Evolving Treatment of Chronic Myeloid Leukemia (CML)

F.M. Siddiqui
Prof. of Medicine

Myeloproliferative disorder

- Chronic Myeloid Leukemia(CML)
- Polycythemia vera (PV),
- Essential thrombocythemia (ET)
- Primary myelofibrosis

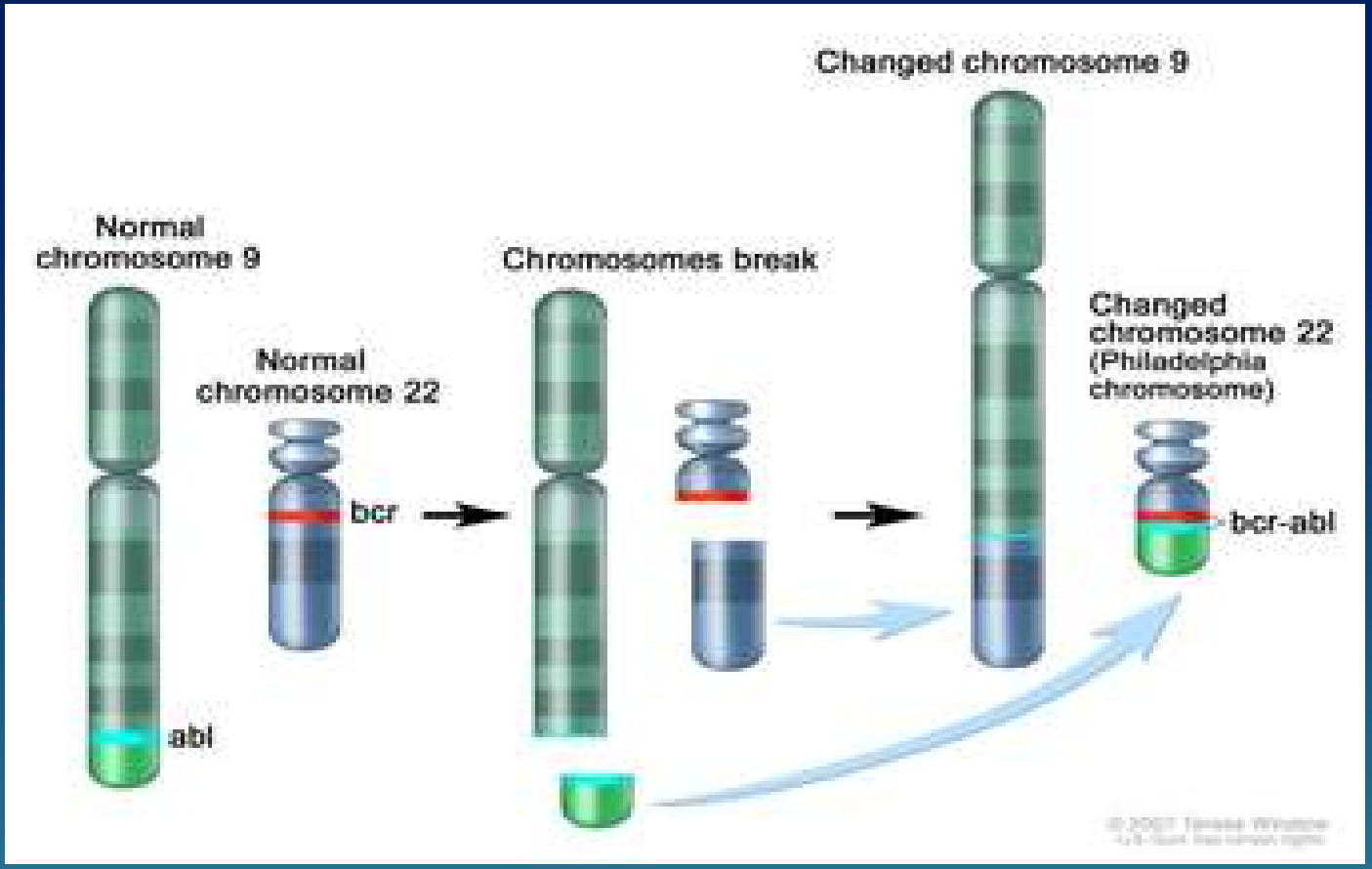
This group of diseases shares several distinct features:

- They are clonal disorders of hematopoiesis that arise in a hematopoietic stem or early progenitor cell.
- They are characterized by the dysregulated production of a particular lineage of mature myeloid cells with fairly normal differentiation.
- They exhibit a variable tendency to progress to acute leukemia.

Cyto-genetic disorder

- CML is associated with the Philadelphia chromosome t(9;22)(q34;q11)
- This genetic abnormality results in the formation of a unique gene product (BCR-ABL1)
- This is a constitutively active tyrosine kinase implicated in the development of CML
- This has become a primary target for the treatment of this disorder.

