بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

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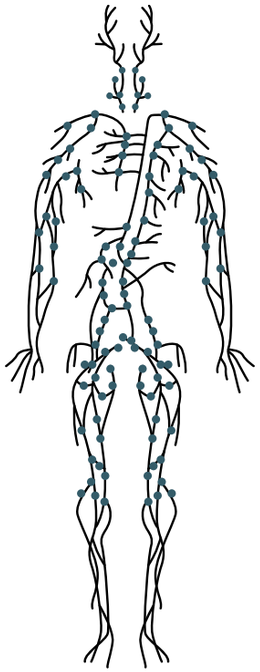
Final | Lecture 6

Chemotherapy cancer

Done by: Sarah Mahasneh



Introduction

- Although **AML** shares some similarities with **ALL**, it is considered a **more aggressive disease,** and therefore, the treatment approach differs.

- **Reason for the Different Approach:**
- ✓ **AML cells are able to synthesize asparagine, unlike ALL cells.**
- ✓ **In ALL, Asparaginase is used as a main therapy** because the **leukemic cells depend on external asparagine** and **cannot produce it themselves.**
- ✓ However, in **AML**, **Asparaginase is ineffective since AML cells can synthesize asparagine on their own.**
- ✓ For this reason, **AML** requires a **more aggressive treatment regimen**, known as the **"3+7 protocol."**
- ✓ 3+7 refers to using **daunorubicin** (not a cell cycle specific) for **3** days followed by **7** days of using **cytosine arabinosides (antimetabolite)** as the two drugs cause **bone marrow suppression,** so we **don't** give them together.

AML: INDUCTION THERAPY

The main concept behind the 3+7 regimen is to induce remission in patients with AML by using:

- Two cycles of cytosine arabinoside + daunorubicin +/-thioguanine and other agents gives remissions in 70-90%

- **Chemotherapy alone has given 30-50 % cure rates.**

· We usually perform sequential (**timed-sequential**) induction therapy, where cytosine arabinoside (**Ara-C**) is given in repeated cycles, with or without additional drugs. This approach—repeating the induction phase **two** or **three** times—has been found to produce better **antileukemic** activity, as shown by a **higher cure rate and more stable remission**.

- **Cure is higher after timed-sequential induction therapy (42% with timed-sequential vs. 27% when done once).**
- **A Short (4-12 months) of post-induction therapy is adequate.**

- **CNS leukemia is less common than in ALL; However, 'prophylaxis' is still preformed using high dose of cytosine arabinoside (Ara-C), administered intravenously or intrathecally (into the cerebrospinal fluid).**

○ **Cytosine arabinoside (Ara-C):** An antimetabolite that mimics deoxycytidine, enter the nucleotide, act as a false nucleotide becoming incorporated into DNA and inhibiting DNA polymerase. It is cell cycle-specific, acting during **the S phase**, where it **blocks DNA synthesis** and induces apoptosis, effectively stopping the proliferation of AML cells.

○ **Daunorubicin**: An anthracycline antibiotic **similar to doxorubicin**, differing slightly in its chemical structure and tissue activity. **Both** drugs act as topoisomerase II inhibitors (**topoisomerase poisons**) by intercalating into DNA and trapping the enzyme in its cleavable complex, leading to DNA breaks. Daunorubicin shows greater efficacy in AML, while doxorubicin is more commonly used for lymphomas and solid tumors.

○ Sometimes **Thioguanine** is being added: A purine antimetabolite that resembles guanine. It becomes incorporated into **DNA and inhibits purine synthesis**, thereby interfering with **DNA replication** and **cell division**.

AML Treatment: Consolidation

- Following induction therapy and achievement of complete remission (CR), we have two main treatment options for the next phase:

- 3-4 cycles of high dose cytosine arabinoside (HiDAC) administered approximately every 5-6 weeks

OR

- Bone marrow (peripheral blood stem cell) transplant

(Depends on degree of risk)

○ **Some patients proceed to the bone marrow (stem cell) transplantation option,** as AML carries a high relapse rate and a relatively **low maximal cure rate** of **42%** .

