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Commentary

Cytogenetic study in CML

Chronic myeloid leukaemia (CML) is a clonal stem cell disorder characterized by increased proliferation of myeloid lineage. 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[1]. 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. CML is the first cancer in which a consistent chromosomal abnormality the Philadelphia chromosome was described by Nowell in 1962. This abnormality was later shown to be due to translocation involving t(9;22) (q34;q11.2) and involved the fusion of genes breakpoint cluster region (BCR) and the Tyrosine Kinase human homologue of the Abelson Murine leukaemia Virus (ABL). During the reciprocal translocation a segment of *ABL* gene (9q34) is moved into one of at least 3 well characterized breakpoints of the *BCR* gene in 22q11[2,3]. This results in two fusion genes *BCR-ABL* and *ABL-BCR*. Of this, the *ABL –BCR* has no identified role in pathogenesis of CML.

The BCR-ABL fusion gene is in frame and is translated leading to formation of an oncoprotein which is a constitutively active tyrosine kinase. Primarily three different fusion transcripts have been characterized resulting in fusion of BCR exon1 9 (e1), exons13/14 (b2/b3) and exons1-19 (e19) to ABL[4]. Very rarely exon6 and exon 8 are involved in *BCR-ABL* translocations. By contrast, the breakpoint in *ABL* occurs almost invariably upstream in ABL exon2 (a2) though occasionally it can occur downstream of exon2 (a3). These results in tyrosine kinase proteins of 185/190, 210 and 230 kilo Dalton sizes respectively. The 210 kilodalton protein (p210) is called the Major transcript or 'M' and the 185/190 Kilodalton is called the minor transcript or 'm'. The knowledge about the fusion transcript is important when doing molecular monitoring of minimal residual disease after treatment with tyrosine kinase inhibitors.

The major modality of treatment of CML inhibitors of the tyrosine kinase, the commonest used is Imatinib. These are chemical competitive inhibitors of ATP which is required for phosphorylation of tyrosine residues of downstream proteins in the signaling pathways of ABL tyrosine kinase. Newer 2nd generation tyrosine kinase inhibitors like Nilotinib and Dasatinib are used in patients resistant to Imatinib. These newer drugs have brought clinical and haematological remissions almost all patients and molecular remissions in about a third of patients. However, it has not resulted in a drug free cure of the disease. The patients have to be on long term monitoring while on therapy[5-9].

In this issue Anand *et al*[10] have reported on the cytogenetic and molecular analyses of CML patients from north India. There are very few studies from India comparing cytogenetics and molecular data in CML patients in India. Cytogenetic facilities are scarce in India and restricted to predominantly academic institutes. Having a baseline karyotyping in CML is essential and additional karyotypic abnormalities predict an advanced stage of the disease and a poorer response to Imatinib. The progress in CML have brought in a paradigm shift in management of many cancers and newer approach to targeting cancers.

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References

1. National Cancer Registry Programme. Two year report of the population based cancer registries 1999-2000. New Delhi: Indian Council of Medical Research; 2005.
2. Bartram CR, de Klein A, Hagemeijer A, van Agthoven T, Geurts van Kessel A, Bootsma D, *et al*. Translocation of c-ab1oncogene correlates with the presence of a Philadelphia chromosome in chronic myelocytic leukaemia. *Nature* 1983; *306* : 277-80.
3. Groffen J, Stephenson JR, Heisterkamp N, de Klein A, Bartram CR, Grosveld G. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. *Cell* 1984; *36* : 93-9.
4. Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. *Blood* 2000; *96* : 3343-56.
5. Hochhaus A, Kantarjian HM, Baccarani M, Lipton JH, Apperley JF, Druker BJ, *et al*. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; *109* : 2303-9.
6. Kantarjian H, Pasquini R, Levy V, Jootar S, Holowiecki J, Hamerschalak N, *et al*. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). *Cancer* 2009; *115* : 4136-47.
7. Kantarjian HM, Giles F, Gattermann N, *et al*. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; *110* : 3540-6.
8. Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Encrico A, *et al*. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. *Haematologica* 2010; *95* : 232-40.
9. le Coutre P, Ottmann OG, Giles F, Kim DW, Cortes J, Gattermann N, *et al*. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or –intolerant accelerated-phase chronic myelogenous leukemia. *Blood* 2008; *111* : 1834-9.
10. Anand MS, Varma N, Varma S, Rana KS, Malhotra P. Cytogenetic & molecular anályses in adult chronic myelogenous leukaemia patients in north India. *Indian J Med Res* 2011; *135* : 42-8.