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Prognostic Evaluation of Chromosomal Aberrations in Acute Lymphoblastic Leukaemia

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ABSTRACT Incidences of leukaemia continues to be increased in India due to environmental deterioration. Acute lymphoblastic leukaemia (ALL) patients generally possess a poor prognosis but require very aggressive chemotherapy. In spite of the limitations in chromosome preparation in ALL, the prognostic value of chromosome analysis has been considered to be of great importance as evident from the findings of different workers. A probable relationship between the prevalence of polyploids in bone-marrow of ALL patients during induction-of-remission and platelet production during maintenance therapy warrants further investigation to evaluate the prognostic approach of the finding. The common feature of t (9:22) in different leukaemias and its possible role in understanding some key mechanism of disease development has been discussed.

Chromosomes, the threads of life, are the bearer of all biological informations of a cell. They can duplicate themselves and can transmit the genetic information very faithfully from cell to cell and generation to generation. Chromatin, the building material of chromosome, is made up of deoxyribonucleic acid (DNA) and the basic protein histone. Octamer beads of four types of histone molecules (H2A, H2B, H3 and H4) remain wrapped by DNA double helical polynucleotide chain which make the primary building blocks for the chromosome architecture called nucleosomes; these appear as thread-like structures inside the nucleus of a cell. The functional cord of DNA is a gene, and genes are known to be linearly arranged along the length of a chromosome. In fact, a gene is a prisoner of chromosome and a chromosome is a prisoner of cell.

A chromosome is made up of two chromatids joined by a centromere. According to the centromeric index, a chromosome may be metacentric, submetacentric, subtelocentric or telocentric. In normal human karyotype, the 46 (23 pairs) chromosomes are arranged in seven groups according to their morphology, *viz*. A (No. 1, 2, 3), B (No. 4, 5), C (No. 6, 7, 8, 9 10, 11, 12 and X), D (No. 13, 14, 15), E (No. 16, 17, 18), F (No. 19, 20) and G (No. 21, 22 and Y). Males are 44 + XY and females are 44 + XX. In recent years, after the introduction of high-resolution G-banding technique by Yunis (1984), it has been possible to precisely examine the chromosomes for identification or characterization of numerical or structural mutation or aberrations like translocation, deletion, inversion etc. from the comparative study of band-profile.

Leukaemia is the malignant proliferation of white blood cells whose abnormal forms are found in blood. Almost all leukaemias possess consistent chromosome defect. It is becoming apparent that the rearrangements themselves can subvert the normal functioning of a particular gene. The most supporting evidence that has revolutionized this concept is the discovery of the expression of oncogenic activity of c-abl gene in case of Philadelphia chromosome (Ph^1) in chronic granulocytic leukaemia (CGL or CML), t(9:22) (9q 34.1: 22q 11.21) (t - translocation; p - short and q-long arm of chromosome; 9 and 22 - chromosome no.; 34.1 and 11.21 - band no.)

(Nowell and Hungerford, 1992; also see Watson et al., 1987).

Acute lymphoblastic leukaemia (ALL) is the neoplastic transformation of lymphoid group of blast cells *i.e.*, T-, B- and null-cell precursors. Chromosome identification is clinically very important in ALL patients since they generally possess a poor prognosis and need very aggressive chemotherapy (Sett, 1988, 1991). It is quite difficult to prepare good chromosome spreads from ALL patients, for mostly the chromosomes appear fuzzy or inconspicuous, reason of which is still unknown (Sett, 1992). Mostly the ALL patients possess clonal chromosome aberrations showing aneuploidy, hyperdiploidy and hypodiploidy (Leukaemia Chromosome Workshop Report, 1980). Particularly the child group having hyperdiploidy greater to 50 chromosomes exhibit best prognosis, and mostly they are null-cell ALL - L1. They possess a good percentage of 8n, 16n, 32n and 64n plates in their bone-marrow, and this n-value increases with the induction-of-remission phase of standard chemotherapy and gradually declines with maintenance-of-remission phase when the patients respond well. A probable cause of this event may be that these polyploid cells are megakaryoblasts which are the precursor of platelets. It is already known that the increase in n-value indicates a boost in platelet production; the last phase of induction-of-remission therapy shows the highest percentage of these poloyploids while the maintenance-of-remission phase shows their decrease, most probably for the increase in platelet production by the fragmentation of those polyploid megakaryoblasts (Sett et al., 1987, 1988).

Numerical aberrations are mostly non-random in ALL with chromosomes 6,8,18 and 21 and X being preferentially gained, and 7 and 20 are preferentially lost. Structural abnormalities found most frequently in ALL are t (9:22) (9q 34.1: 22q 11.21); t(4:11) (4q 21 : 11q 23); t(8:14) (8q 24.13 : 14q 32.33); $14q^{+}$ and $5q^{-}$ (+ and – indicate addition and deletion, respectively). The t(9:22) patients are mostly adult while the t(4:11) are mostly children, most of which are again less than one year old. Patients without apparent chromosomal abnormalities also show prognosis, while those with t(4:11) or t (8:14) respond poorly and have the shortest lifespan (Leukaemia Chromosome Workshop Report, 1982).

The reciprocal translocation in t(4:11) is cytologically diagnosed as ALL-L2. They present acute anemia, marked leucocytosis and splenomegaly. Immunologically this leukaemia is of the non-T, non-B type, and by electron microscopy it represents the characteristics of myelomonoblasts.

The t(9:22) ALL are cytologically diagnosed as ALL-L1 and L2. Mostly they possess basophilic or a mixed lymphocytic-granulocytic proliferation. An interesting feature of t (9:22) positive ALL is that in some adults with this disorder, if complete remission is achieved, the blood picture reverts to a chronic phase resembling CGL and a few patients develop features of acute granulocytic leukaemia (AGL or AML). These interrelationship of symptom-development amongst these disorders strongly indicates that there may exist some basic key phenomenon which may be common for the development of t(9:22) positive CGL, ALL and ANLL (Acute Non-Lymphoblastic Leukaemia). Whether Ph^{1} positive ALL represents a primitive form of ANLL, or a lymphoid-granulocytic stem-cell leukaemia, remains to be determined using immunological markers and electron microscopy. Analysis of finely banded chromosomes in case of Ph^{1} positive CGL, ANLL and ALL revealed that in all cases the breakpoint in chromosome 22 occured at subband q11.21 and that chromosome 9 had a breakpoint at q34.1 (Prakash and Yunis, 1984).

In spite of the difficulties in chromosome preparation and analysis in ALL, it is now evident that chromosome analysis has become an independent prognosticator for this dreaded disease.

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