○ Additionally, some studies suggest that consolidation therapy **should not rely solely on the same induction drug,** since resistance or reduced efficacy may develop after initial treatment.

Common side effects

- More than 10 in every 100 people have one or more of the side effects listed below.
- Fatigue (tiredness) during and after treatment – most people find their energy levels are back to normal after 6 months to a year.
- Fatigue due to anemia, bone marrow suppression, decreased energy level.
- Soreness at the injection site (if you are having injections under the skin)
- Women may stop having periods (amenorrhoea) but this may only be temporary

Occasional side effects

- Dizziness: A characteristic side effect of cytosine arabinoside (Ara-C), particularly at high doses or with intrathecal administration.

- Remember:
  - **Vincristine causes constipation**
  - **Doxorubicin and daunorubicin cause cardiotoxicity.**

This topic is not required for the exam

CLL – treatment

- **Watch and wait (no immediate treatment if symptoms are mild)**
- **Monotherapy**
  - glucocorticoids
  - alkylating agents (Chlorambucil, Cyclophosphamide)
  - purine analogues (Fludarabine, Cladribine, Pentostatin)
- **Combination chemotherapy**
  - Chlorambucil/ Cyclophosphamide + Prednisone
  - Fludarabine + Cyclophosphamide +/- Mitoxantrone
  - CVP, CHOP
- **Monoclonal antibodies (monotherapy and in combination)**
  - Alemtuzumab (anti-CD52)
  - Rituximab (anti-CD20)

- The doctor mentioned, its important to know Two key points about CLL:
The treatment **approach** is different.
The **type** of treatment is different.

It's not required

Treatment of CLL

- We depend on:
· Chemotherapy, mainly fludarabine alone or in combination.
· Targeted Therapy.
· **choice depends on the risk of the disease.**

- We consider CLL cells as CD20+

Categorize According to Risk

(FISH, CD38, ZAP-70, Ig mutational status)

Low Risk

· Give one drug only

Minimally toxic therapy

- Rituximab
- Chlorambucil
- Fludarabine

Intermediate Risk

Nucleoside analog combination regimens

- Fludarabine and cyclophosphamide (DNA alkylating agent).
- Fludarabine and rituximab (Anti-CD20).
- Fludarabine, cyclophosphamide, and rituximab

High Risk

- Clinical trial
- BMT, usually myeloablative or non-myeloablative

Also this☺

Rituximab as part of first-line therapy for CLL: Rationale

- Rituximab monotherapy is moderately active in CLL
  - Activity is dose dependent (between 500–2250 mg/m2)1

- Rituximab acts synergistically with other cytotoxic agents *in vitro*
  - Increases fludarabine activity in NHL cell lines
  - Increases activity of bendamustine, mitoxantrone and other chemotherapeutic agents in CLL cells

○ Rituximab – Also used in non-Hodgkin lymphoma, because the tumor cells are $CD20^{+}$.

CLL

The disease may take 10–15 years before symptoms appear, so a “watch and wait” approach is often used. Determining when to start treatment and by what means is often difficult; studies have shown there is no survival advantage to treating the disease too early.

Imatinib

● In **CML**, we will learn about the pharmacogenetics of cancer, which studies **how genetics influence cancer treatment.**

○ Most new cancer drugs are designed based on the genetic makeup of the cancer cells, but sometimes we also **consider the patient's own genetic profile** when selecting therapy.