Philadelphia Chromosome



Treatment of Chronic Myeloid Leukemia (CML)

DISEASE PHASE

There are three general disease phases:

- Chronic stable phase
- Accelerated phase
- Blast crisis

OVERVIEW OF TREATMENT OPTIONS

Available treatment options include:

- Potential cure with allogeneic hematopoietic cell transplantation (HCT)
- Disease control without cure using tyrosine kinase inhibitors (TKIs)
- Palliative therapy with cytotoxic agents

Treatment of CML

- Before Tyrosine Kinase Inhibitors (TKIs)
- After Tyrosine Kinase Inhibitors (TKIs)

Before the era of TYSOSIN KINASE INHIBITORS (TKIs)

Palliative treatment

1. Busulfan
2. Hydroxiurea
3. Interferon Alpha with or without cytarabin

- Interferon therapy had been the standard of care prior to the availability of imatinib
- These are considered palliative therapy since they are not curative, do not prolong overall survival, and only rarely result in attainment of a cytogenetic response.

Tyrosine Kinase Inhibitors (TKIs)

- The development of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of CML
- The first drug to be introduced in this category is **Imatinib** approved by USFDA in 2001
- TKIs are the initial treatment of choice for the majority of patients with CML.

First generation TKIs

- Imatinib (400mg PO/day)

Second generation TKIs

- Nilotinib(300mg twice/day)
- Dasatinib(100mg once/day)
- Bosutinib(500mg/day)
- Ponatinib (45 mg/day in patient with T3151 mutations)

Second generation TKIs (Cont.)

- Second generation TKIs that have been studied most extensively are dasatinib, nilotinib, and bosutinib.
- Dasatinib and nilotinib have been approved by the US Food and Drug Administration for Treatment of patients with previously untreated CML
- Recommended for patients intolerant or have a primary or secondary resistance to imatinib.
- Patients of accelerated / blast phase before HCT

Hematopoietic cell transplantation

- Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment option
- HCT is associated with increased morbidity and mortality, despite the possibility of cure.
- HCT is currently not offered as initial therapy, except in rare circumstances

Monitoring Response

- Response is assessed with standardized real quantitative polymerase chain reaction and/or cytogenetics at 3, 6, and 12 months.

Response criteria

Responses are defined in the following categories:

1. Hematologic response
2. Cytogenetic response &
3. molecular response

Hematologic response

Complete hematologic response (CHR) is defined by

- White blood cell count <10000/microL with no immature granulocytes
- <5 percent basophils on differential
- platelet count <450,000/microL
- spleen not palpable.

Cytogenetic response

Cytogenetic response is assessed by chromosome banding analysis

Classified according to the percent of Philadelphia chromosome positive cells

- No response (>95 percent),
- Minimal (66 to 95 percent),
- Minor (36 to 65 percent),
- Major (1 to 35 percent), and
- Complete Cytogenetic Response(CCyR) (no Philadelphia chromosome positive cells).

Cytogenetic response (Cont.)

Fluorescence In Situ Hybridization(FISH):

Complete cytogenetic response can also be documented by **Fluorescence In Situ Hybridization(FISH)** of peripheral blood interphase cell nuclei demonstrating <1 percent BCR-ABL1-positive nuclei of at least 200 nuclei.

