www.ijmio.com

International Journal of Molecular and Immuno Oncology

Review Article

Genetic diversity and variation in chronic myeloid leukemia patients of Indian origin- Implications for treatment response and prognosis

Arthi Elango[1]

[1]Department of Medical Oncology, Max Superspeciality Hospital, New Delhi, India.

***Corresponding author:**
Arthi Elango,
Department of Medical Oncology, Max Superspeciality Hospital, New Delhi, India.

drarthielango@gmail.com

Received: 16 April 2024
Accepted: 26 November 2024
Published: 27 December 2024

DOI
10.25259/IJMIO_11_2024

Quick Response Code:

ABSTRACT

Chronic myeloid leukemia (CML) is a prevalent blood malignancy characterized by the breakpoint cluster region - abelson tyrosine kinase gene translocation (BCR-ABL1) fusion gene. In India, CML accounts for a significant portion of adult leukemias, with a notable male preponderance and an increasing trend in young adult patients. Most patients present in the chronic phase, and the Sokal/ European treatment and outcome study score (EUTOS)/ Hasford scoring systems may be used for risk stratification. The advent of imatinib revolutionized CML treatment, making it more accessible, although challenges such as intolerance and treatment failure persist. Cytogenetic analysis is essential for diagnosis and monitoring, with molecular assessments indicating treatment response. Compliance plays a crucial role in achieving optimal outcomes, with non-adherence associated with poorer prognosis. Mutational analysis aids in treatment decisions for patients with suboptimal response to tyrosine kinase inhibitors, revealing resistance patterns. Toxicity profiles resemble Western data, with anemia being the most common hematological toxicity. Despite limitations in resources and late presentations, Indian CML outcomes mirror Western standards, highlighting the importance of standardized cytogenetic testing for improved clinical outcomes.

Keywords: Chronic myeloid leukemia, Indian, Genetic diversity, Chronic myeloid leukemia Treatment response, Chronic myeloid leukemia prognosis

INTRODUCTION

One of the most prevalent malignancies of the blood is chronic myeloid leukemia (CML). The hematological condition is identified by the presence of the BCR-ABL1 fusion gene [Figure 1]. Cytogenetic analysis is essential for CML diagnosis and monitoring.

Incidence of CML in India is slightly lower than that in the West. Median age was 44 years, 10 years less than the median age at diagnosis in the United states.[1,2] CML is one of the most common adult leukemias in Indian population accounting for 30% to 60% of all adult leukemias.[3] A slight male preponderance has been observed in India. The male to female sex ratio varied from 1:08.[4,5] A recent observation of increasing number of young adult patients has been a cause of concern, with an unidentified etiology for the same adding depth to the concern.

CML Phases

During the first evaluation of patients at the time of diagnosis, 89.5% of patients were in the chronic phase (CP), 4.7% in accelerated phase and 4.3% in blast crisis (BC). The percentage of patients

presenting in CP varied from 85% to 97%, with a median of 89.5%, whereas in European data, the presentation of CML in CP has been reported to be as high as 96.8% [Chart 1].[1,6,7]

Scoring systems

The Sokal scoring system is used for risk stratification of patients. Majority of the patients in Indian series were in Intermediate risk category ranging from 27% to 47%, with 25–55% patients in the low-risk category and 12–28% of patients in the high-risk category.[5]

Other scoring systems used to risk stratify patients with CML include the EUTOS and the Hasford scales. The EUTOS score is calculated based on the basophil count and spleen size at diagnosis ([7×basophils in %] + [4× spleen size in cm below the costal margin]), with low-risk (score ≤87) and high-risk (score >87).[8] The Hasford score is calculated using age, blast percentage, basophil and eosinophil percentage, platelet count, and spleen size in cm (0.6666 × age [0 when <50 years, 1 otherwise] + 0.042 × spleen size in cm + 0.054 × blast cell percentage + 0.0413 × eosinophil cells percentage + 0.2039 × basophil cells percentage [0 when <3%, 1 otherwise] + 1.0956 × platelet count [0 when <1500 × 109/L, 1 otherwise] × 100). The EUTOS score correlates with molecular response in CML patients undergoing imatinib therapy.