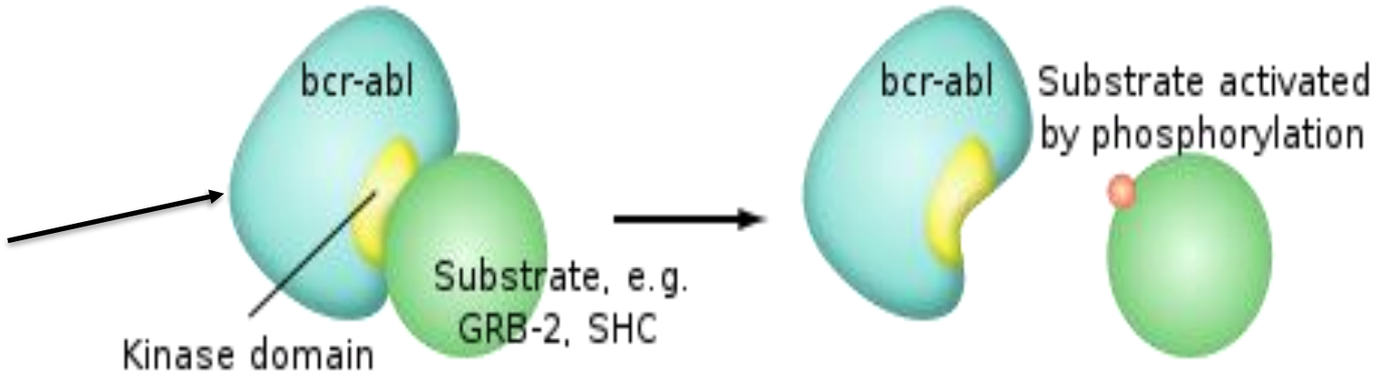
- Philadelphia chromosome or Philadelphia translocation is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

- This translocation of Philadelphia chromosome results in the Bcr-Abl (the only driver of CML) fusion protein, the causative agent in CML, and is present in up to 95% of patients with this disease.

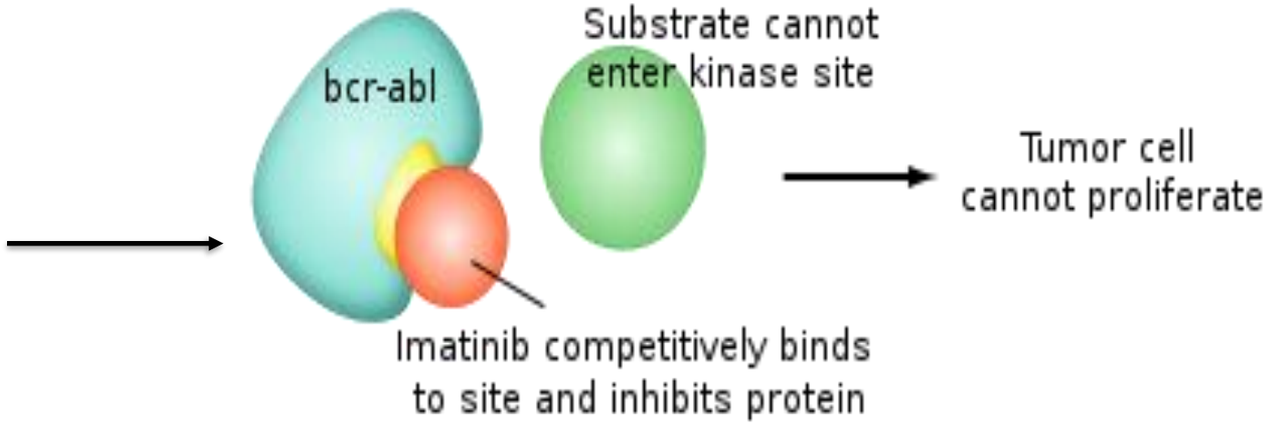
- Imatinib is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP.

• By blocking the main driver of CML with imatinib, we can stop disease progression and transform CML from a deadly condition into a manageable, chronic disease that the patient can live with.

BCR-ABL is a **constitutively active tyrosine kinase** that **phosphorylates downstream signaling molecules**, leading to the **activation** of multiple cell signaling pathways that promote **cell proliferation**, **survival**, and **tumorigenicity**.



