

Side Effects of Gleevec

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Sources:

- Novartis:
 - gleevec.com
 - Full Prescribing Information
- www.medscape.com
- drugs.com

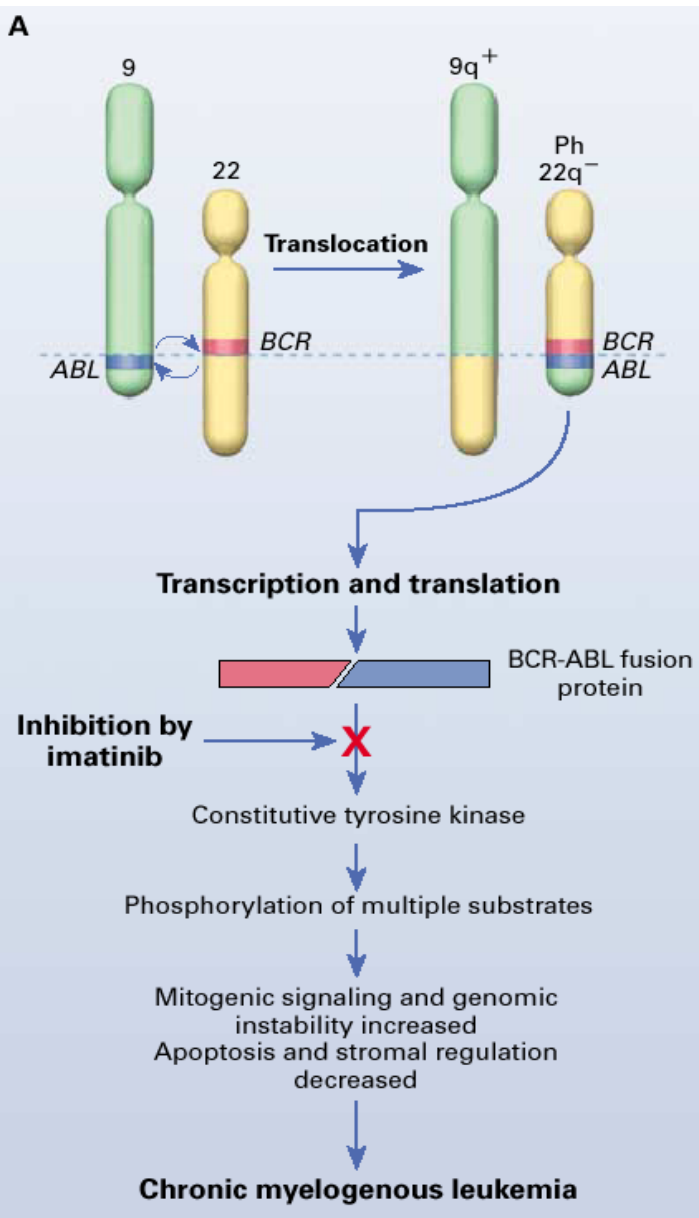


What is Gleevec?

- Developed by Novartis
- Imatinib Mesylate (Gleevec, Glivec)
- FDA Approval 2001 for treatment of chronic myelogenous leukemia (CML).
- Made cover of Time as “magic bullet” for cancer
- Also approved for: gastrointestinal stromal tumors (GISTs)
- Possible new uses in mastocytosis, hypereosinophilic syndrome and dermatofibrosarcoma protuberans.



Mechanism of Gleevec



- Considered a model of rational drug design

- In CML, target is the Philadelphia (Ph) Chromosome

- Formed by chromosome translocation $t(9;22)(q34;q11)$.