Patients are then classified into different risk groups based on the scores obtained.[9] Low risk was defined as score ≤780, intermediate risk as score 781–1480, and high risk as score >1480.[9]

Evolution of treatment

The treatment of CML underwent a dramatic shift with the discovery of imatinib. CML has served as the poster child for targeted therapy in oncology and remains one of the most successful examples of personalized treatment.

In India, patients with CML were traditionally treated with hydroxyurea or busulfan. In the 1990s, the few patients who could afford the cost received interferon-based therapy or stem cell transplantation. When imatinib became available, few patients in India could afford the cost of the innovative product. Subsequently, patient-support programs, such as the Glivec International Patient Assistance Program, and cheaper generics made the medicine almost universally available to patients in the country.

Indian studies have also compared the responses of innovator Glivec to the Indian IM and found similar hematological responses, cytogenetic and better molecular responses with generic.[4,10] Unfortunately, a significant number of patients in the Glivec arm were not tested for molecular responses for economic reasons making the difference artifactual.

As a result, patients are these days started upfront on imatinib in many oncology centers and enjoy the longevity offered by the drug. The starting dose of imatinib was uniformly 400 mg in all the studies with all the authors preferring to increase the dose of imatinib if inadequate response was witnessed or milestones not achieved, probably the alternatives being too expensive.

The major barrier -drug resistance" and the underlying molecular mechanisms

However, this longevity is not without problems. One of the most significant of them is intolerance to imatinib and the other is treatment failure. Therefore, these patients end up needing therapy with more expensive, second-line tyrosine kinase inhibitors (TKIs).

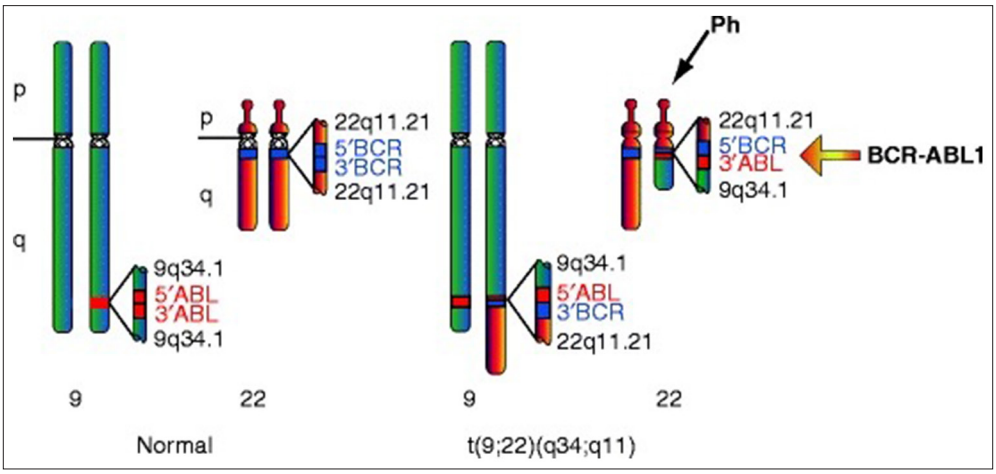

Figure 1: Ideogrammatic representation of chromosomes 9 and 22 before (*left*) and after (*right*) recombination between the *BCR* and *ABL1* genes to form the leukemia-initiating hybrid *BCR-ABL1* gene - taken from Springer nature.com.

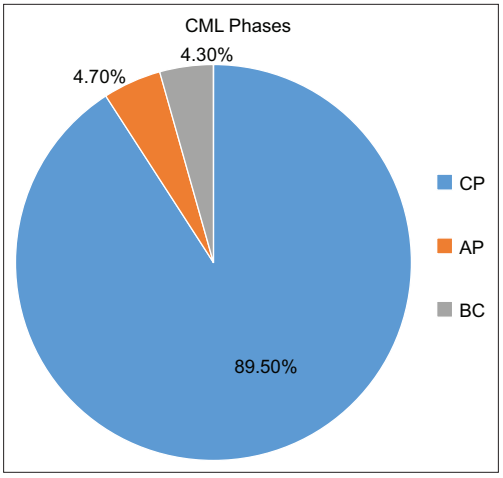

Chart 1: Distribution of different phases of chronic myeloid leukemia (CML) as observed in quoted studies. CP: Chronic phase, AP: Accelerated phase, BC: Blast crisis