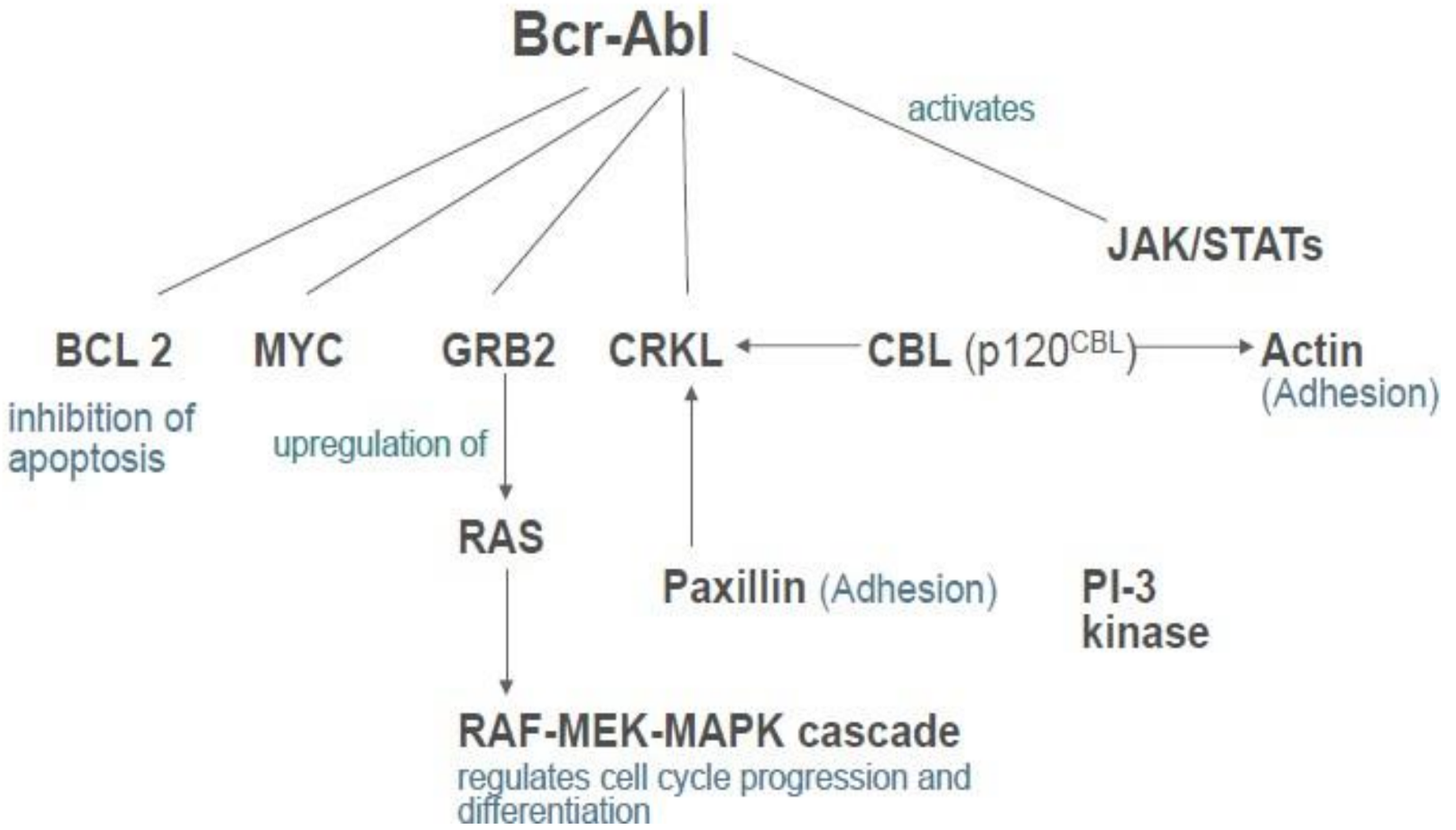
Imatinib acts as a **competitive inhibitor** by binding to the **ATP-binding** site of BCR-ABL, blocking **its kinase activity and preventing activation of adaptor proteins** such as **SHC** and **GRB2**, thereby **inhibiting tumor growth**.



Gleevec is one of the most effective modern medications for cancer treatment,.

