Increasing Role of Cytogenetics in the Diagnosis and Stratification of Childhood Leukaemia

Leukaemias are the most common cancers affecting children accounting for 32% of all occurences of cancer in children younger than 15 years and 27% of occurrences of children younger than 20 years.(1) With the advent of multiagent chemotherapy, improved supportive care and targeted therapy over the years, there has been improved outcome of children with leukaemia immensely. Leukaemia particularly ALL which had a cure rate of <10% in the sixties has now become 80-90%, in the developing and around 60% in the country like ours. (1, 2)

Interestingly the diagnosis and stratification of leukaemias which were solely on the morphological basis had subsequently had their stratification done by cytochemistry and immunephenotyping but lately the cytogenetics in many instances has become the determining feature defacto for different leukemias in childhood.

Cytogenetic analysis of leukaemic cells has become an important technique in studies of leukaemia. This is mostly due to improvement in high resolution banding technique, characterization of chromosome in regions by Flourescence in Situ Hybridization (FISH) and cell culture and the identification of cytogenetics abnormality specific for a small subset which allows a better diagnosis and prognosis. (3, 4)

Cytogenetic analysis and molecular cytogenetic studies such as Flourescence in situ hybridization (FISH) reveal recurring chromosome abnormalities in approximately 80% of ALL include numerical and structural changes such as translocation, inversion and deletion. These structural and numerical abnormalities occur constantly and provide important prognostic information. The most common rearrangement in B-ALL is the t (12;21) (p13;q22) rearrangement that encodes ETV6-RUNX1 also referred to as TEL-AML1. It is found in 25% of ALL and is associated with favourable prognosis. Also the BCR-ABL gene fusion is the consequence of translocation t (9;22) called the Philadelphia chromosome (ph1). Although rare in paediatric patients with a frequency of less than 5% ph1+ALL is classified as high or very high risk with unfavourable outcome. Other chromosomal abnormalities are the translocation t (4;11) most frequently in infants and associated with a unfavourable prognosis and translocation t(1;19) in pre-B-ALL. There is most frequent translocation in mature B cell leukaemia is t(8;14) less frequent t(2;8) on t(8;22), all of these translocation involve c-myc proto oncogene which is located on chromosome 8. Typical translocations in T-cell ALL are t (1;14) and t(11;14). The numerical abnormalities occur in 25% of ALL and mostly hyper diploidies. Hypodiploidies are rare and prognostically unfavourable. (5)

AML comprises 15 to 20% of acute leukaemias diagnosed in children under 15 years of age. Paediatric AML'S exhibit heterogenous but characteristics clinical and biological features which reflect underlying molecular and cytogenetic abnormalities. The major FAB morphological subtypes of AML are in general associated with typical balanced chromosomal translocation. (6)

Major Molecular cytogenetics aberration in AML recognized in the WHO classification systems are the following in AML with translocation t(8;21), (q22;q22) (AML1 -ETO), AML with abnormal Bone marrow eosonophilia and inv(16),

(p13;q32),t (16;16).Acute promyelocyte leukaemia t(15;17),(q22;q21) PML-RARA and variants and AML with q11 q23 (MLL) abnormalities. It has been estimated that t(8;21), t(15;17), inv (16) and MLL translocations are present in 12%,7%and 12%, 7% respectively. (6,7)

CML constitute 15 to 20% of all leukaemias but accounts for only 1% to 3% of all childhood lekaemias. The CML Particularly the adult type has a distinct translocation of t (9; 22) (q34;q11)in 90% of cases. This translocation causes a BCR-ABL fusion gene which will predict about the outcome of the disease with subsequent tyrosine kinase inhibitor therapy. The BCR-ABL positive CML produces a protein (p210) in contrast to Ph1 positive ALL where the protein is p190. Not only for the treatment outcome but for the regular follow up and treatment response assessment, the cytogenetics is also necessary.

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