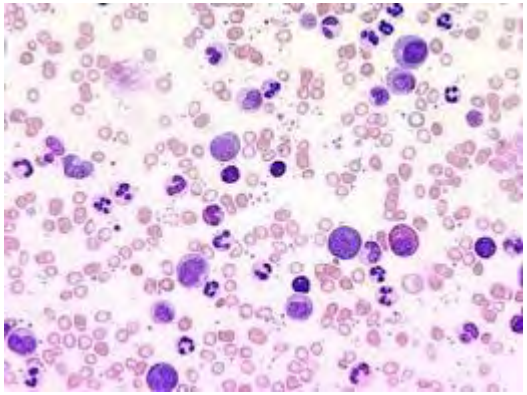
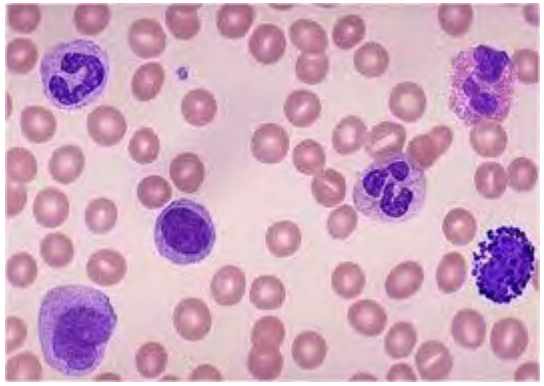
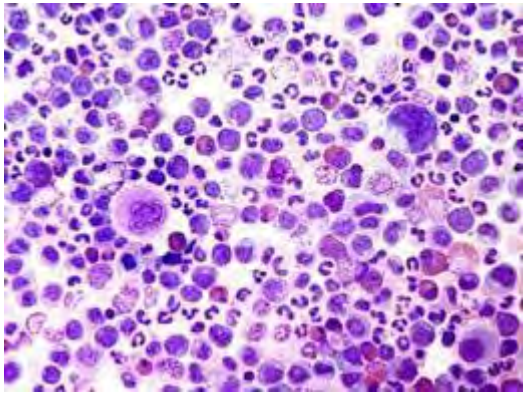
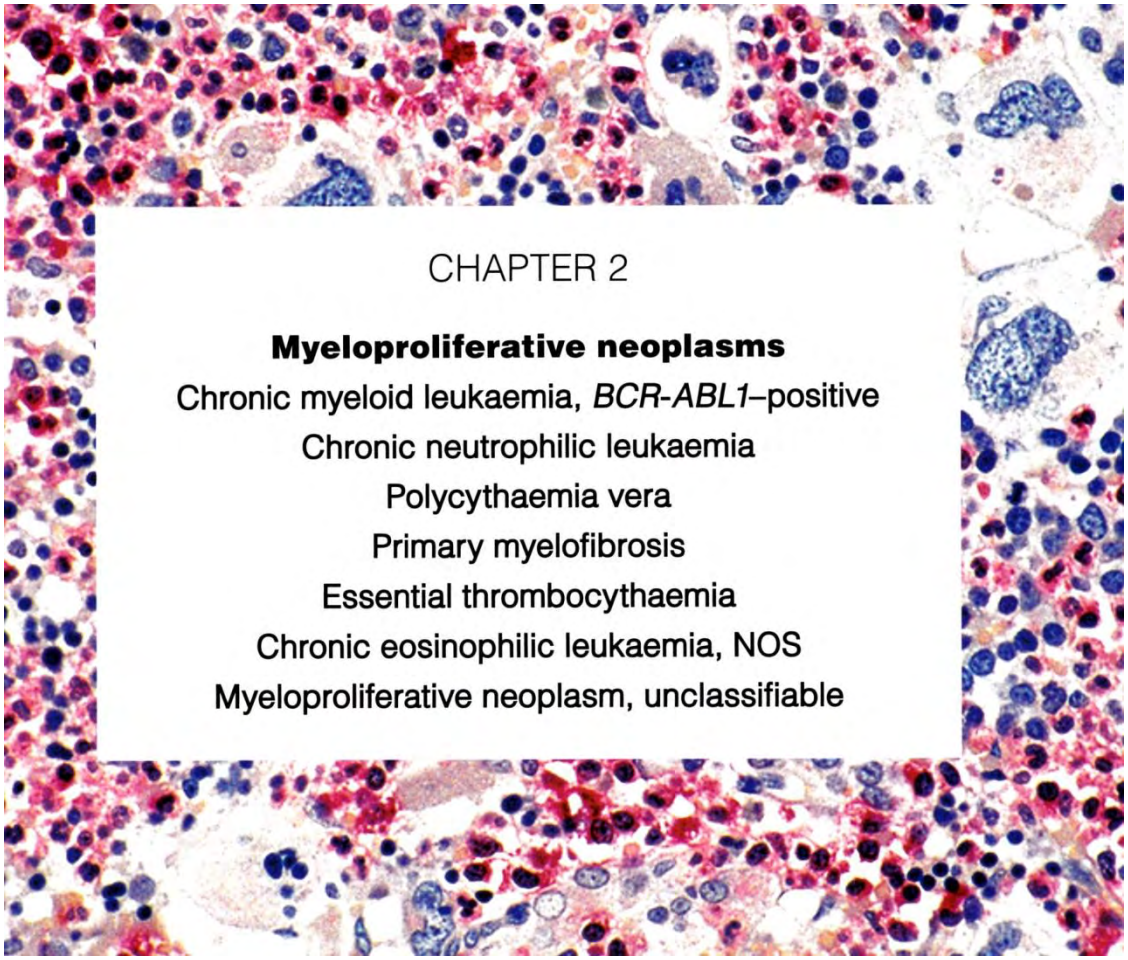
LEUCEMIA MIELOIDE CRONICA









