

# Success and Challenges in the Management of Chronic Myeloid Leukemia

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Ann Natl Acad Med Sci (India) 2019;55:135–137

## Abstract

Chronic myeloid leukemia (CML) is one of the most common myeloproliferative neoplasms characterized by the presence of Philadelphia chromosome, that is, t(9:22), a reciprocal translocation between long arms of chromosomes 9 and 22. In its natural course CML has three phases, that is, chronic phase, accelerated phase, and blast crises phase. Peripheral blood shows marked leukocytosis and left shift. Diagnosis is confirmed by demonstration of specific molecular abnormality by polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) method or cytogenetics. The drug of choice is tyrosine kinase inhibitor (TKI); imatinib. Other TKIs are dasatinib and nilotinib. Most patients respond and have almost normal life span. However, challenges remain. At present the drug is prescribed for lifelong. Recent studies have shown that the drug may be stopped in certain groups of which around 50% remain in long term remission (operational cure). However, around 20% did not respond and showed resistance. Research is in progress to find out the mechanism of resistance and newer therapeutic modalities or agents.

## Keywords

- ▶ chronic myeloid leukemia
- ▶ tyrosine kinase inhibitor
- ▶ imatinib

## Introduction

Chronic myeloid leukemia (CML) is one of the most common myeloproliferative neoplasms and commonest type of leukemia in India. It was the first malignancy found to be associated with a cytogenetic abnormality.<sup>1</sup> It is the first disease to have a successful molecularly targeted therapy. CML is characterized by the presence of Philadelphia chromosome, that is, t(9:22), a reciprocal translocation between long arms of chromosomes 9 and 22. Shortened chromosome 22 is known as Philadelphia chromosome.<sup>2</sup>

It is a myeloproliferative neoplasm that originates in an abnormal pluripotent bone marrow stem cell and is consistently associated with a Philadelphia (Ph) chromosome and/or the BCR-ABL fusion gene. t(9:22) leads to fusion of c-abl gene on chromosome 9 and breakpoint cluster region (BCR) on chromosome 22 leading to formation of BCR-ABL transcript. This leads to the formation of BCR-ABL fusion protein which has tyrosine kinase activity. This tyrosine kinase activity leads to phosphorylation of substrates and activates many downstream signaling pathways leading to cell

proliferation, prolonged survival, and decreased apoptosis. Tyrosine kinase inhibitors including imatinib bind to the ATP binding pocket of BCR-ABL transcript and inhibit of substrate phosphorylation.<sup>3</sup>

## Clinical Presentation

Median age of CML varies between 32 and 38 years in India compared with 50 to 55 years in the West.<sup>1,2</sup> Usually patients present with heaviness and dragging sensation in left hypochondrium due to enlarged spleen. Often diagnosis is incidental while routine workup or workup for some other unrelated disease. Patients also complained about weakness, fatigue, and weight loss. Rarely can it present with infection, thrombosis, bleeding, priapism, and visual disorders. In its natural course, CML has three phases, chronic phase, accelerated phase, and blast crises phase. About 80 to 90% patients present in chronic phase. About 10 to 20% patients present with either accelerated phase or blast crises. Criteria for accelerated phase are, blast 10 to 20%, basophils > 20%, platelets < 100,000 without treatment, or > 100,000 on

treatment or cytogenetic clonal evolution. Blast crises are characterized by blasts > 20% in peripheral blood or bone marrow or extramedullary blast collection. Blast crises can be myeloid, lymphoid, or mixed. Survival in blast phase or accelerated phase is very dismal without treatment. With availability of various tyrosine kinase inhibitors (TKIs) and SCT, there is possibility of better outcomes in these scenarios.<sup>2</sup>

## Diagnosis

Although we have to do molecular test to diagnose CML, peripheral blood and bone marrow examination gives some very important clues. Peripheral blood shows marked leukocytosis and left shift, eosinophilia, and basophilia. Bone marrow shows marked myeloproliferation with myelocyte bulge in routine bone marrow differentials. Diagnosis is confirmed by demonstration of molecular abnormality by polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) method, or cytogenetics.<sup>1</sup> We have seen a tremendous rise in number of CML patient in our outpatient department. Number of CML patient in 2007 were around 100 which increased to 500 in 2014 and 1,400 in 2019. Less than 10% of our patients present with upfront accelerated phase/blast crisis (AP/BC). Before 2008, median duration of symptoms before diagnosis was around 20 months which is now <5 months. This is possibly due to increased awareness about the disease and availability of diagnostic facilities in primary and secondary health care set up.

