RESPONSE TO IMATINIB THERAPY IN CHRONIC MYELOID LEUKEMIA PATIENTS ATTENDING HAEMATOLOGY CLINIC OF NORTH OKKALAPA GENERAL AND TEACHING HOSPITAL

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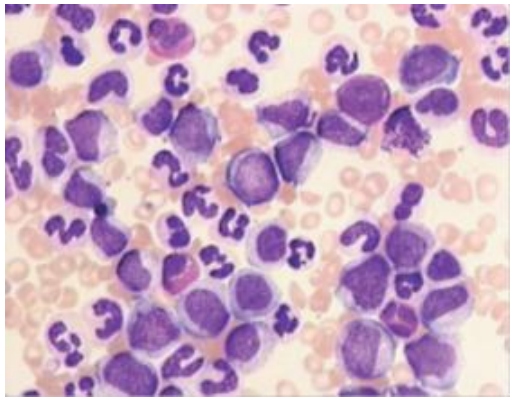
Introduction

Chronic myeloid leukemia (CML)

- acquired myeloproliferative disorder
- clonal expansion of haemopoietic stem cells
- gradually displacing normal haemopoiesis
- greatly expanded total myeloid mass
- 15 % of adult leukemias

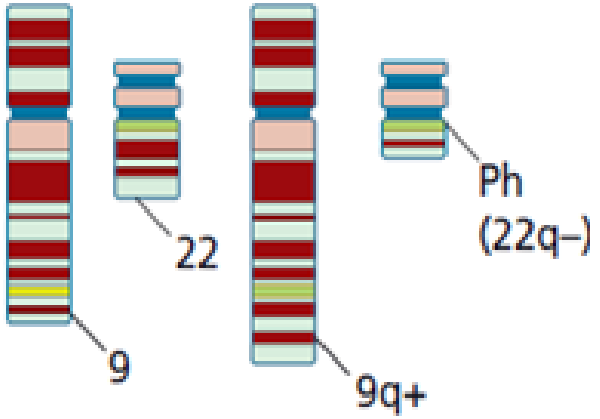


Three different clinical phases:

- **Chronic phase**: progress to advanced phase in 3-5 years without specific therapy

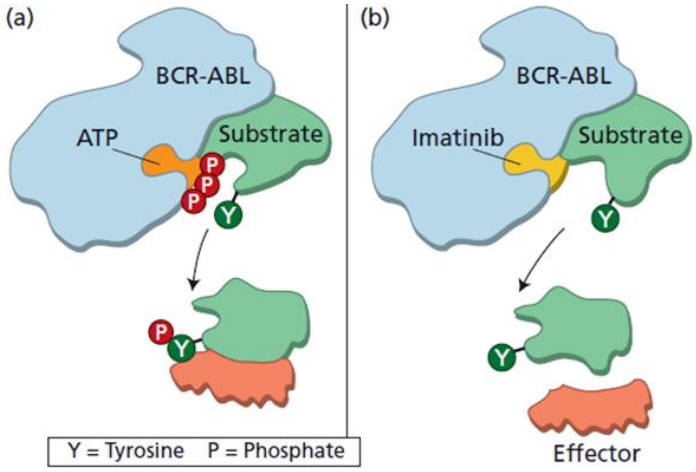
- **Accelerated phase**
- **Blast phase**: survival -three to six months

Philadelphia chromosome (hallmark of CML)



- a reciprocal translocation between long arms of chromosomes 9 and 22
- head-to-tail fusion of ABL 1 gene and BCR gene
- production of BCR-ABL 1 fusion gene
- encodes for a fusion protein with deregulated tyrosine kinase activity

Imatinib Mesylate



- ***selective inhibitor of BCR-ABL 1 tyrosine kinase***
- ***the world's first targeted therapy***
  - a revolutionary change in CML management
  - ***International Randomized Study of Interferon vs STI 571(IRIS)***
    - newly Dxed CML patients treated with imatinib
    - at median follow up of 19 months
    - ***73.8 % achieved complete cytogenetic response*** compared to only 8.5 % in patients treated with interferon plus cytarabine