CHAPTER 2

Myeloproliferative neoplasms

Chronic myeloid leukaemia, *BCR-ABL1*–positive

Chronic neutrophilic leukaemia

Polycythaemia vera

Primary myelofibrosis

Essential thrombocythaemia

Chronic eosinophilic leukaemia, NOS

Myeloproliferative neoplasm, unclassifiable

Definition of CML

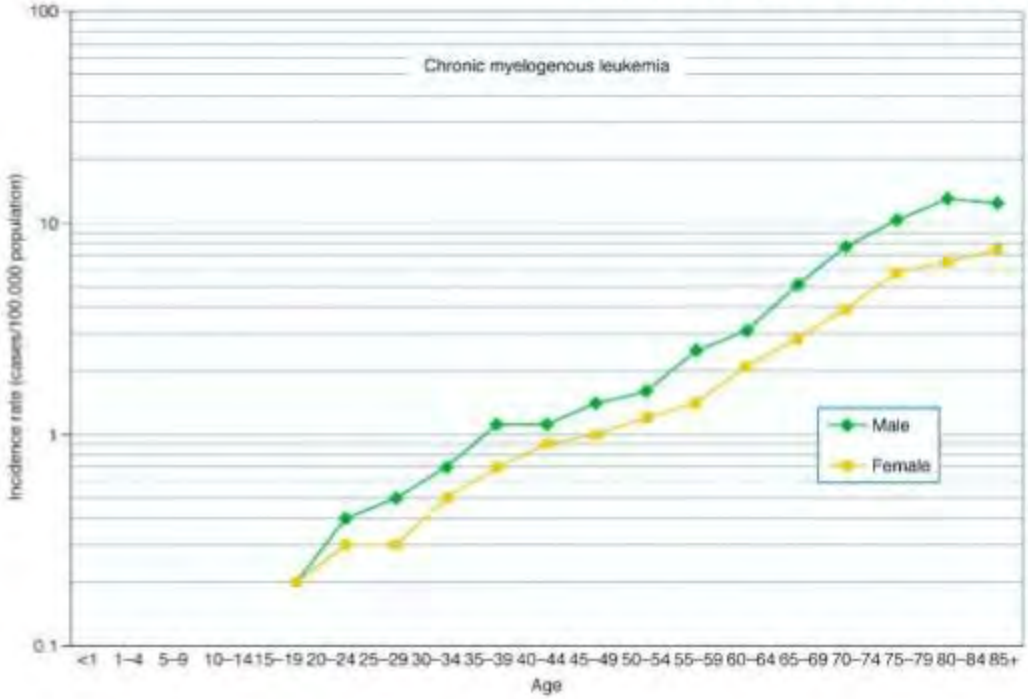
1. Clonal
2. Myeloproliferative disorder
3. Involves early progenitor hematopoietic stem cell.
4. Characterized by presence of Ph chromosome
5. And BCR-ABL fusion gene

A small subset (<5%) of CML is Ph -ve and BCR-ABL –ve

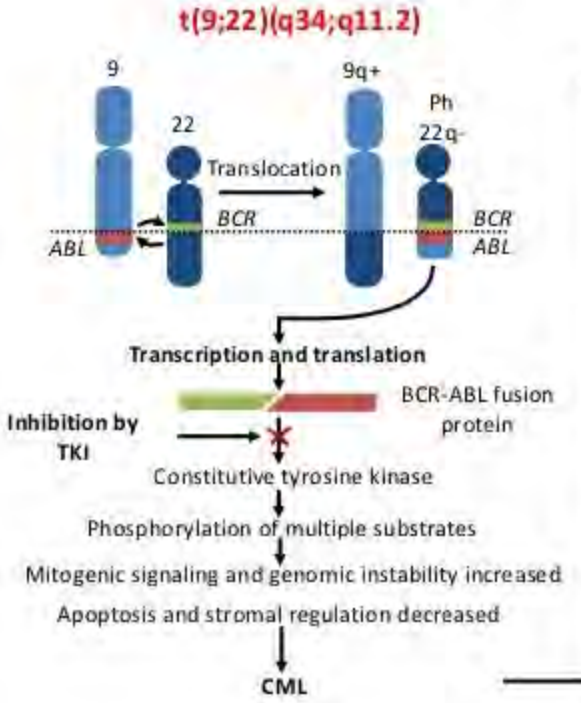
Epidemiology

- Incidence 1.5 cases per 100,000
- M:F - 1.6:1
- Median age 55-65 years
- Prevalence increasing every year (plateau at 20 years)

