SIGNIFICANCE OF KARYOTYPING IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

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Abstract

Treatment of childhood acute lymphoblastic leukemia has become a success story due to risk adapted chemotherapy regimens. Despite advances in molecular biology like fluorescence in-situ hybridization, polymerase chain reaction and microarray technology, conventional karyotyping has important role in risk stratification. This review gives simple description of karyotyping abnormalities with their clinical importance.

Introduction

Due to risk-adapted therapy used in various clinical trials, the outcome for children with acute lymphoblastic leukaemia (ALL) is now extremely favourable. Various clinical and biological features have been used to classify patients into risk groups, opening up the possibility for modification of therapy where appropriate. The karyotype now plays a vital role in risk assessment with an impact on patient management.

Various karyotype abnormalities in childhood ALL

The majority of patients with ALL demonstrate an abnormal karyotype, either in chromosome number (ploidy) or as structural changes. The frequency of particular genetic subtype differs in children and adults, significantly contributing to the outcome. Hyperdiploidy and t(12;21) are more common in children, while t(9;22) is more common in adults.(1)

Ploidy: Ploidy can be determined directly by the classic method of counting the modal number of chromosomes in a metaphase karyotype preparation or by measuring DNA index (DI) by flow cytometry. Normal diploid or pseudodiploid cells (cytogenetically normal but having a normal DNA content) have a DI of 1.0. Although the absolute number of chromosomes chosen as the cut-point for analysis may vary slightly between studies, cases of childhood ALL with higher ploidy (>50 chromosomes except extreme hyperploidy: near triploidy and near tetraploidy) have the best prognosis. Worse prognosis occurs in hypodiploid (30-40 chromosomes) and near haploid (24 to 28 chromosomes) ALL. (2)

Trisomies of virtually every chromosome have been described in ALL, but the most commonly found include trisomy 4, 6, 10, 14, 17, 18, 21, and X. Trisomy 8, the most common chromosomal numerical abnormality seen in acute myeloid leukemia (AML), occurs rarely in ALL, and when examined by fluorescent in-situ hybridization (FISH), translocations or duplications of the 8q24 band may be identified. Thus, the finding of trisomy 8 in leukemic lymphoblasts should prompt a reexamination of the available data to be sure that by morphology, histologic staining, immunophenotype, and karyotype that the patient has pre-B ALL and not L3 ALL or AML. (3) Most trisomies appear to be prognostically neutral in the hyperdiploid context in which they are found. Children’s Cancer Group (CCG) and Pediatric Oncology Group (POG) found low risk of treatment failure in combined trisomies (trisomies 4 and 10; trisomies 10 and 17; triple trisomies 4,10 and 17). (4) Although monosomy 7 and deletions of 7q are primarily associated with myeloid disorders, they are also found in approximately 4% of pediatric ALL cases. These abnormalities are more likely to be observed in poor risk patients. (5)

Structural chromosomal abnormalities: Translocations are the most common structural abnormalities that are detectable by standard G-banding techniques in about 40% of cases. The translocations are more frequent in the pseudodiploid and hypodiploid groups that may partially explain their relatively poor prognoses.

The t(12;21)(p13;q22) is the most common ALL translocation found in about 22% of pre-B ALL by FISH. By standard karyotyping, approximately 5% of ALL patients have visible deletions of 12p13 and rearrangements. This rearrangement results in TEL-AML1 (ETV6-RUNX1) fusion gene that confers good prognosis independent of clinical risk factors. (6)

The pre-B ALL cases that have the t(1;19)(q23;p13) and express E2A-PBX1 protein have a poor prognosis (higher risk of central nervous system relapse) on standard therapies specially but have better outcomes when therapy is intensified specially with high dose methotrexate. (2)

The t(17;19) with E2A-HLF fusion occurs in 1% of childhood ALL and appears to define a poor-prognostic group of adolescent patients who have an unusual clinical presentation characterized by hypercalcemia, an increased risk of disseminated intravascular coagulation, and a pro-B (clgM+), low CD10 positivity immunophenotype. (2)

The 8q24 translocations e.g. t(8;14), t(2;8) and t(8;22) leading to Myc protein activation can be identified in virtually every case of mature B-cell ALL, also called as Burkitt’s leukaemia (BL) or ALL-L3 as per French-American-British (FAB) classification. Patients with BL respond quite poorly to conventional ALL treatment but fare better on therapy similar to that used for Burkitt’s lymphoma.

Structural abnormalities (including translocation, deletion, and partial duplication) of chromosome band 11q23 are present in 5% to 10% of pediatric ALL, 60-70% of infant leukemia, and 85% of secondary leukemia. Virtually all of these 11q23 abnormalities have occurred in the same region of a gene named MLL (myeloid/lymphoid leukemia gene or mixed lineage leukemia). More than 40 partner genes have been found for MLL, the most common of which are located on chromosomes 4, 6, 9, and 19. ALL patients, especially infants, with rearrangements involving 11q23/MLL have significantly poorer treatment outcomes. Allogeneic transplantation with haemopoietic stem cells from an HLA-matched related donor does not seem to improve the clinical outcome in patients with t(4;11)-positive leukaemia.(7)
The t(9;22) or Philadelphia (Ph) chromosome remains the translocation with the worst prognosis in pediatric ALL. This translocation results in bcr-abl fusion gene coding for activated tyrosine kinase. Children with Ph+ ALL tend to be older, have higher initial leukocyte counts, a higher frequency of central nervous system leukemia and respond poorly to therapy. Early bone marrow transplantation (BMT) is traditionally recommended, but molecularly targeted therapy (imatinib or dasatinib) may obviate the need for early BMT in future trials. (8)

Abnormalities in 9p, del 6p and breakpoints at known immunoglobulin and T-cell rearrangement (TCR) genes are commonly found in T-cell ALL without any known prognostic significance.

Recent data from United Kingdom Medical Research Council (UK MRC) ALL 97/99 study confirmed independent prognostic significance of ETV6-RUNX1, high hyperdiploidy, iAMP21, t(9;22), loss of 13q, and abnormal 17p. Based on these data, patients were classified into good, intermediate, and poor cytogenetic risk groups (Table-1). The authors found a strong correlation between poor-risk cytogenetics and slow early response, as well as early relapse. (6)

**Advantages and disadvantages of conventional karyotyping (G-banding):**

The detection of clonal chromosome abnormalities, especially 9p abnormalities, t(12;21), and some of the 11q23 rearrangements, by conventional G-banded analysis is often unsuccessful in ALL, because of poor chromosome morphology, cryptic rearrangements, imperfect banding and a low mitotic activity of the malignant cell population. G-banding is still regarded as being the gold standard for genetic tests, since it is the best one currently available for assessing the whole karyotype at once. Both FISH and comparative genomic hybridization (CGH) are regarded as additional powerful techniques complementary to G-banding in cases with an unsuccessful, incomplete or complex G-banded karyotype. (9)

**Conclusion:**

Considering the usefulness of conventional karyotyping, a dedicated cytogenetics laboratory with clearly defined standard operating procedures and quality control and a successful working relationship with the clinician are required to increase the success rate of conventional karyotyping. (10)

**References:**


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