Monitoring of Treatment Response

- ✓ **Heamatologic response**
- ✓ **Cytogenetic response**
- ✓ **Molecular response**
  - in patients treated with imatinib, achievement of cytogenetic response is an important prognostic indicator for long term survival (Druker et al., 2006) (Lavallade et al., 2008)

CML in Myanmar

- paucity data related to Myanmar CML patients
- molecular detection of BCR-ABL transcript has been available to most of the patients only in the recent years
- Ministry of Health has started supplying imatinib to the patients 2015
- Haematology Clinic at the NOGTH is one of the centers providing treatment

Aim

- to observe the response to imatinib therapy in chronic phase CML patients

Methods

- Period: 1st January 2014 to 31st December 2016 (Three years)
- Record review: medical records and follow up data of CML patients attending to the clinic were retrospectively reviewed
- Inclusion criteria: **Chronic phase** CML receiving Imatinib
- Exclusion criteria: accelerated phase and blast phase patients were excluded by using WHO (2008) criteria

WHO criteria for accelerated and blast phases of CML (2008)

❖ Accelerated phase (any one or more)

- Blasts (myeloblasts) 10 – 19% of white blood cells in peripheral blood and/or of nucleated bone marrow cells
- Peripheral blood basophils ≥ 20%
- Persistent thrombocytopenia (< 100 × 109/L) unrelated to therapy, or persistent thrombocytosis (> 1000 × 109/L) unresponsive to therapy
- Increasing spleen size and increasing white blood cell count unresponsive to therapy
- Cytogenetic evidence of clonal evolution

❖ Blast phase (any one or more)

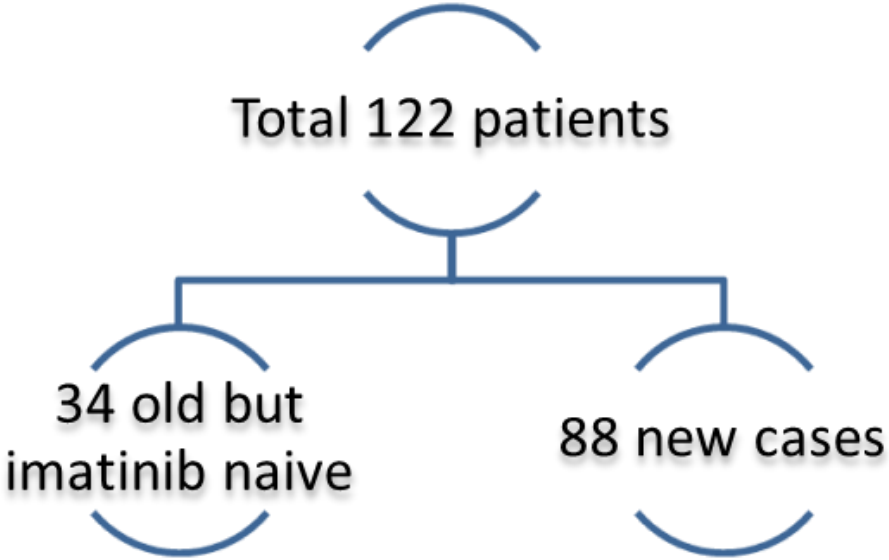
- Blasts > 20% of peripheral white blood cells or of nucleated bone marrow cells
- Extramedullary blast proliferation
- Large foci or clusters of blasts in the bone marrow biopsy

Methods- cont.