EPIDEMIOLOGY



Philadelphia Chromosome Translocation in CML Results in BCR-ABL Oncogene



- Gene Transcription
- Inhibits Apoptosis
- Excessive proliferation
- Cytoskeletal organization
- Degradation of inhibitory proteins

Cell lines affected

1. Erythroid
2. Myeloid
3. Monocytic
4. Megakaryocytic
   - Less commonly- B cells
   - Rarely- T cells and marrow fibroblasts

ETIOPATHOGENESIS

1. **Environmental Leukemogens**
   - Very high doses of ionizing radiation*
   - Chemical leukemogens - benzene and alkylating agents – are not causative – increased incidence of AML
   - No concordance of the disease between identical twins
   - Several large studies – no links with smoking/diet/lifestyle

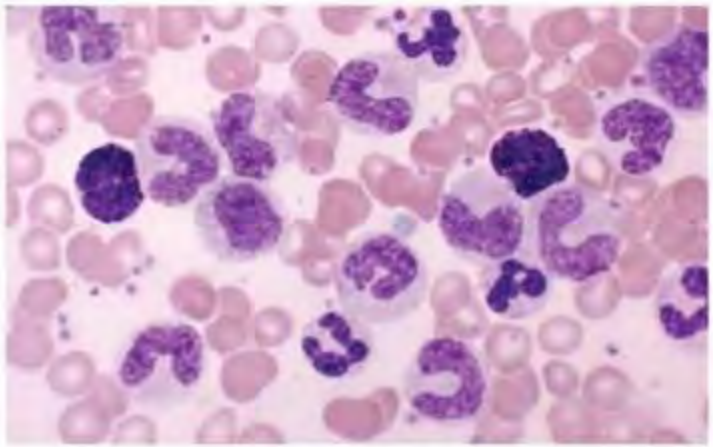
DIAGNOSIS

A. Laboratory studies

Blood counts and blood smear

- Hemoglobin concentration is decreased
- Nucleated red cells in blood film
- The leukocyte count above 25,000/µl (even > 1,00,000/µl),
- Hypersegmented neutrophils
- The basophil and eosinophil counts are increased (Absolute)
- The platelet count is normal or increased
- Blast cells ~ 3 % (<10% in the chronic phase)

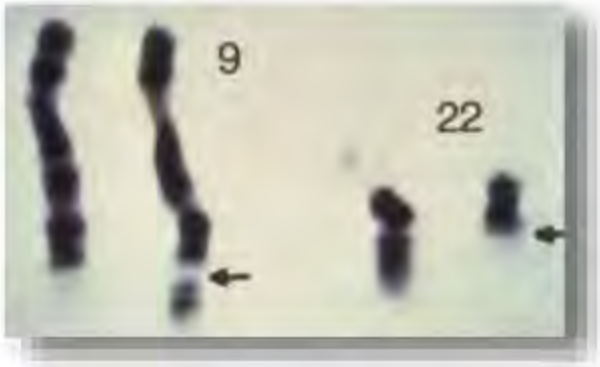
A. Laboratory studies



Peripheral smear

B. Cytogenetics

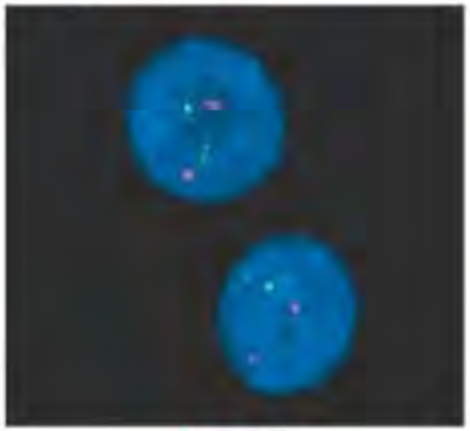
- Study of the number and structure of chromosomes
- Samples from bone marrow myeloid cells
- The presence of the Philadelphia chromosome – shortened chromosome 22*
- Cytogenetics cannot identify complex translocations



