prolongation**

Nilotinib has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner , Prolongation of the QT interval can result in a type of ventricular tachycardia which may result in syncope, seizure, and/or death.

ECGs should be performed at baseline, 7 days after initiation of Nilotinib, and periodically as clinically indicated .

Nilotinib

- **Cardiovascular Events**

Cases of cardiovascular events included ischemic heart disease-related events , peripheral arterial occlusive, and ischemic cerebrovascular events , **actively managed during Nilotinib therapy according to standard guidelines**

- **Pancreatitis and Elevated Serum Lipase**

Nilotinib can cause increases in serum lipase. Patients with a previous history of pancreatitis may be at greater risk of elevated serum lipase.

If lipase elevations are accompanied by abdominal symptoms, **interrupt dosing and consider appropriate diagnostics to exclude pancreatitis. Test serum lipase levels monthly or as clinically indicated.**

Nilotinib

- **Hepatotoxicity**

Nilotinib may result in hepatotoxicity as measured by elevations in bilirubin, AST/ALT, and alkaline phosphatase. Monitor hepatic function tests monthly or as clinically indicated , Nilotinib exposure is increased in patients with impaired hepatic function. **Use a lower starting dose for patients with mild to severe hepatic impairment at baseline**

- **Electrolyte Abnormalities**

The use of Nilotinib can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. **Electrolyte abnormalities must be corrected prior to initiating Nilotinib and these electrolytes should be monitored periodically during therapy .**

- Elevated cholesterol and glucose level , should be monitored before and during treatment .

Nilotinib

Embryo-Fetal Toxicity

There are no adequate and well controlled studies of Nilotinib in pregnant women. However, Nilotinib may cause fetal harm when administered to a pregnant woman. Nilotinib caused embryo-fetal toxicities in animals at maternal exposures that were lower than the expected human exposure at the recommended doses of nilotinib.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed about the potential hazard to the fetus. Women of child-bearing potential should avoid becoming pregnant while taking Nilotinib .

Dasatinib

- Myelosuppression

Treatment with Dasatinib is associated with severe thrombocytopenia, neutropenia, and anemia.

complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Dasatinib temporarily or dose reduction .

- **Bleeding related events :**

In addition to causing thrombocytopenia in human subjects, **Dasatinib caused platelet dysfunction in vitro.** In all clinical studies, **severe central nervous system (CNS)** hemorrhages, including fatalities, occurred in 1% of patients receiving Dasatinib .

Dasatinib

Severe gastrointestinal hemorrhage, including fatalities, occurred in 4% of patients and **generally required treatment interruptions and transfusions**. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia.

- **Fluid Retention**

- Dasatinib is associated with fluid retention. In clinical trials, severe fluid retention was reported in up to 10% of patients. Severe ascites, pulmonary edema, and generalized edema and pleural effusion .
- Patients who develop symptoms suggestive of **pleural effusion**, such as dyspnea or dry cough**, should be evaluated by chest x-ray , Severe pleural effusion may require thoracentesis and oxygen therapy.**
- Fluid retention events were typically **managed by supportive care measures that include diuretics or short courses of steroids.**

Dasatinib

- **QT Prolongation**

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval).

Dasatinib administered with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines , hypokalemia or hypomagnesemia should be corrected prior to Dasatinib administration.

Dasatinib

- **Congestive Heart Failure, Left Ventricular Dysfunction, and Myocardial Infarction**

Cardiac adverse reactions were reported in 7% of 258 patients taking Dasatinib , including, 1.6% of patients with cardiomyopathy, heart failure congestive, diastolic dysfunction, fatal myocardial infarction, and left ventricular dysfunction. **Monitoring patients for signs or symptoms consistent with cardiac dysfunction should be done and treat appropriately .**

- Pulmonary Arterial Hypertension

Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur any time after initiation. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention.

If PAH is confirmed, Dasatinib should be permanently discontinued.

Dasatinib

- **Embryo-fetal Toxicity**

- Dasatinib can cause fetal harm when administered to a pregnant woman. Adverse fetal and infant outcomes have been reported from women who have taken Dasatinib
- During pregnancy. In animal reproduction studies, embryo-fetal toxicities, including skeletal malformations, were observed in rats and rabbits at plasma concentrations
- **Females of reproductive potential to avoid pregnancy, which may include the use of contraception, during treatment with Dasatinib .**


Thank
You