- Imatinib has been the drug of choice for chronic myeloid leukemia (CML) for **over two decades**, allowing patients to live normal lives with **long-term therapy.**
- The medication **must be taken daily** to maintain continuous inhibition of the BCR-ABL kinase and prevent disease relapse

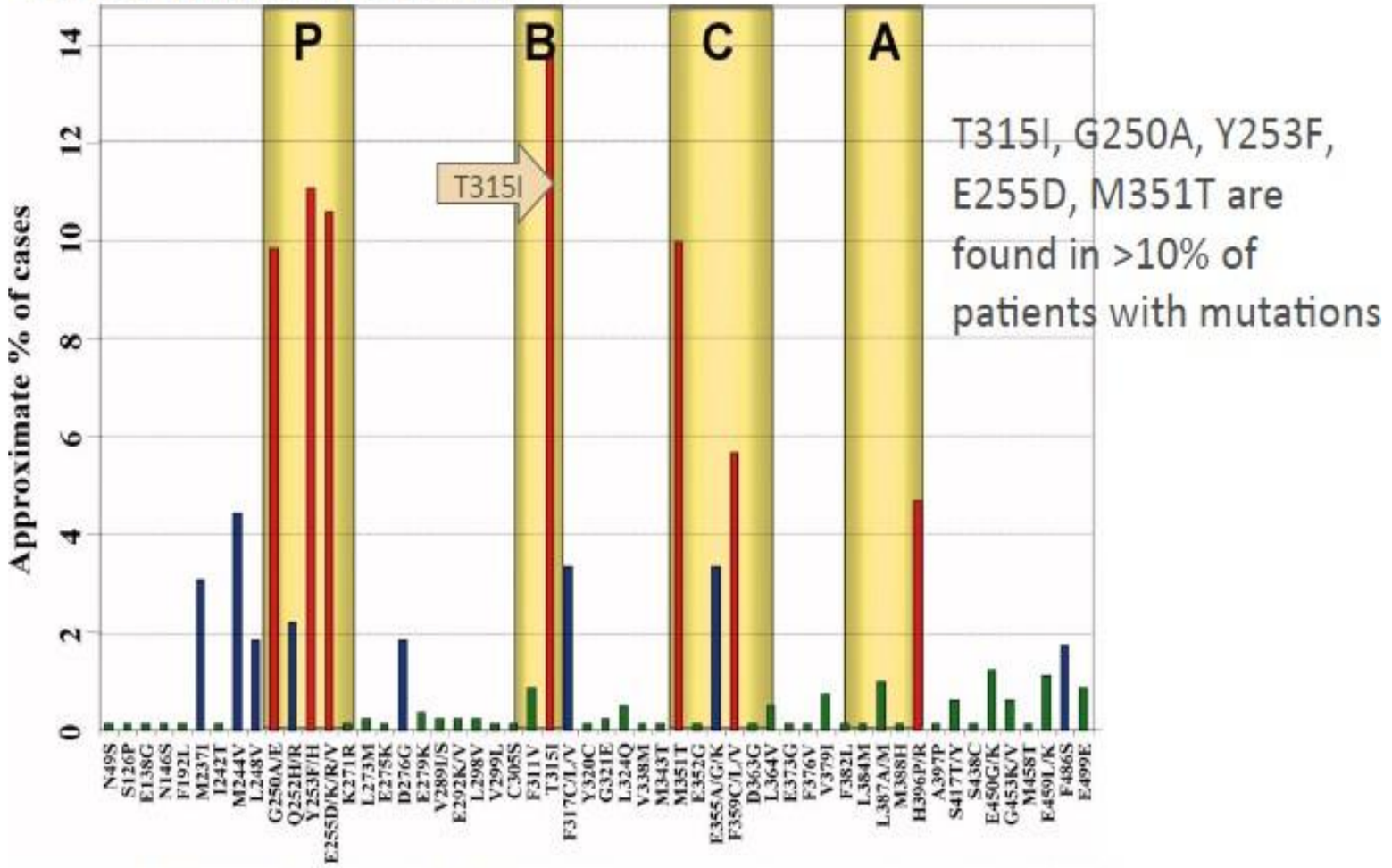
Bcr-Abl Signal Transduction Pathways



· **Imatinib** acts by competitively binding to the ATP-binding site of the Bcr-Abl tyrosine kinase, thereby **blocking its phosphorylation activity**.
· Once **Bcr-Abl is inhibited**, **all** of its downstream oncogenic pathways (such as **GRB2/RAS/MAPK, JAK/STAT, and BCL-2)** are **deactivated**. This **stops abnormal proliferation, removes the block on apoptosis, and allows leukemic cells to undergo programmed cell death.**

· Therefore, by targeting the **single driving mutation (Bcr-Abl),** Imatinib effectively shuts down all malignant signaling processes.