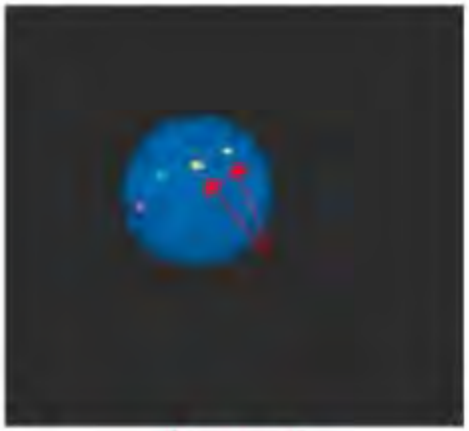
C. Molecular Probes

i. *FISH (Fluorescence In Situ Hybridization)*

- *Detect the BCR-ABL* fusion gene on chromosome 22
- Qualitative



Normal



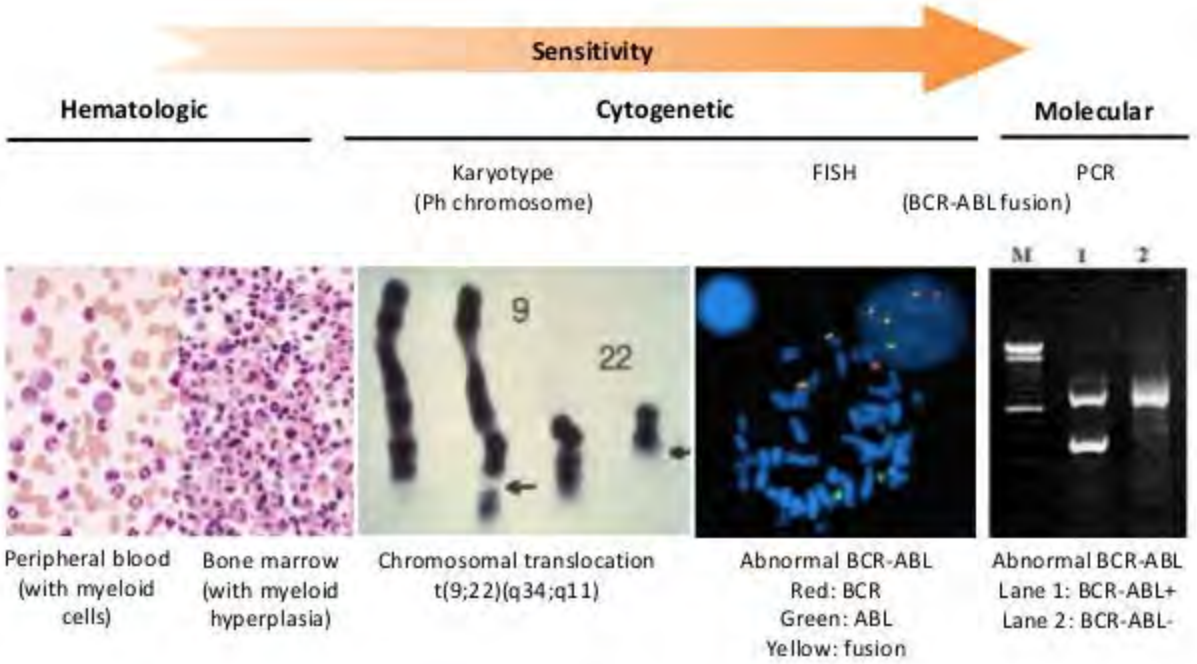
Abnormal

C. Molecular Probes

ii. PCR (Polymerase Chain Reaction)

- Most sensitive test to identify and measure the *BCR-ABL* gene (Quantitative)
- Can be performed on blood/marrow cells
- Amplifies the BCR-ABL derived abnormal mRNA
- One abnormal cell in one million cells can be detected

Diagnosis of CML



CLINICAL FEATURES

A. Symptoms

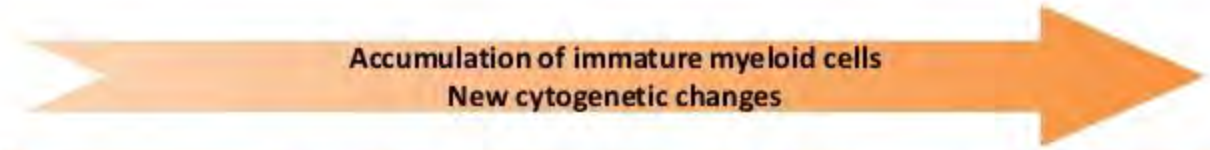
- At diagnosis – 70% symptomatic
  - Easy fatigability
  - Loss of sense of well-being
  - Decreased tolerance to exertion
  - Anorexia
  - Abdominal discomfort
  - Early satiety *
  - Weight loss
  - Excessive sweating

