Review Article

Acute Lymphoblastic Leukemia: Characterization and its Prognostic Values

Neelkamal, *Radha Rathee

Department of Genetics, M. D. University, Rohtak, Haryana, India.

ABSTRACT

Acute lymphoblastic leukemia is a type of leukemia which is characterized by 20% or more lymphoblasts in the bone marrow and/or the blood. It is a rapidly developing, abnormal growth of the cells that are precursors of lymphoblasts. The peak incidence occurs between age 2 and 5 years. The most frequent signs are lymphadenopathies, hepatosplenomegaly, fever, anemia, signs of hemorrhage, and bone tenderness. Biological findings include hyperleukocytosis due to circulating lymphoblasts. Most of the cases of acute lymphoblastic leukemia show chromosomal and genetic abnormalities. These anomalies occur spontaneously in important regulatory genes in a lymphoid cell population. The causative factors may be like smoking, high birth weight, diet, and high socioeconomic status, electromagnetic field, being exposed to radiation, pesticides, past treatment with chemotherapy or other drugs that weaken the immune system. It is a biologically heterogeneous disorder, so that morphologic, immunologic, cytogenetic, and molecular genetic characterizations of leukemia lymphoblasts are needed to establish the diagnosis or to exclude other possible causes of bone marrow failure and, finally, to classify its subtypes. The survival rate for children younger than 15 years of age reaches about 75%, but, despite the significant improvement of outcome during the last decades, still roughly 25% of patients suffer from a relapse of the disease. With the need to stratify patients in risk groups and to provide risk-adapted therapy, treatment requires high levels of organization, expertise and knowledge.

Keywords: Acute lymphoblastic leukemia, associated risk factor, etiology, prognosis.

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***Address for correspondence:**
Radha Rathee
Research Scholar, Lab No. 22, Dept. of Genetics, M. D. University, Rohtak-124001, Haryana, India.
E-mail: radharathee@gmail.com

INTRODUCTION

Leukemia is a cancer of the blood or bone marrow characterized by an abnormal increase of blood cells, usually white blood cells or leukocytes. Acute lymphoblastic leukemia is a rapidly developing, abnormal growth (neoplasm) of the cells that are precursors of lymphoblasts. The French-American-British Cooperative Working Group defines three categories of lymphoblasts i.e. L1, L2 & L3. L1 lymphoblasts are small cells characterized by a high nucleus-to-cytoplasm ratio [1]. The pale blue cytoplasm is scanty and is limited to a small portion of the perimeter of the cell. The L2 lymphoblasts have indistinct nucleoli and nuclear membranes that vary from round to clefted [2]. L3 lymphoblasts are a heterogeneous group of cells identical to Burkitt-like leukemia and characterized by deeply basophilic cytoplasm and prominent cytoplasmic vacuolization. Approximately 85% of children with ALL have predominant L1 morphology, 14% have L2, and 1% has L3, while the L2 subtype is more common in adults [3]. Individual chromosomal abnormalities are strong independent indicators of outcome, especially risk of relapse. Diagnostic cytogenetics identifies patients with a higher rate of relapse and those who are likely to have a high-risk relapse [4].

Epidemiology:

Reported annual incidence of ALL is approximately 9-10 cases per 100,000 populations in childhood [5]. The overall survival according to age, with follow-up of all patients in December 2008 through the population registry supports the strong correlation between age and outcome [6, 7].

In 2013, leukemia is expected to strike approximately 12 times as many adults (43,749) as children and adolescents younger than 15 years (3,605) [1, 8]. In India, 60-85% of all leukemias reported are acute lymphoblastic leukemia [3]. There were geographic variations in frequency of leukemia [9]. ALL is reported to be the most frequent in the south [10] and intermediate in the East, West [11] and central India [12]. Interestingly, the incidence of ALL is lesser in east India [13] as well as Northern areas [14]. In a study from Haryana by Kumar et al, there were 70.2% children and 29.8% adult patients of ALL in which male to female ratio was 2.03:1 (Fig.1) that is much higher than what is seen in the developed world [15]. In developed countries, the age distribution of ALL shows a major peak at pre-school age (between 1 and 5 years of age) with a slow decline toward adolescence [16]. The age distribution of children of ALL in developed countries shows a very marked early peak between 2-5 years, followed by a small peak between 11-15 years and the median age of 4 years [17, 18, 19]. There has been a gradual increase in the incidence of ALL in the past 25 years [20].