Molecular response

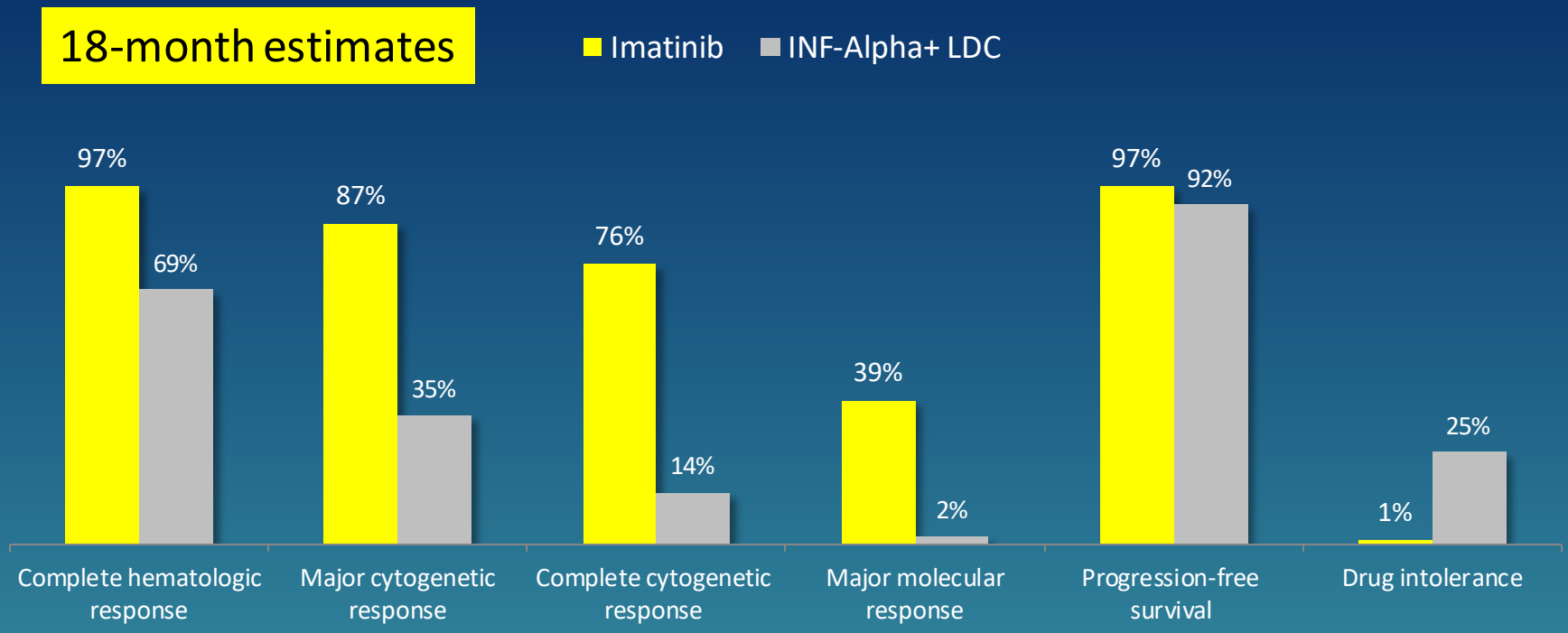
Molecular response is assessed by real quantitative PCR (Q-PCR) of the peripheral blood and defined according to the level of detection of the assay.

- **Response is assessed at 3, 6 and 12 months.**
- BCR-ABL1 transcript levels≤10% at 3 months,<1% at 6 months, and≤0.1% from 12 months onward define **optimal response**
- >10% at 6 months and>1% from 12 months onward define **failure**

European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013 Aug;122(6):872-84. Epub 2013 Jun 26.

IRIS trial

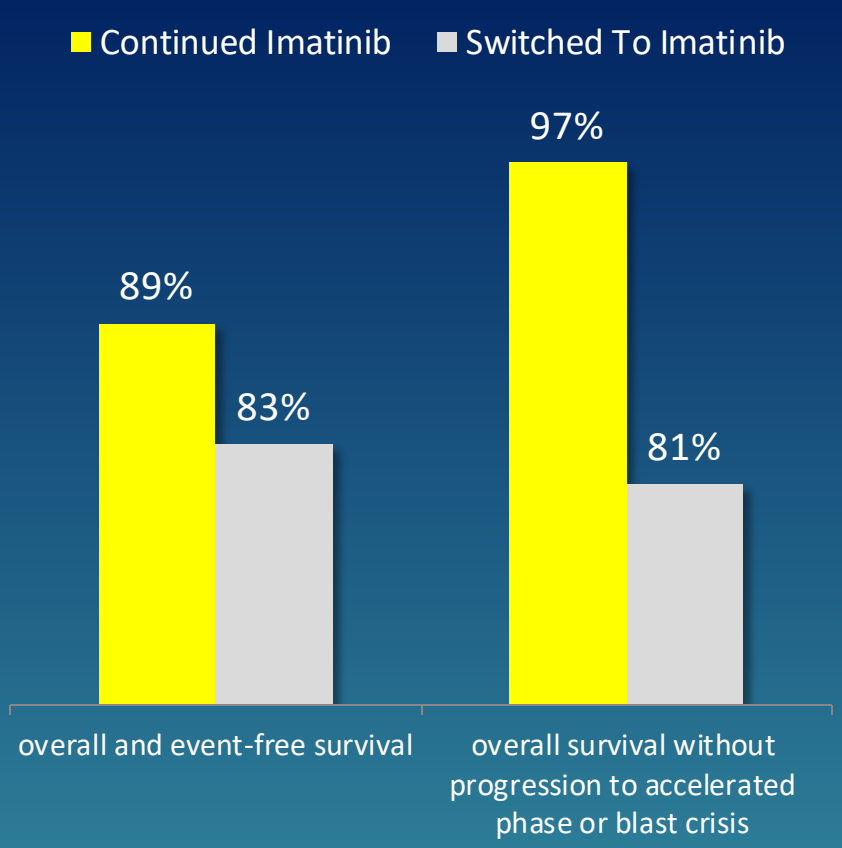
Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia.