Incidence of BCR-ABL Mutations After Imatinib Failure



T315I, G250A, Y253F, E255D, M351T are found in >10% of patients with mutations

p = P-loop, b = imatinib binding, c = catalytic domain, a = activation loop.

See the next slide...

· **CML** can develop **resistance** through **multiple mutations in the BCR-ABL gene**.
This gene is a fusion between the **BCR** gene on chromosome **22** and the **ABL** gene on chromosome **9**, producing an abnormal BCR-ABL fusion protein with **continuous tyrosine kinase activity.**

· **One of the most problematic mutations is T315I.**
In this mutation, **threonine** (T) is replaced by **isoleucine** (I) at position **315**, which **blocks imatinib binding** by **preventing** the drug from forming its key **hydrogen bond** within the ATP-binding pocket.
<u>As a result, imatinib becomes ineffective.</u>

· Some patients may already carry this mutation **before** therapy, while others **acquire it during treatment**, leading to loss of response over time.
· This is why regular molecular monitoring is essential – therapy must sometimes be adjusted based on the patient's mutation profile (pharmacogenetics).

· If the patient has mutations **other** than T315I, they can usually be treated successfully with second-generation TKIs such as **Nilotinib** or **Dasatinib**, and the choice between them depends mainly on **side-effect profiles**.

Nilotinib and Dasatinib

(**More potent than imatinib)**

- Nilotinib (AMN107)
  - Developed from imatinib
  - Structure similar; altered to allow for greater ABL potency and selectivity
  - 20-50x more potent *in vitro*
  - Active against some imatinib resistant Abl kinase mutants except T315I
  - FDA approved Nov 2007
- Dasatinib (BMS 354825)
  - Developed as an inhibitor of Src kinase
  - Structure different than imatinib; greater potency; able to bind different conformations
  - ~300x more potent *in vitro*
  - Active against some imatinib resistant Abl kinase mutants except T315I
  - FDA approved June 2006

ENESTnd: Cardiovascular Events by Year of Treatment

"Incidence and Timing of Cardiovascular Events in CML Patients Treated with Nilotinib vs. Imatinib (ENESTnd Trial)"

First Cardiovascular Event by Year, n (%)[a]	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg QD (n = 280)
< 1 y	4 (1.4)	10 (3.6)	2 (0.7)
≥ 1 y to < 2 y	4 (1.4)	6 (2.2)	0
≥ 2 y to < 3 y	7 (2.5)	6 (2.2)	1 (0.4)
≥ 3 y to < 4 y	4 (1.4)	4 (1.4)	1 (0.4)
≥ 4 y to < 5 y	1 (0.4)	6 (2.2)	1 (0.4)
≥ 5 y to < 6 y	5 (1.8)	9 (3.2)	1 (0.4)
≥ 6 y to < 7 y	3 (1.1)	2 (0.7)	1 (0.4)
≥ 7 y to < 8 y	0	1 (0.4)	0

Year of first cardiovascular event was assigned based on the start date of the first cardiovascular event reported in each patient. Patients with multiple events were counted only once under the year during which their first cardiovascular event was reported.

- If we look at **nilotinib** administered at doses of **300 mg** or **400 mg twice daily (BID)**, the **incidence of cardiovascular events—the main adverse effect associated with these drugs—** is approximately **10** for the **400 mg** dose and **4** for the **300 mg** dose, compared with **only 2 patients** in the **imatinib** group.
- **The risk increases over time and leads to more patients developing cardiovascular disease, so stay on Imatinib as the side effect profile for nilotinib is really bad.**

	Recorded in CML Patients treated with* Dasatinib*	Nilotinib*
Pleural effusion	+++	+/-
Pulmonary hypertension	+	+/-
Pericardial effusion	+	+/-
Viral reactivation	+	+/-
Increase in NK cells	++	+/-
Peripheral edema	++	++
Skin rash	+++	+++
Major bleeding	+	+
Diarrhea	+++	+++
Increase in fasting glucose	+/-	+++
Increase in pancreatic enzymes	+/-	+++
Progressive peripheral arterial occlusive disease	- (n.r.)**	++**

