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Chronic Myeloid Leukemia in India: A Review

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ABSTRACT

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of a pluripotent stem cell. CML is the commonest adult leukaemia in India and the annual incidence ranges from 0.8–2.2/100,000 population in males and 0.6–1.6/100,000 population in females in India. The median age of diagnosis is 38-40 years. Chronic myeloid leukemia is divided into three phases based on clinical characteristics and laboratory findings. CML prognostic scoring systems stratify patients into risk groups based on patient and disease related characteristics at diagnosis **.** With the introduction of the Tyrosine Kinase Inhibitor, imatinib, the treatment and natural history of CML has changed dramatically in recent years, with an improvement in the 5-year survival rate from little more than 20% to over 90%.This article presents a brief review about chronic myeloid leukemia and its therapy.

Keywords: Chronic myeloid leukemia, CML, pluripotent stem cell, leukaemia in India.

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of a pluripotent stem cell. It is characterized by the Philadelphia (Ph) chromosome, which occurs due to a balanced reciprocal translocation between chromosome 9 and 22 t(9;22)(q34.1;q11.2). It was the first malignancy that had a specific chromosomal abnormality uniquely linked to it. This chromosomal abnormality is so named because it was first discovered and described in 1960 by two scientists from Philadelphia, Pennsylvania: Peter Nowell of the University of Pennsylvania and David Hungerford of the Fox Chase Cancer Center at Temple University.(Nowell-PC). [1] In 1973, Janet D. Rowley at the University of Chicago identified the mechanism by which Philadelphia chromosome arises as a translocation.

Epidemiology of Chronic Myeloid Leukemia

Global burden of Chronic Myeloid Leukemia:

The incidence of CML around the world varies by a factor of approximately twofold. The lowest incidence is in Sweden and China (approximately 0.7 per 100,000 persons), and the highest incidence is in Switzerland and the United States (approximately 1.5 per 100,000 persons). [2]

CML accounts for approximately 15 percent of all cases of leukemia, or approximately 5000 new cases per year in the United States. The age-adjusted incidence rate in the United States is approximately 2.0 per 100,000 persons for men and approximately 1.1 per 100,000 persons for women. The age-specific incidence rate for CML in the United States increases from approximately 0.2 per 100,000 persons younger than 20 years to a rate of approximately 10.0 per 100,000 octogenarians per year. [3]

Although CML occurs in children and adolescents, less than 10 percent of all cases occur in subjects between 1 and 20 years old. CML represents approximately 3 percent of all childhood leukemias. Multiple occurrences of CML in families are rare. No concordance of the disease between identical twins has been found. Analytical epidemiologic evidence for a familial predisposition in CML has also not been found. [4]

Chronic myeloid leukemia in INDIA

CML is the commonest adult leukaemia in India and the annual incidence ranges from 0.8–2.2/100,000 population in males and 0.6–1.6/100,000 population in females in India. The median age of diagnosis is 38-40 years. This is a decade earlier than the median incidence in the western world. Though CML is predominantly a disease affecting adults, a minority of patients are children and young adults. [5]

BCR-ABL Transcripts

The *BCR/ABL fusion* oncogene, the product of the t(9;22) Philadelphia chromosome (Ph), exists in three principal forms (P190, P210 and P230). These proteins arise from distinct breakpoints in the BCR gene on chromosome 22. This occurs due to autosplicing, which causes translocation of BCR exon 1, exons 1-12/13, or exons 1-19, respectively, to the c-ABL gene on chromosome 9.These different genes give rise to three distinct fusion proteins of molecular mass 190, 210 and 230kD. These proteins contain the same portion of the c-ABL tyrosine kinase in the COOH terminus but include different amounts of Bcr sequence at the NH_2 terminus.

- **Major (M-BCR):** The e13a2 (b2a2)/e14a2 (b3a2) fusion transcripts encode for a 210-kDa protein.
- **Minor (m-BCR**): The e1a2 encodes for a 190-kDa protein (P190BCR-ABL).
- **Micro (□-BCR)**: The e19a2 encodes for a 230-kDa protein (P230BCR-ABL)

Major BCR-ABL (M-BCR): More than 95% Ph-positive CML patients present with a breakpoint in the M-BCR region. The most common BCR-ABL transcripts in CML are e13a2 (b2a2) and e14a2 (b3a2). Two major breakpoints are found after the 13^{th} exon resulting in a b2a2 (e13a2) fusion or after the 14^{th} exon resulting in a b3a2 (e14a2) fusion. Both of these fusion mRNAs are translated into p210BCR-ABL protein. The P210 form of *BCR/ABL* is found in hematopoietic cells of patients with chronic myeloid leukemia (CML) in stable phase, and in acute lymphoid and myeloid leukemias. [6]

Minor (m-BCR): The breakpoint in the m-BCR region results in an e1a2 junction which is translated into a p190 BCR-ABL protein. Some acute lymphoblastic leukemia (ALL) are induced by this protein. [7]