A. Symptoms

- Uncommon symptoms
  - Night sweats
  - Heat intolerance

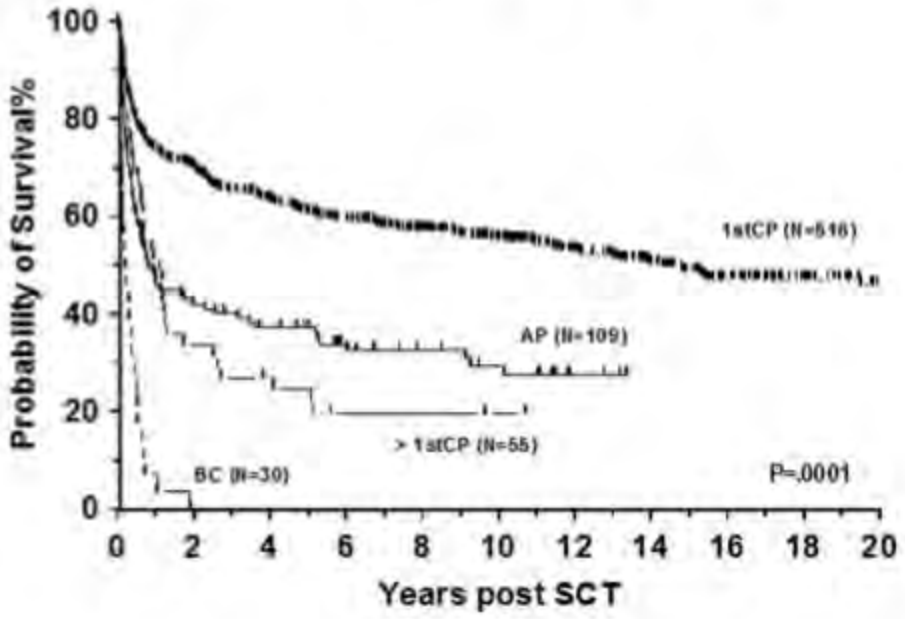
  ] Mimics thyrotoxicosis
  - Gouty arthitis
  - Left upper-quadrant and left shoulder pain*
  - Urticaria
  - Hyperleukocytic Syndrome —dyspnea, tachypnea, hypoxia, lethargy, slurred speech

Natural History of CML



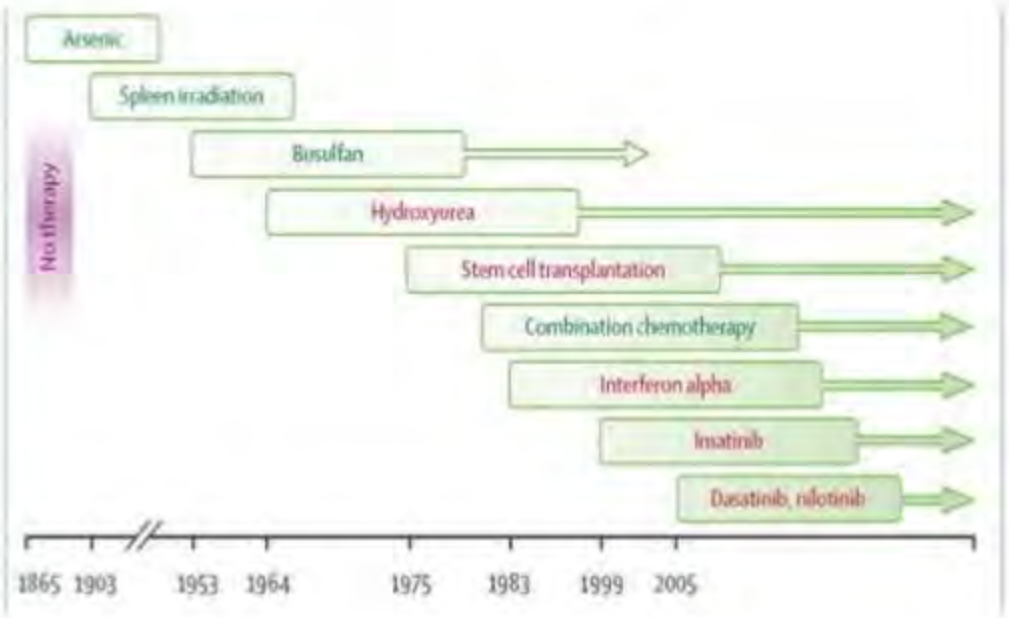
	Chronic Phase	Accelerated Phase	Blast Phase
Duration	If untreated, 3-5 yrs	Varies	Median survival of several mos
Prognosis	Responsive to treatment	Decreased responsiveness	Resistant to treatment
Symptoms	Asymptomatic **OR** Fatigue Weight loss Abdominal pain or discomfort Night sweats	Progressive splenomegaly Myelofibrosis	Bleeding complications Infection complications