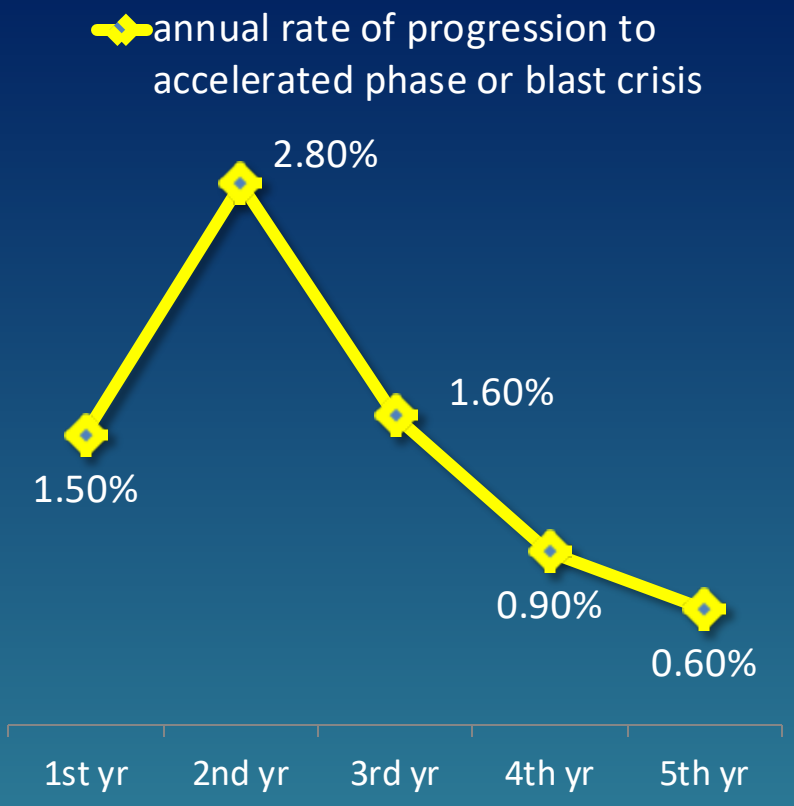


N Engl J Med. 2003;348(11):994.

IRIS trial

5 year follow up





N Engl J Med. 2006;355(23):2408.

IRIS trial

8 years follow up

Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib.

Blood. 2009;114:126.

Duration of treatment

- Once optimal response is achieved therapy with the TKI is continued indefinitely at the same dose as tolerated.
- Patients who continue imatinib progress at an annual rate of 0.6 per year onwards after 5 years
- The relapse rate in patients who have achieved a complete cytogenetic response is very low
- If a TKI is discontinued, a substantial proportion of patients relapse (over 50 percent during the next year) since tumor cells remain in a quiescent state despite therapy

Rousselot P et al Blood. 2007;109(1):58.

Treatment of chronic myeloid leukemia in accelerated phase

WHO defined the accelerated phase by the presence of one or more of the following features:

- 10 to 19 percent blasts in the peripheral blood or bone marrow
- Peripheral blood basophils ≥20 percent
- Platelets <100,000/microL, unrelated to therapy
- Platelets >1,000,000/microL, unresponsive to therapy
- Progressive splenomegaly and increasing white cell count, unresponsive to therapy
- Cytogenetic evolution (defined as the development of chromosomal abnormalities in addition to the Philadelphia)

Treatment overview

- If patient is on Imatinib dose may be increased to 600mg/day
- Mutation analysis and using specific TKIs
- Second generation TKIs Nilotinib,Dasatinib Bosutinib
- Hematopoietic Cell Transplantation(HCT)
- Omacetaxine

Treatment of chronic myeloid leukemia in Blast Crisis

WHO defines blast crisis by the presence of one or more of the following findings:

- ≥20 percent peripheral blood or bone marrow blasts
- Large foci or clusters of blasts on the bone marrow biopsy
- Presence of extramedullary blastic infiltrates (eg, myeloid sarcoma also known as granulocytic sarcoma or chloroma)

Types of Blast Crisis

Myeloid Blast Crisis (AML)-70%

- Preferred treatment is seond line TKIs followed by allogenic HCT

Types of Blast Crisis (Cont.)

Lymphoid Blast Crisis (ALL)-30%

- Treated as Ph+ ALL(combination chemotherapy)
- Allogenic HCT

Conclusion

- The understanding of the chromosomal abnormalities in CML with the advent of TKIs completely changed the treatment scenario and prognosis of the disease.
- Only a small number of patients would be required to opt for HCT
- Robust studies with 1st and 2nd generation TKIs are in progress and showing encouraging results.
- Disease free survival of CML patients (in absence of other co morbidities) with TKIs may lead to almost normal life expectancy.


Thank you!