*+++, reported in >15% of all patients; ++, reported in 5-14% of all patients; +, reported in 1-4% of all patients; +/-, recorded in less than 1% of patients. *Data refer to previous studies performed in CML patients given dasatinib (100-140 mg daily) or nilotinib (2x300 or 2x400 mg*

-The doctor mentioned the underlying side effects Especially **pleural effusion** and **peripheral edema** as more common with **Dasanitib** except for **progressive peripheral arterial occlusive disease** which is more common with **Nilotinib** (it also causes clotting).

· That's why we generally avoid starting treatment with these drugs, as both have a broad and significant side effect profile.

Ponatinib:
A Pan-BCR-ABL Inhibitor

Rationally designed inhibitor of BCR-ABL

Active against T315I mutant

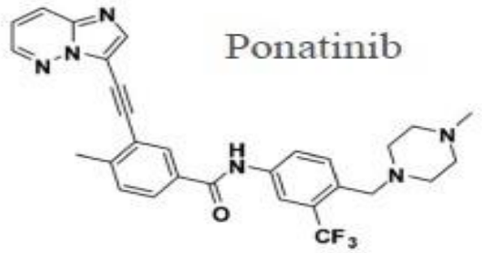
- Unique approach to accommodating gatekeeper residue
- Binds inactive (closed) ABL conformation

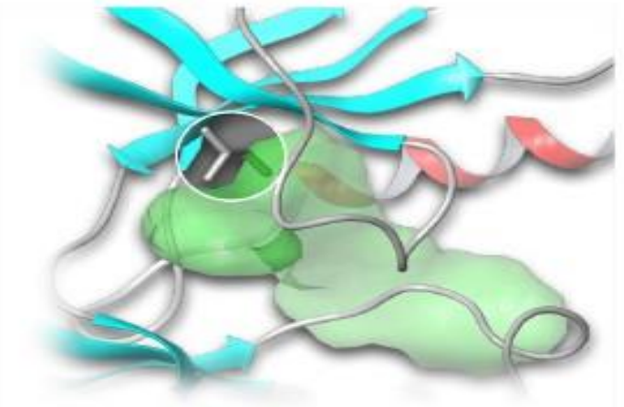
Broad spectrum of activity against an array of BCR-ABL variants

Multi-targeted kinase inhibitor

- Tyrosine kinases, including VEGF, FGF, and PDGF receptors, c-KIT and SRC kinase

Once-daily oral activity in murine models





Ponatinib cocrystal structure with ABL^{T315I}

- In **patients harboring the T315I mutation**, which **confers resistance to first- and second-generation tyrosine kinase inhibitors**, **Ponatinib** represents an **effective** therapeutic option.
- This agent is designed to bind to the ATP-binding pocket of the BCR-ABL kinase even in its closed conformation, thereby retaining activity regardless of the mutation's structural alterations. **Ponatinib** demonstrates **superior potency and efficacy compared with earlier TKIs**.
- However, its clinical use is limited by significant adverse effects, including hepatotoxicity, cardiotoxicity, arterial and venous occlusive events, and an increased risk of thrombosis.

Choosing the Right Drug According to the Mutation

· When a patient on imatinib develops resistance because of a mutation, the next treatment depends on the type of mutation found.

- If the mutation is **not** T315I: We can use **dasatinib** or **nilotinib**.
Dasatinib often causes **pleural effusion** and **peripheral edema**.
Nilotinib can cause **blood clots** and **arterial blockages**
- **Both** drugs can be **cardiotoxic**, so they should be used carefully in patients with heart disease.

· **If the mutation is T315I**:The drug of choice is **ponatinib**.
Ponatinib is effective because it can still bind to the BCR-ABL enzyme even when this mutation is present.
- However, it also has serious side effects, including **liver problems**, **heart issues**, and **blood vessel blockages.**

Pharmacology Quiz 6

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			