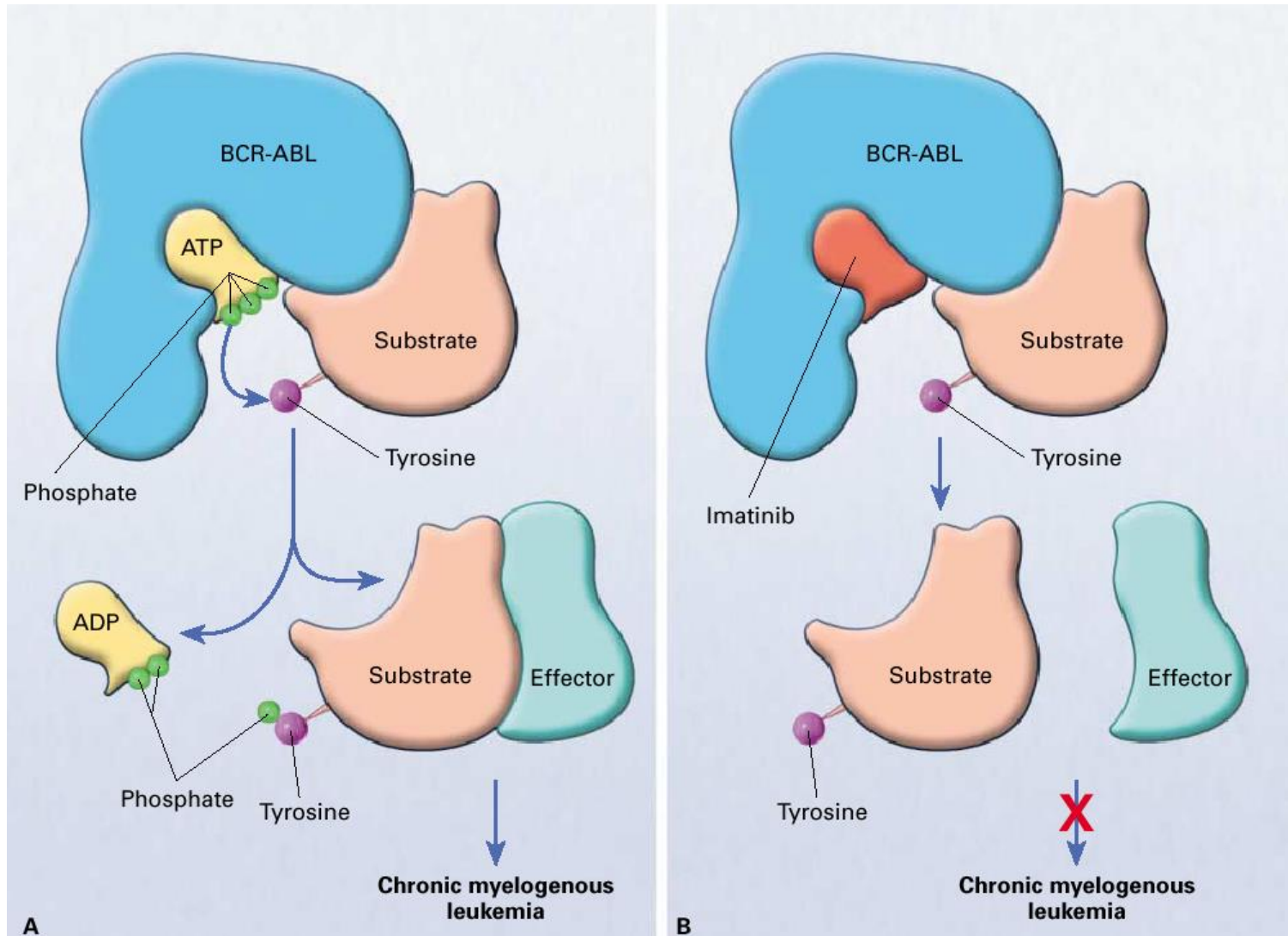
 - ABL chr 9 – a tyrosine kinase

 - BCR chr 22

- Ph protein acts as constitutive tyrosine kinase – permanent growth signaling

- Other targets: c-KIT (a cytokine receptor), platelet derived growth factor

Gleevec targets the BCR-ABL kinase pocket, preventing substrate phosphorylation



Common side effects of GLEEVEC



- Most side effects are mild to moderate in severity:
- Fluid retention
- Muscle cramps or pain
- Abdominal pain
- Vomiting
- Diarrhea
- Hemorrhage
- Nausea
- Fatigue
- Rash

Side Effects of Gleevec

More serious side effects:

- fever, sore throat, and headache with a severe blistering, peeling, and red skin rash;
- nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);
- fever, chills, body aches, flu symptoms;
- black, bloody, or tarry stools;
- coughing up blood or vomit that looks like coffee grounds;
- pale skin, easy bruising or bleeding, unusual weakness;
- feeling short of breath, even with mild exertion;
- swelling, rapid weight gain;
- urinating more or less than usual, or not at all; or
- sudden, severe headache or pain behind the eyes.

Less serious Gleevec side effects may include:

- mild nausea, diarrhea, upset stomach, gas;
- muscle or joint pain;
- Skin rashes
- headache, dizziness;
- stuffy nose, cough, sore throat;
- depression, sleep problems (insomnia); or tired feeling.

Adverse Reactions in Newly Diagnosed CML Trial (≥10% of Gleevec Treated Patients, N-551)

- Fluid Retention (Sup. Edema) 61.7 (Superficial Edema 59.9)
- Nausea 49.5
- Muscle Cramps 49.2
- Musculoskeletal Pain 47.0
- Diarrhea 45.4
- Rash and Related Terms 40.1
- Fatigue 38.8
- Headache 37.0
- Joint Pain 31.4
- Abdominal Pain 36.5
- Nasopharyngitis 30.5
- Hemorrhage 28.9 (GI 1.6; CNS Hemorrhage 0.2)
- Myalgia 24.1
- Vomiting 22.5
- Upper Resp. Tract Infection 21.2
- Cough 20.0
- Dizziness 19.4; Dyspepsia 18.9; Pharyngolaryngeal Pain 18.1; Pyrexia 17.8; Weight Increased 15.6; Insomnia 14.7
- Depression 14.9; Influenza 13.8; Bone Pain 11.3; Constipation 11.4; Sinusitis 11.4

Drugs that interact with Gleevec

- Gleevec interacts with CYP3A4:
 - Avoid CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin)
 - If CYP3A4 inducer co-administered, Gleevec dosage should be increased by at least 50%
 - Gleevec inhibits CYP3A4 and may increase response of other drugs
- Anticoagulation: avoid warfarin, use heparin instead
- Acetaminophen exposure expected to increase when coadministered with Gleevec
- Possible interactions with:
 - cyclosporine; dexamethasone; St. John's wort;
 - antibiotics such as azithromycin; antifungal medication - itraconazole
 - antidepressants such as citalopram; barbiturates such as amobarbital
 - calcium channel blocker such as diltiazem
 - cholesterol-lowering medicines such as lovastatin
 - ergot medicine such as ergotamine
 - HIV medication such as nevirapine
 - sedatives such as alprazolam
 - seizure medication such as carbamazepine or phenytoin

Conclusion

- Gleevec is generally well tolerated
- Specifically targets oncogene (Ph, c-KIT), not normal healthy cells
- Fewer side effects compared to alternative treatments for CML:
 - Chemotherapy (Hydroxyurea, Busulfan)
 - Bone marrow transplant
 - Interferon-alpha
- Advances in personalized medicine may reduce side effects by tailoring therapy to:
 - Normal genes of the patient
 - Genes of the neoplasm
 - Genes of the pathogen

