Significance of bcr-abl molecular detection in chronic myeloid leukemia patients

Important advances in the understanding of the molecular basis of chronic myeloid leukemia have resulted in the development of new therapies and changed the paradigm for managing this myeloproliferative disease. The reciprocal translocation of the abl (Abelson murine leukemia) proto-oncogene on chromosome 9 to the bcr (breakpoint cluster region) gene on chromosome 22 creates a transcriptionally active, chimeric bcr-abl gene and gives rise to the Philadelphia chromosome.¹

The genetic hallmark of chronic myeloid leukemia (CML) is the Philadelphia chromosome (Ph), which occurs in at least 95% of CML cases as well as some cases of acute lymphocytic leukemia (ALL; approximately 5% for children, 20% for adults). It also has been reported in some other hematologic disorders, albeit rarely.²⁻⁴

The bcr-abl gene encodes a 190 or 210 kd protein product, which is an active, deregulated, intracellular tyrosine kinase.¹ By this mechanism, the fusion protein is thought to induce malignant transformation of hematopoietic stem cells.^{5,6}

The reciprocal translocation between chromosomes 9 and 22 places the 59 regulatory domains of the BCR gene from chromosome 22 in juxtaposition with the 39 tyrosine kinase domains of ABL from chromosome 9. This unique gene fusion leads to the expression of chimeric bcr-abl messenger RNA (mRNA) and the production of functional BCR-ABL fusion protein. The bcr-abl gene and its mRNA transcript are tumor-specific markers. The chimeric bcr-abl mRNA is an attractive target for monitoring minimal residual disease (MRD) by reverse transcriptase

polymerase chain reaction (RT-PCR) assays.

The fused BCR-ABL gene and its gene products provide specific markers for diagnosis and disease monitoring. Polymerase chain reaction (PCR) permits specific and sensitive detection of Ph-positive cells through the amplification of the BCR/ABL fusion transcripts.^{7,8} Owing to its high sensitivity, this assay is a powerful tool for the detection of subclinical minimal residual disease; however, its clinical usefulness is hampered by difficulties in quantification.

PCR technology has evolved into real-time fluorescence detection. One of the detection methods takes advantage of the 5'→3' exonuclease activity of Taq DNA polymerase, which hydrolyzes a double-labeled fluorogenic probe upon annealing to the target PCR products during the PCR sequence extension phase.⁹ Since fluorescence acquisition is monitored cycle-by-cycle, product analysis can be performed while PCR is in progress. It provides not only detection but also quantification of the accumulated target PCR products.

Currently at our lab Cancer Diagnostic & Research Centre, Department of Immunology & Molecular Medicine, SKIMS is focusing to understand the molecular pathobiology of various cancers, like blood cancer, colon cancer and Lung cancer. The main focus is to understand the molecular basis of leukemia. In this context, both qualitative and quantitative diagnosis of bcr-abl in leukemia patients is in progress. The early diagnosis helps to provide a first-line treatment for leukemia patients. The early detection of such mutations allows timely treatment intervention to prevent or overcome resistance.

Acknowledgment:

We sincerely acknowledge the financial support of Department of Biotechnology, Government of India (Grant

Correspondence

Dr. Manzoor A. Malik, Ph.D

Assistant Professor,

Department of Immunology & Molecular Medicine,
SKIMS, Srinagar

E-mail: maliksgpgi@gmail.com

REFERENCES

1. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999; 340:1330-1340.
2. Svarch E, de la Torre E. Myelomonocytic leukaemia with a preleukaemic syndrome and Ph1 chromosome in monozygotic twins. *Arch Dis Child*. 1977; 52:72-74.
3. Hoppin EC, Lewis JP. Polycythemia rubra vera progressing in Ph1-positive chronic myelogenous leukemia. *Ann Intern Med*. 1975;83:820-823.
4. Price CM, Rasool FS, Shivji MK. Rearrangement of the breakpoint cluster region and expression of p210 bcr-abl in a "masked" Philadelphia chromosome positive acute myeloid leukemia. *Blood*. 1988;72:1829-1832.
5. Daley GQ, van Etten RA, Baltimore D. Induction of chronic myeloid leukemia by the p210 bcr/abl gene of the Philadelphia chromosome. *Science*. 1990;247:824-830.
6. Muller AJ, Young JC, Pendergast AM. BCR first exon sequences specifically activate the bcr/abl tyrosine kinase oncogene of Philadelphia chromosome positive human leukemia. *Mol Cell Biol*. 1991;11:1785-1792.
7. Kawasaki ES, Clark SS, Coyne MY. Diagnosis of chronic myelogenous leukemia and acute leukemia by detection of leukemiaspecific mRNA sequences amplified *in vitro*. *Proc Natl Acad Sci USA*. 1988; 85: 5689-5692.
8. Lee M-S, Lemaistre A, Kantarjian HM et al. Detection of two alternative bcr/abl mRNA junctions and minimal residual disease in Philadelphia chromosome positive chronic myelogenous leukemia by polymerase chain reaction. *Blood*. 1989; 73: 893-897.
9. Holland PM, Abramson RD, Watson R et al. Detection of specific polymerase chain reaction product by utilizing the 5' to 3' exonuclease activity of *thermus aquaticus* DNA polymerase. *Proc Natl Acad Sci USA*. 1991; 88: 7276-7280.

Manzoor Ahmad Malik, Ph.D., Shahid Mudasir Baba, Ph.D., Rafia Anjum Baba, Ph.D.
Cancer Diagnostic & Research Centre Lab,
Deptt. of Immunology & Molecular Medicine,
SKIMS, Soura, Srinagar, Kashmir,