Cytogenetic analysis is crucial for diagnosing leukemia patients. The importance of cytogenetic analysis as a prognostic indicator for continued care in CML patients with an increasing frequency of the Philadelphia chromosome being observed in recent years has been observed in many studies.

Most of the reports from Indian institutional series show complete hematological response (CHR) of 85–98.7% between 1 and 3 months of therapy with most managing to keep the hematological remissions for at least 2–3 years. However, the data on molecular assessment were unequal and incomplete warranting improvement.[7]

On Cox regression analysis, age under 40 years, low Sokal score, CHR, and complete cytogenetic response (CCYR) were significant predictive factors for event-free survival (EFS), whereas on multivariate analysis, low Sokal score and early CP were the significant predictive factors for CCyR.[11] The 5-year EFS and overall survival (OS) in this study were 72% and 87%, respectively; however, no specific predictive factors for OS were obtained from this study.[11]

It has been observed that early chronic phase (ECP), better tolerability to the drug, and no primary resistance are significant indicators of better survival of patients with CML.[12]

The importance of compliance was emphasized in studies where the CCyR rate in patients taken with > or < 4-week gap irrespective of brands was 57 and 80%, respectively.[4] One other study also looked at the aspect of > 1 week of non-adherence. The 5-year EFS in adherent and non-adherent patients was 76.7% and 59.8%, respectively ($P < 0.011$, log rank test). Non-adherent patients were less likely to achieve complete cytogenetic responses (26% vs. 44%; $P = 0.004$; χ^2 test) at any point.[13]

The EUTOS score correlates with molecular response in CML patients undergoing imatinib therapy. Mutational analysis of the BCR-ABL1 kinase domain aids in treatment decisions for CML patients with suboptimal response to TKIs.

Promoter hypermethylation of genes such as Autophagy related 16-like 2 (ATG16L2), Transcription factor alpha 2A (TFAP2A), Early B cell factor 2 (EBF2), and calcitonin, along with ABL1 kinase domain T315I mutation, is associated with imatinib resistance in CML patients.

Deep sequencing has been used to identify BCR-ABL1 mutations in imatinib-resistant CML cases, emphasizing the importance of genetic analysis in treatment resistance.

One of the studies done had mutation analysis done in 101 patients showing poor response. 73% of the patients had no known mutation. The most common mutation seen was T315I and M351T.[14] In another single institutional study of 90 patients, 32.2% patients were found to have detectable kinase domain mutation. The most common mutation was T315I in 31% patients, and 12.2% of all patients (38% of all mutations) had a P-loop mutation. N374Y was a novel mutation and has not been reported before. The study showed that dose escalation to 800 mg resulted in CCgR in 27.7% patients, partial cytogenetic response in 11.3% patients, with a 2-year EFS in 34%, and 2-year OS rate of 93%.[15]

Toxicity profile was similar to that observed in the western data. The most common non-hematological toxicity observed was change in skin pigmentation of around 47%, (375/742 patients) followed by weight gain, edema, diarrhea, myalgia, arthralgia, and transaminitis. Other toxicities observed are ototoxicity, decrease in vision and second malignancies. The hematological toxicities seen were anemia (most common) in 31% of patients, thrombocytopenia between 31%, and neutropenia in 27%. Grade IV toxicities were observed only in 10/792 patients, reiterating a good tolerability profile.[16]

The available data suggest that Indian CML has patterns of OS, response in CP and CCyR with compliance (or noncompliance) similar to the Western population. However, similar the patterns, what is striking is that these are despite several limitations in treatment, monitoring of disease, availability of second-generation TKIs, late presentations, and significant population coming from low SE strata, in contrast to the Western population. The overall survival based on multiple studies ranges from 81% to 100%.