- **Diagnosis Confirmation**: molecularly by ***BCR-ABL transcript detection***
- **Treatment:** All patients received ***imatinib 300 mg to 800 mg per day***
- Demography, date of diagnosis, blood counts, spleen size at diagnosis, imatinib dose, tolerability, the side effects and its outcome in terms of remission status and haematologic response, cytogenetic response and molecular response when feasible were reviewed
- **Follow up**: minimum follow up 6 months
  - most patients had been monitored with blood counts only
  - cytogenetic and molecular assessment was done only in few patients who were affordable

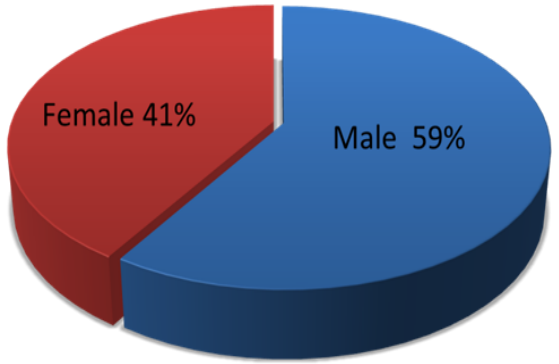
Results

- within three years period



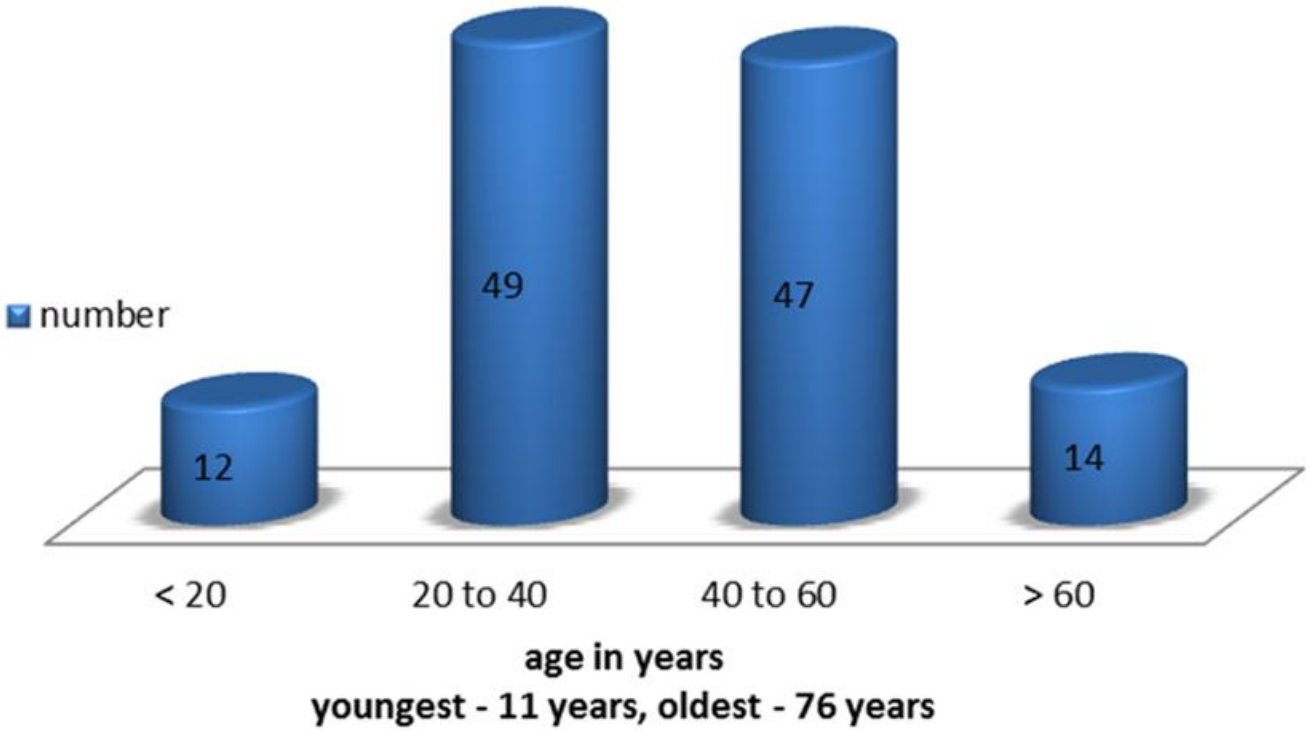
Gender

- male to female ratio of 1.4:1



Age

- median age at diagnosis was 42 years (range 11 – 76)
- 78.68 % were between 20 to 60 years