Long term outcomes with Allo- HSCT

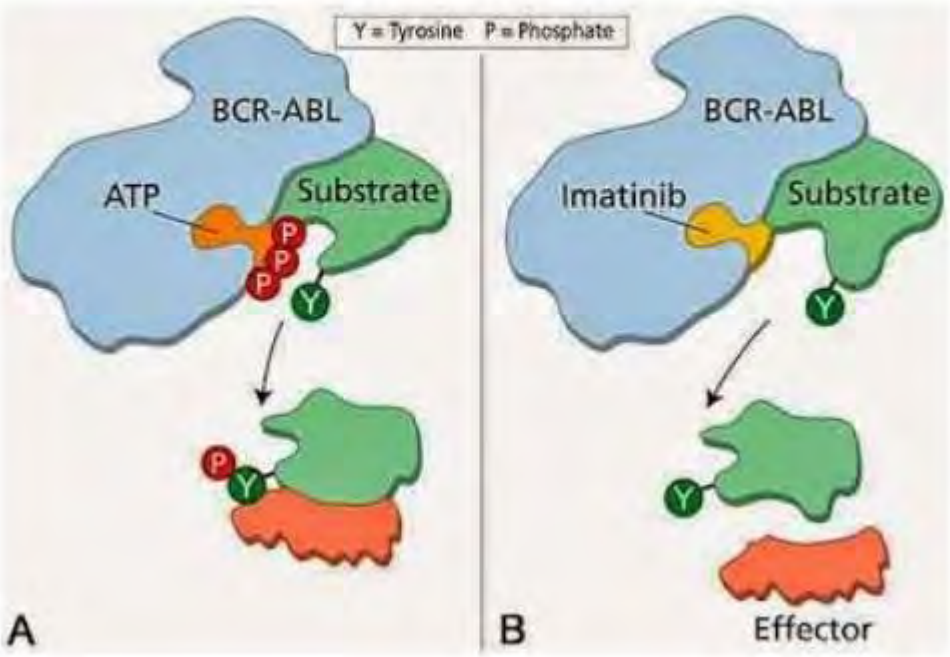


Hammersmith Hospital, London,

Evolution of Therapy for Chronic Myeloid Leukemia

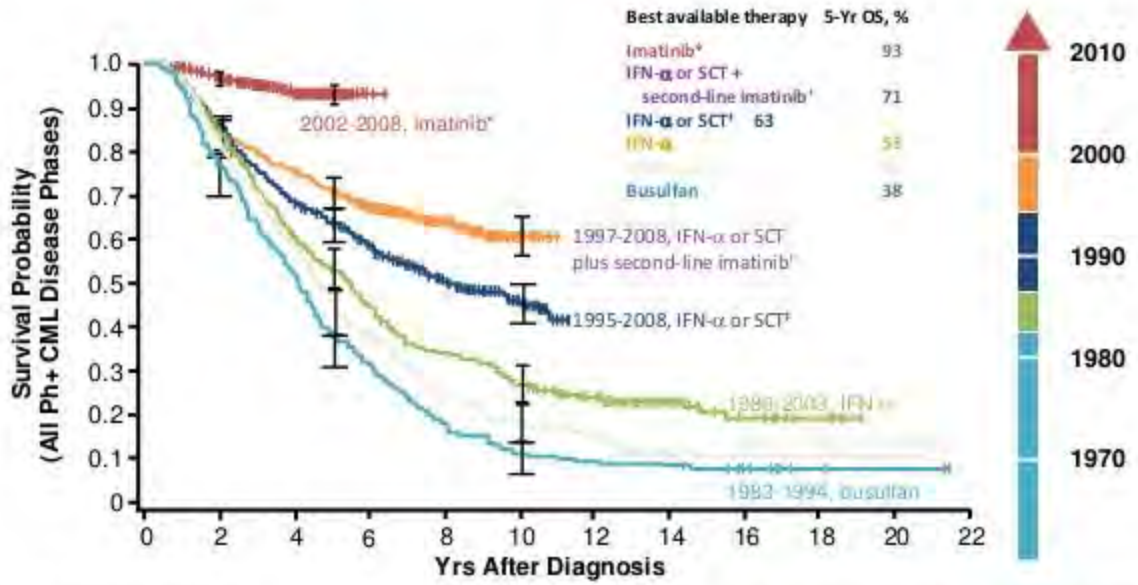


Era of Tyrosine Kinase Inhibitors



l'imatinib è un
potente inibitore della tirosin chinasi c-kit che agisce legandosi al sito dell'ATP impedendo all'enzima di fosforilare i substrati.

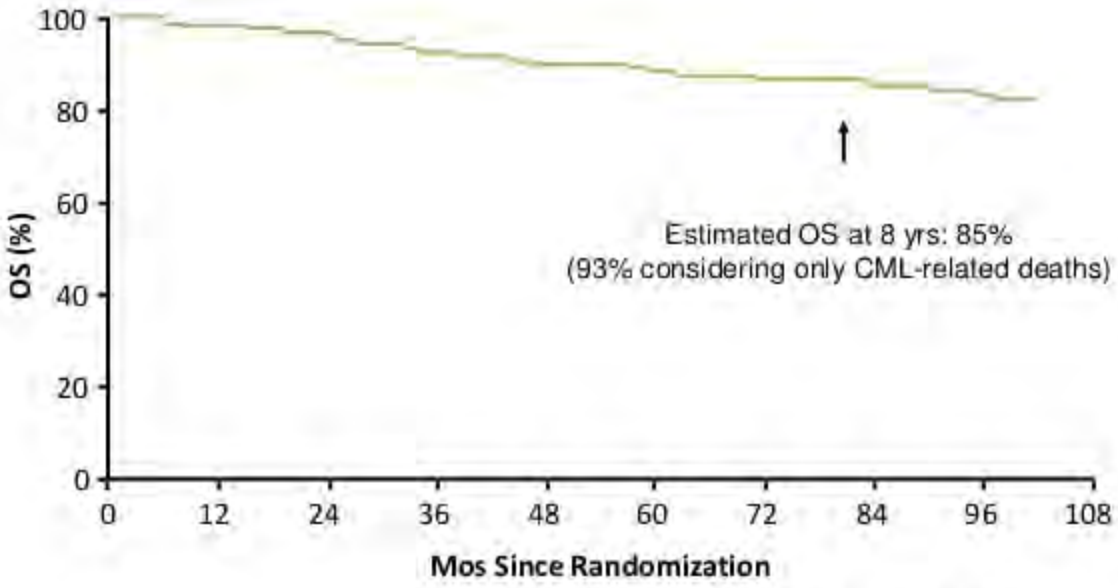
Imatinib Changed the Therapeutic Landscape for Patients With Ph+ CML



*CML IV. †CML IIIA. ‡CML III.