Micro(μ-BCR): There is a third BCR-ABL protein: p230. It consists of more than 90% of p160 because the breakpoint is located in the 3-end of the BCR gene, in the -BCR region. Its transcript contains a e19a2 junction. The micro breakpoint position has been associated mainly with a mild form of CML, defined as Philadelphia chromosome-positive chronic neutrophilic leukaemia (Phpositive CNL). [8]

BCR-ABL AND SIGNAL TRANSDUCTION [9]

The tyrosine phosphoprotein kinase activity of p210BCR-ABL has been causally linked to the development of Ph-chromosome–positive leukemia in man. p210BCR-ABL is, unlike the ABL protein that is located principally in the nucleus, located in the cytoplasm making it accessible to a large number of interactions, especially components of signal transduction pathways. It binds and/or phosphorylates more than 20 cellular proteins in its role as an oncoprotein. The pathways and interactions invoked by BCR-ABL acting on mitogen-activated protein kinases are multiple and complex. [10]

A subunit of phosphatidylinositol 3'-kinase (PI3K) associates with p210BCR-ABL; this interaction is required for the proliferation of *BCR-ABL*–dependent cell lines and primary CML cells. p210BCRABL [11] regulates an RAF-encoded serine-threonine kinase. Downregulation of RAF expression is found to inhibit *BCR-ABL*–dependent growth of CML. [12] Cell transformation by *BCR-ABL* is affected by an adaptor protein that can relate tyrosine kinase signals to RAS. This involves growth factor receptor bound protein-2 (GRB2). p210BCR-ABL has been found to activate multiple alternative pathways of RAS. PI3K is constitutively

activated by BCR-ABL, generates inositol lipids, and is dysregulated by the downregulation by BCR-ABL of polyinositol phosphate tumor suppressors, such as PTEN and SHIP. [13]

The adaptor molecule CRKL is a major *in vivo* substrate for p210BCR-ABL as it acts to relate p210BCR-ABL to downstream effectors. CRKL is a linker protein that has homology to the v-*crk* oncogene product. Antibodies to CRKL can immunoprecipitated paxillin. Paxillin is a focal adhesion protein [14] that is phosphorylated by p210BCR-ABL. The p210BCR-ABL may be physically linked to paxillin by CRKL. CRKL binds to CBL, an oncogene product that induces B cell and myeloid leukemias in mice. The Src homology 3 domains of CRKL do not bind to CBL, but they do bind *BCR-ABL*. Therefore, CRKL mediates the oncogenic signal of *BCR-ABL* to CBL. The p210BCR-ABL may, therefore, induce the formation of multimeric complexes of signaling proteins. These complexes contain paxillin and talin and explain some of the adhesive defects of CML cells.

Hef2 also binds to CRKL in leukemic tissues of p190BCR-ABL transgenic mice. Hef2 is involved in the integrin signaling pathway [15] and encodes a protein that accelerates GTP hydrolysis of RAS-encoded proteins and neurofibromin. The latter negatively regulates granulocyte-monocyte colony-stimulating factor (GM-CSF) signaling through RAS in hematopoietic cells. Nuclear factor (NF)-B activation is also required for p210BCR-ABL mediated transformation. Expression of p210BCR-ABL leads to activation of NF B–dependent transcription via nuclear translocation.

Cell lines that express p210BCR-ABL also demonstrate constitutive activation of Janus-associated kinases (JAKs) and signal transducers and activators of transcription (STATs), usually STAT5. STAT5 is also activated in primary mouse marrow cells acutely transformed by the *BCR-ABL*. p210BCR-ABL co-immunoprecipitates with and constitutively phosphorylates the common subunit of the IL-3 and GMCSF receptors and JAK2. Both *ABL* and *BCR* are also multifunctional regulators of the GTP-binding protein family Rho and the growth factor-binding protein GRB2, which links tyrosine kinases to RAS and forms a complex with *BCR-ABL* and the nucleotide exchange factor Sos that leads to activation of *RAS*. The p210BCR-ABL activates Jun kinase and requires Jun for transformation.

Reactive oxygen species are increased in BCR-ABL–transformed cells. These act as a second messenger to modulate enzymes regulated by the redox equilibrium. An increase in these reactive oxygen products is also believed to play a role in the acquisition of additional mutations through the chronic phase, contributing to the progression to accelerated phase. [16]

STAGING OF CML

Chronic myeloid leukemia is divided into three phases based on clinical characteristics and laboratory findings. In the absence of intervention, CML typically begins in the chronic phase and over the course of several years progresses to an accelerated phase and ultimately to a blast crisis.