Duration of symptoms

- < 6 months – 16 (13.11%)
- 6 – 12 months – 28 (22.95%)
- 12 -24 months – 44 (36.07%)
- > 24 months – 34 (27.87%)

Spleen size at diagnosis

- Not palpable (splenomegaly with USG) – 9 (7.38%)
- < 10 cm (from left costal margin) – 33 (27.05%)
- ≥ 10 cm (from left costal margin) – 80 (65.57%)

Haematological parameters

	Median	Range
Total WBC at diagnosis (x 109/L)	221.95	23.32 - 685
Hb at diagnosis (mg/dl)	9.2	2.7 - 15.6
Platelet at diagnosis (x 109/L)	495	39 – 2101

Risk Score

- 105 patients were low risk, 15 were intermediate risk, 2 were high risk according to **Sokal score** and 116 patients were low risk, 6 were intermediate risk and no high risk patient according to **Hasford score**

Follow Up

median follow up of 24 months (range 6 – 127 months)

- 14 (11.48%) progressed to accelerated phase
- 17 (13.93%) got blast crisis (16 died, 1 lost to follow up)
- 9 (7.38%) were lost to follow-up
- 82 patients (67.21%) were still in haematological remission

Cytogenetic and Molecular Response

- 17 patients (cytogenetic & molecular assessment after 1 year of treatment)
- Complete cytogenetic response: 15 (88.24%)
- Molecular response: 6 cases (35.29%) BCR-ABL transcript below detection limit by RT-PCR
- All these patients received imatinib within 6 months of symptoms and at Dx

Side effects

- 78 patients (63.93%) had no side effect
- 18 (14.75%) got mild GI discomfort
- 12 (9.84%) experienced mild muscle aches
- 3 patients developed significant thrombocytopenia
  - one had to reduce imatinib 300 mg OD for one year
  - another one had to be maintained on imatinib 300 mg OD
  - the third got pancytopenia in which bone marrow revealed as aplastic anaemia, later developed blast crisis
  - one patient got generalized oedema and one got severe bone pain, resolved by temporary withdrawn of imatinib

Discussion

❖median age of onset

- 42 years
- 50 – 60 years with slight male preponderance in the west
- Thailand 36 – 38 years (Au et al, 2008)
- Asia Collaboration of CML Research data in 2011 revealed the incidence is highest among 30 to 40 years of age

Haematological response rate in this study - **67.21%**

Response rates to imatinib in Asian CP-CML patients (Au et al.,2008)

Country, reference	Patients number	Complete haematology response(%)	Major cytogenetic response(%)	Complete cytogenetic response(%)
IRIS Trial; O'Brien et al.	553	95	85	74
Europe; Lahaye	139	97	61	49
US; Cortes et al.	488	98	83	77
China; Jiang et al.	54	98	70	51
Hong Kong	49	100	Not reported	88
India; Arora et al.	79	96	30	24
The Philippines	Not reported	91	45-52	Not reported
Singapore	48	Not reported	61	49
South Korea	171	100	90	84
Thailand	96	90	70	55

Reason for lower response rate

- Haematological reeponse rate lower than other countries (67.21%)

➢ late presentation and initiation of therapy

Cytogenetic response

- complete cytogenetic response is better in patients presented early and treated immediately (88.24%)

Conclusion

- targeted therapy by imatinib
- change the natural course of chronic myeloid leukemia
- from a fatal malignancy to a chronic stable disease
- which patients can live normal lives provided they adhere to medication

❖**early initiation of therapy is essential**

❖***laboratory facilities including molecular and cytogenetic diagnostic and monitoring services are urgently needed to guide the effective treatment of CML in Myanmar***

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THANK YOU