Leitner AA, et al. Internist (Berl). 2011;52:209-217

IRIS 8-Yr Update: OS (ITT) With Imatinib Treatment in CML



Deininger M, et al. ASH 2009. Abstract 1126.

2. Tyrosine Kinase inhibitor therapy

Imatinib Mesylate

90-96%

Cytogenetic Response (CyR)	
Complete (CCyR)	Ph+ 0%
Partial (PCyR)	Ph+ 1%-35%
Minor	Ph+ 36%-65%
Minimal	Ph+ 66%-95%
None	Ph+ >95%
Major – partial + complete	

2. Tyrosine Kinase inhibitor therapy

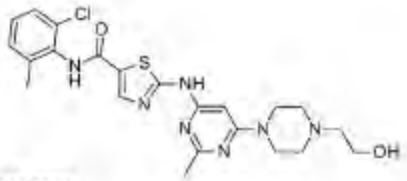
Imatinib Mesylate

~63%

Molecular Response (MR) [*BCR-ABL* to control gene ratio	
Complete	Transcripts nonquantifiable and nondetectable
Major (MMR)	≤0.1%*

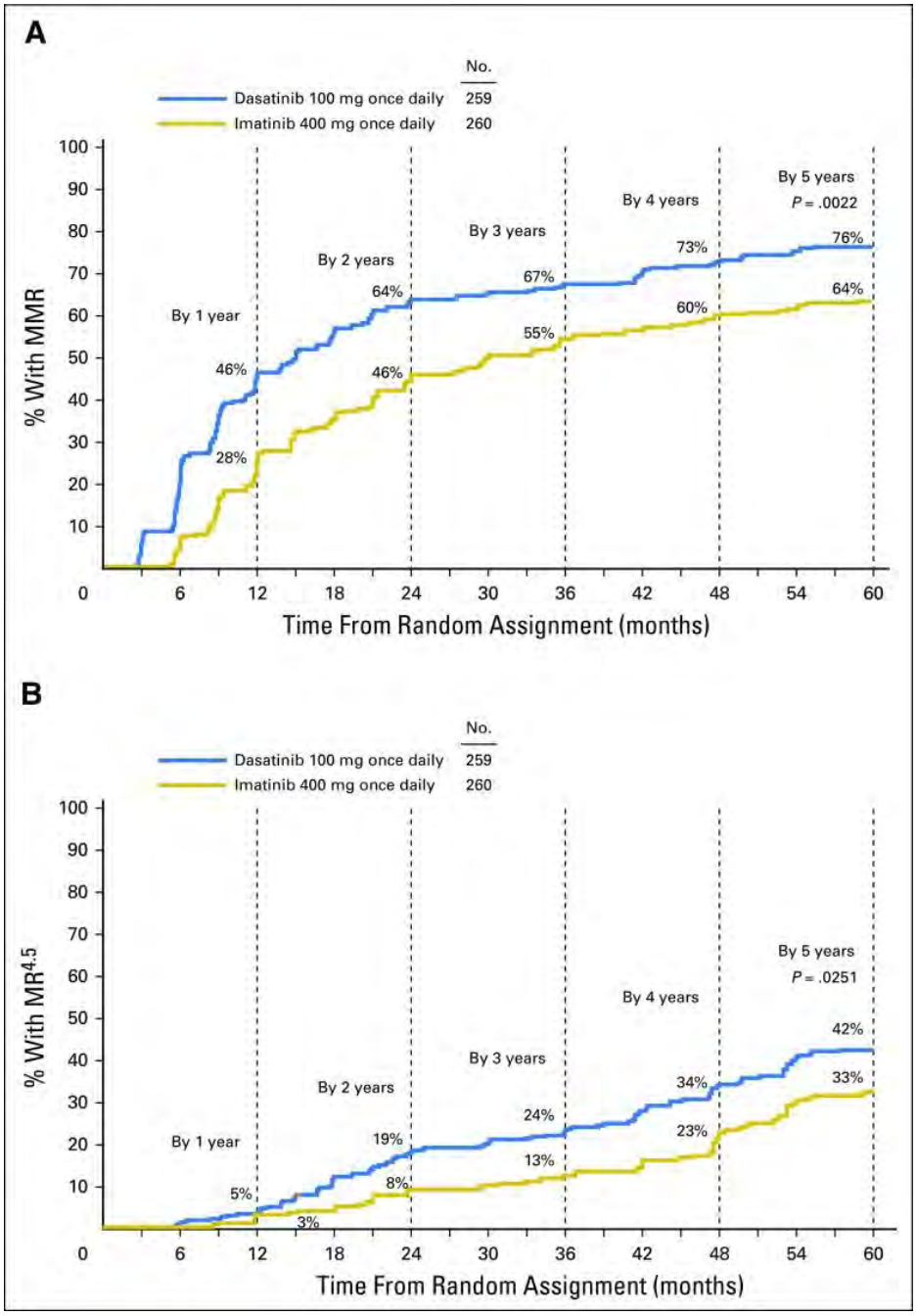
2. Tyrosine Kinase inhibitor therapy

2nd Generation TKI



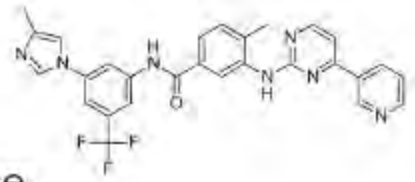
1. *Dasatinib*
   - Used in imatinib resistance or intolerance
   - 325-fold more potent than imatinib
   - 100 mg/day, administered in chronic phase CML
   - Unlike imatinib, dasatinib penetrates the blood–brain barrier
   - Cytopenia, followed by fluid retention, diarrhea, and skin rash

DASATINIB


A
No.
Dasatinib 100 mg once daily 259
Imatinib 400 mg once daily 260
% With MMR
By 1 year
By 2 years
By 3 years
By 4 years
By 5 years
P = .0022
46%
28%
64%
46%
67%
55%
73%
60%
76%
64%
Time From Random Assignment (months)
B