CONCLUSION

Indian CML is very much similar to the Western understanding of the disease. Cytogenetic and molecular testing will require to be made more easily available to enhance standardization and for assessment of genetic

variations. This is very crucial in understanding patterns of resistance and hence predicting treatment response and improving clinical outcomes in the Indian population.

Ethical approval

Institutional review board approval is not required.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Tardieu S, Brun-Strang C, Berthaud P, Michallet M, Guilhot F, Rousselot P, *et al*. Management of chronic myeloid leukemia in France: A multicentered cross-sectional study on 538 patients. Pharmacoepidemiol Drug Saf 2005;14:545-53.
2. Cortes JE, Richard TS, Hagop K. In: Padzur R, Coia LR, Hoskins WJ, Wagman LD, editors. Chronic myelogenous leukemia. Cancer management: A multidisciplinary approach. 10th ed. Lawrence: CMPMedica; 2007. p. 789.
3. Bhutani M, Kochupillai V. In: Kumar L, editor. Hematological malignancies in India. Progress in hematologic oncology. New York: Pub. The Advanced Research Foundation New York; 2003. p. 10.
4. Parikh P. Report of chronic myeloid leukemia in chronic phase from Tata Memorial Hospital, Mumbai, 2002-2008. Indian J Med Paediatr Oncol 2013;34:164-7.
5. Deotare UR, Chudgar U, Bhagat E. Report of patients with chronic myeloid leukemia, from hematology clinic, Ahmedabad, Gujarat 2000-2010 at 1st myelostone meeting: Indian evidence of chronic myelogenous leukemia. Indian J Med Paediatr Oncol 2013;34:193-5.
6. Prasad RR, Singh P. Report of chronic myeloid leukemia from Indira Gandhi Institute of Medical Sciences, Regional Cancer Center, 2002-2009. Indian J Med Paediatr Oncol 2013;34:172-4.
7. Malhotra P, Varma N, Varma S. A short report on chronic myeloid leukemia from Post Graduate Institute of Medical Education and Research, Chandigarh. Indian J Med Paediatr Oncol 2013;34:186-8.
8. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, *et al*. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: The EUTOS score. Blood 2011;118:686-92.
9. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, *et al*. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-8.
10. Malhotra H, Sharma R, Singh Y, Chaturvedi H. Report of chronic myeloid leukemia SMS Medical College Hospital, Jaipur. Indian J Med Paediatr Oncol 2013;34:177-9.
11. Agarwal MB, Agarwal UM, Rathi SS, Masurkar S, Zaveri B. Report of chronic myeloid leukemia in chronic phase from Ashirwad Hematology Centre, Mumbai, 2002-2009. Indian J Med Paediatr Oncol 2013;34:199-203.
12. Bansal S, Advani SH. Report of chronic myelogenous leukemia in chronic phase from, Asian Institute of Oncology, Mumbai, 2002-2010. Indian J Med Paediatr Oncol 2013;34:168-71.
13. Ganesan P, Sagar TG, Dubashi B, Rajendranath R, Kannan K, Cyriac S, *et al.* Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. Am J Hematol 2011;86:471-4.
14. Babu G. Report of patients with chronic myeloid leukemia Kidwai Memorial Institute of Oncology, Bangalore over 15 years. Indian J Med Paediatr Oncol 2013;34:196-8.
15. Rajappa S, Mallavarapu KM, Gundeti S, Paul TR, Jacob RT, Digumarti R. Kinase domain mutations and responses to dose escalation in chronic myeloid leukemia resistant to standard dose imatinib mesylate. Indian J Med Paediatr Oncol 2013;34:221-3.
16. Shah SA. The treatment of chronic myeloid leukemia, data from Gujarat Cancer and Research Institute, Ahmedabad. Indian J Med Paediatr Oncol 2013;34:189-92.

How to cite this article: Elango A. Genetic diversity and variation in chronic myeloid leukemia patients of Indian origin-implications for treatment response and prognosis. Int J Mol Immuno Oncol. 2024;9:100-3. doi: 10.25259/IJMIO_11_2024