- **Chronic phase**: Approximately 85% of patients with CML are in the chronic phase at the time of diagnosis. During this phase, patients are usually asymptomatic or have only mild symptoms of fatigue or abdominal fullness. The duration of chronic phase is variable and depends on how early the disease was diagnosed as well as the therapies used. Ultimately, in the absence of curative treatment the disease progresses to an accelerated phase. It is characterized by peripheral blood blasts fewer than 10% in the blood and bone marrow.
- **Accelerated phase:** [16] WHO criteria define accelerated phase by
  - Blasts in blood or marrow 10-19%
  - Basophils in blood ≥ 20%

- Persistent thrombocytopenia ($<100\times10^9$/L) unrelated to therapy
- CCA/Ph1 on treatment Thrombocytosis ($>1000 \times 10^9$ /L) unresponsive to therapy
- Increasing spleen size and increasing white blood cell count unresponsive to therapy. The accelerated phase is significant because it signals that the disease is progressing and transformation to blast crisis is imminent.

➢ **Blast crisis in CML:** [16] Blast crisis is the final phase in the evolution of CML and behaves like an acute leukemia with rapid progression and short survival. Blast crisis is diagnosed by the following criteria:

- Blasts in blood or marrow ≥ 20%
- Extramedullary blast proliferation, apart from spleen
- Large foci or clusters of blasts in the bone marrow biopsy

PROGNOSTIC SCORES

CML prognostic scoring systems stratify patients into risk groups based on patient and disease related characteristics at diagnosis. [17] The table below mentions two of these prognostic scores.

TABLE 1: PROGNOSTIC SCORES FOR CML

S.NO.	SCORE	CALCULATION	RISK DEFINITION BY CALCULATION
1.	***SOKAL***	Exp[0.0116*(age-43.4)]+(0.0345*spleen size7.51)+[0.188*(platelet /700)^2)-0.563]+[0.087*(blasts-2.10)]	Low risk < 0.8 Intermediate risk : 0.8-1.2 High risk : > 1.2
2.	***EUTOS*** (European Treatment and Outcome Study)	Spleen*4+ basophils*7	Low risk ≤87 High risk >87

THERAPY OF CHRONIC MYELOID LEUKEMIA [18]

Before the advent of TKIs, treatment options included cytotoxic chemotherapy (cytarabine, busulfan, hydroxyurea) or IFN-α. These treatments are still valuable and potentially curative for patients who do not respond to newer therapies. With the introduction of the Tyrosine Kinase Inhibitor, imatinib, the treatment and natural history of CML has changed dramatically in recent years, with an improvement in the 5-year survival rate from little more than 20% to over 90%.Imatinib was first approved in the USA in 2001 for the treatment of the advanced phases of CML, although guidelines currently recommend therapy to be continued indefinitely. Imatinib was established as the standard of care for patients with CP-CML based on the results of the International Randomized Study of Interferon and STI571 (IRIS) trial. This trial included 1,106 patients newly diagnosed with CML who were randomized to either imatinib or IFN plus cytarabine. After a median follow-up of 19 months, the major cytogenetic response (MCyR) rate was statistically significantly higher with imatinib compared with the IFN–cytarabine combination (87.1% vs 34.7%, respectively; $P< 0.001$). The rate of freedom from progression to the accelerated phase at 18 months was also significantly higher in patients treated with imatinib than in those who received the IFN-α/ cytarabine combination (96.7% vs 91.5%, respectively; $P< 0.001$). Six- and eight-year follow-up of patients who received imatinib in the IRIS trial demonstrated an overall survival (OS) rate of 88% and 85%, respectively. An evaluation of data from the Imatinib LongTerm Side Effects trial has shown that for patients who achieve a stable cytogenetic response (CyR) with imatinib, OS is 95.2% at 8 years and is not statistically significantly different from that of the general population.

Unfortunately, a significant proportion of patients respond suboptimally or have no response to imatinib and they require an alternative treatment strategy to prevent progression to the accelerated phase. In IRIS for example, at the 8-year data cut-off 16% of patients had

discontinued because of an unsatisfactory therapeutic response to imatinib treatment. [19]

Two "second-generation" TKIs have been approved for the first-line treatment of CML. Dasatinib was initially approved in 2007 for the treatment of patients who are either resistant to or intolerant of imatinib; nilotinib was subsequently approved for the same indication. Both dasatinib and nilotinib were approved as first-line treatment options in 2010 following demonstration of high CyR and molecular response (MR) rates. Among 50 patients with early CP-CML treated with dasatinib as initial therapy, 49 (98%) achieved a complete CyR (CCyR) with 41 (82%) achieving a major MR (MMR) after at least 3 months of follow-up. Similarly encouraging response rates were reported for nilotinib, with CyR rates >96% and MR rates >76% in several independent cohorts of patients with CML. [20]

CONCLUSIONS

The latest European Society for Medical Oncology guidelines and National Comprehensive Cancer Network Guidelines In Oncology (NCCN Guidelines) recommend imatinib, nilotinib, or dasatinib as firstline therapy for patients newly diagnosed with CPCML. The European Leukemia Net (ELN) guidelines have also recently been updated to include recommendation of nilotinib or dasatinib, as well as imatinib, in this indication, with the suggestion that patients with an intermediate or high risk score may preferentially benefit from dasatinib or nilotinib.

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