## Treatment

Busulphan, interferon, and hydroxyurea have all been used extensively in past for treatment of CML. They were able to control counts in CML, reduce size of spleen, and relieve symptoms of this disease to a great extent but were unable to prolong the survival. Since 1973, bone marrow transplant for CML is available. Although it cured the disease, it is associated with high mortality. Targeted therapy became available in 1999 and imatinib (Gleevec) was the first molecule to be available for use.<sup>3</sup> Dasatinib became available in 2006 and nilotinib in 2007. TKI in CML is the success story of molecularly targeted therapy. Treatment with TKI and response assessment is guided by the European Leukemia Network (ELN) guidelines 2013. In due course around 25 to 30% of patient on imatinib show resistance. Mutation analysis can identify the underlying abnormality and can tell about the sensitivity and MIC of other TKI like nilotinib and dasatinib.<sup>4</sup> On imatinib, approximately 10% do not tolerate, all do not respond, and those who respond may eventually fail. Mutations leading to resistance to imatinib are the most common cause for imatinib failure. We studied pattern of kinase domain mutations in 40 patients of CML who either lost their response or did not achieve it in defined time points.<sup>4</sup> Loss of molecular response was the most common indication for mutation analysis. Sixteen patients were found to have detectable mutations. M351T was the most common tyrosine kinase mutation followed by Y253H and H396R. Two patients had two mutations simultaneously. M351T is the

most common mutation in our patient population. Need for prolonged treatment (usually lifelong) and long-term toxicities are other concerns with tyrosine kinase inhibitors.<sup>5</sup>

## Challenges

CML is the most common leukemia in India and it occurs in India in younger age. The cause for this is not known. We studied various CYP 3A5 polymorphisms (CYP 3A5 \*1/\*1, CYP 3A5 \*1/\*3, CYP 3A5 \*3/\*3) and could not find any difference in cases and controls.<sup>5</sup> We also studied glutathione S transferase (GSTM1 and GSTT1) null type in patients and controls. Although null type was slightly more common in CML cases but not statistically different from cases.<sup>6-8</sup> It is not clear if the early onset of disease and its higher incidence in India could be attributed to genotypic variations in xenobiotic enzymes activity.

We have performed studies to know the predictive factors in CML, such as S-phase fraction (SPF) and aneuploidy. SPF was significantly higher in CML-chronic phase (CP) and CML-AP compared with controls.<sup>9</sup> Those patients with higher SPF converted more commonly to accelerated phase. Seventy five percent of patients with SPF  $\geq 7\%$  converted to accelerated phase. Similarly patients with aneuploidy were more likely to convert to accelerated phase compared with no aneuploidy patients. Status of lipid peroxidation is also a predictive factor in CML. Plasma levels of malondialdehyde and protein carbonyl were studied and found to be significantly elevated in accelerated phase compared with controls and CML-CP.<sup>10-12</sup>

Another challenge in the management of CML patient is that around 20% patients do not optimally respond to TKIs. Hence we sought to understand the mechanism of imatinib resistance using K562 (BCR-ABL+) cell lines. Nitric oxide (NO) is known to regulate cell proliferation, as well as apoptosis. Free radical generation (superoxide, Mitochondrial reactive oxygen species [ROS], ROS and/or reactive nitrogen species) and H<sub>2</sub>O<sub>2</sub> level were more in Drug naïve and imatinib resistant in patients. Recovery in these parameters was observed in patients showing optimal response to imatinib. NO level was less in drug naïve and imatinib resistant CML patients (cell proliferation potential enhanced), while NO level was augmented in imatinib responders (optimal proliferation and enhanced apoptosis). Inducible nitric oxide synthase (iNOS) mRNA and protein expression was less in drug naïve and imatinib resistant CML patients. NO generation and iNOS expression was enhanced in those CML patients who exhibit optimal response to imatinib. Less NO/iNOS seems to be associated with cell proliferation and reduced apoptosis in BCR-ABL+ cells.<sup>13,14</sup>

NF- $\kappa$ B, a transcription factor regulates expression of iNOS. Expression of NF- $\kappa$ B (p50/p65) is several folds more in CML cells. Binding of NF- $\kappa$ B to iNOS promoter is less in BCR-ABL+ cells. Imatinib increased binding of NF- $\kappa$ B to iNOS promoter. Increased binding augmented NO generation/iNOS expression and apoptosis and decreased cell proliferation. In drug naïve and imatinib resistant patients low NO/iNOS is due to less binding of NF- $\kappa$ B to iNOS promoter.<sup>14</sup>

We also studied newer compound Aryl NaphthylScaffold (MND) for imatinib resistant CML. MND was able to cause

apoptosis in CML cell lines, as well as CML cells from the patients. CD34<sup>+</sup> hematopoietic stem cells known to be responsible for disease relapse were isolated from imatinib resistant patient sample and were treated as indicated for cell viability assay. T315I is multidrug resistant mutant and many other mutations form and PBMCs from Imatinib resistant CML patient were found to be more sensitive to MND than drugs already in use.

## Conclusion

CML is cytogenetically defined chronic leukemia with available treatment options which target the molecular defect. Even after availability of TKIs, many patients still progress to accelerated phase and blast crises. Need for search of various mechanisms other than tyrosine kinase mutations exists. Average survival of patients with CML has improved and it is shown that most patients with CML live normal life span on TKI treatment. Operational cure is possible in 40 to 50% of patients who have shown prolonged and very good response (deep molecular response) to TKIs and are adherent to the monitoring protocol.

### Note

The author was selected for Dr. V.R. Khanolkar Oration for the year 2018–2019.

### Conflict of Interest

None declared.

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