No.
Dasatinib 100 mg once daily 259
Imatinib 400 mg once daily 260
% With MR4.5
By 1 year
By 2 years
By 3 years
By 4 years
By 5 years
P = .0251
5%
3%
19%
8%
24%
13%
34%
23%
42%
33%
Time From Random Assignment (months)

2. Tyrosine Kinase inhibitor therapy

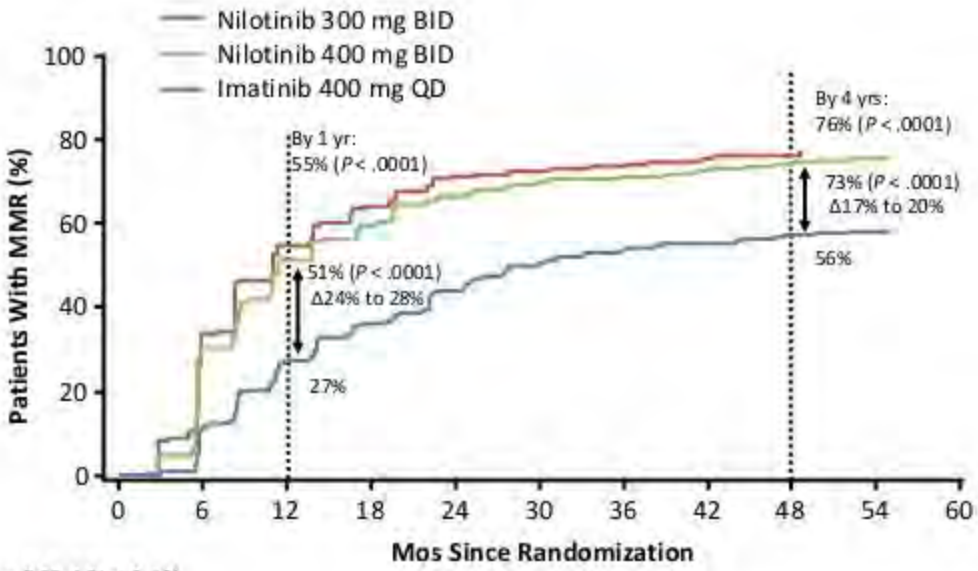
2nd Generation TKI



2. *Nilotinib*
   - Used in imatinib resistance or intolerance
   - 30 times more potent than imatinib
   - ATP-competitive inhibitor of BCR-ABL
   - 400 mg every 12 hours
   - Neutropenia, hyperbilirubinemia, hypophosphatemia, QT interval prolongation
   - Imatinib and nilotinib in combination may have additive or synergistic effects

NILOTINIB

ENESTnd 4-Yr Update: Cumulative Incidence of MMR in CP CML

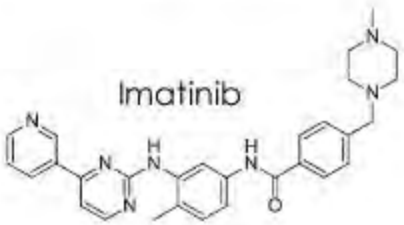


MMR = BCR-ABL ≤ 0.1%.

Kantarjian HM, et al. ASH 2012. Abstract 1676.

2. Tyrosine Kinase inhibitor therapy

- First generation
  - Imatinib



- Second generation
  - Dasatinib
  - Nilotinib
  - Bosutinib
  - Ponatinib
  - Bafetinib

8. Treatment cessation

- Despite achieving deep and lasting remissions
- CML is not curable
- Patients with remissions still have residual CML cells (PCR)
- Available evidence suggests that people who receive TKIs may remain in remission for very long periods
- Research still underway