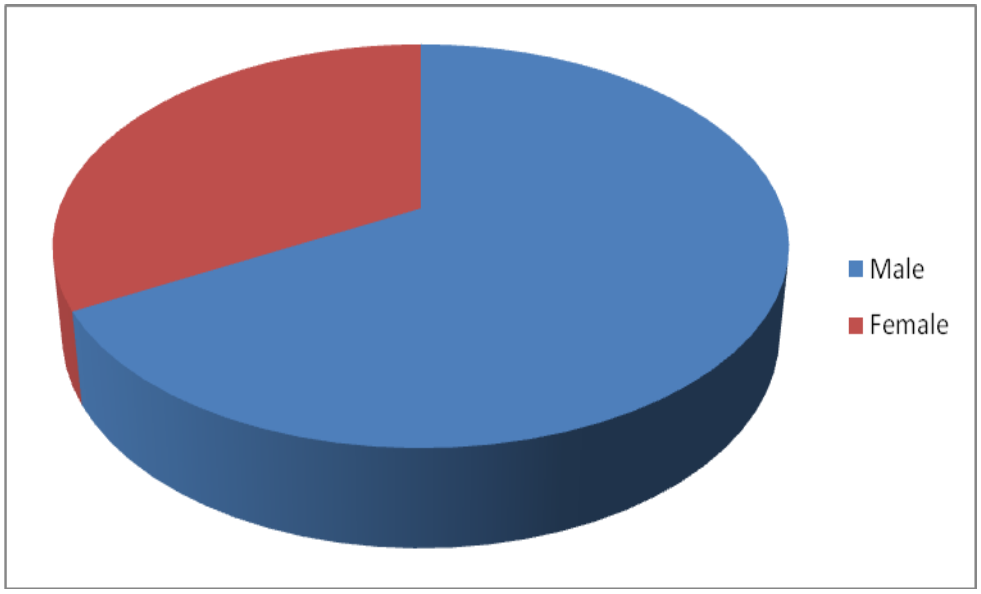

Figure 1: Percentage Frequency of Sex Ratio in Patients of Acute Lymphocytic Leukemia.

Etiology:

In ALL lymphoblast are produced by a part of DNA which is called proto-oncogene. Most of the proto-oncogenes involved in leukemia encode transcription factors, many of which have revealed to be important regulators of the proliferation, differentiation and survival of blood cell precursors [21, 22]. In leukemia's, including ALL, chromosomal translocations occur regularly. It is thought that most translocations occur before birth during fetal development. These translocations create a rearrangement of genes, which leads a so-called protooncogene to transform into an oncogene. The oncogene causes leukemia either by stimulating cell division or by inhibiting the programmed cell death called apoptosis. A translocation can activate a proto-oncogene by two different mechanisms. A more frequent event is a merger of two genes to form a fusion gene that produces abnormal chimaeric protein inducing leukemia. As an example, translocation t (1; 19) in ALL creates the fusion of *E2A* (immunoglobulin enhancer binding factors *E12/E47*) and *PBX1* (pre-B-cell leukemia transcription factor 1) genes. In the *E2A-PBX1* fusion protein transactivating domains of *E2A* are joined to the DNA-binding domain of *PBX1*, which alters the transcriptional properties of the *PBX1* transcription factor [23, 24].

Another event that may initiate leukemia is inactivation of a tumor suppressor gene. Tumor suppressor genes are essential for

normal cell development and they prevent carcinogenesis. Very few tumor suppressor genes have been reported in acute leukemias. Screening for chromosomal regions with loss of heterozygosity (LOH) is one way to track novel tumor suppressor genes. In childhood ALL, the regions that most frequently show LOH are the short arms of chromosomes 9 and 12 (in about 30-40% and 25-30% of the patients, respectively) [25, 26].

Scientific research has shown that all malignancies are due to subtle or less subtle changes in DNA that lead to unimpaired cell division and breakdown of inhibitory processes. Many of the described molecular mutations bear evidence of immunoglobulin joining region (VDJ) and T-cell receptor (TcR) recombinase activity. A few other studies have also evaluated the possible role of infections during infancy in the etiology of ALL, with some showing a protective effect [27] and others suggesting the opposite [28].

Another mechanism by which a translocation causes leukemia is transfer of a normally quiet transcription factor gene to the neighborhood of active promoter or enhancer elements, which accelerate the function of the gene. For example, in translocations t(8;14), t(2;8) and t(8;22) in Burkitt leukemia, the gene encoding the *MYC* transcription factor is exposed to the enhancer elements of an immunoglobulin gene. These enhancer elements cause over expression of the *MYC* gene, which is important in the regulation of cell division and cell death [29]. Further characterization of these genes revealed that they are often involved directly or indirectly in the development and homeostasis of normal blood cells, and that abnormal protein products of fusion genes created by specific translocations and inversions can deregulate proliferation, differentiation or programmed cell death (apoptosis) of blood cell precursors [30, 31].

Risk Factors:

The causative factor of ALL is unknown but there are some risk factors which are known to be associated with ALL. These factors are like ionizing radiation, pesticides, smoking, chemicals, and EMFs. Ionizing radiation is considered a 'known' cause of childhood leukemia. The risk is also higher for those exposed at an earlier age [32] and secondary leukemias in the individuals treated by radiotherapy [33]. Radiation from nuclear power plants is also a known cause for both kinds of leukemia [34]. X-ray examinations of pregnant women may be associated with increased risk of subsequent childhood ALL [35]. A study found that exposure to X rays after birth increased the risk of leukemia. Infants receiving diagnostic X-rays had 60% more leukemia than other children [36]. The exposure to post-natal diagnostic X-rays is associated with increased risk of childhood ALL, specifically B-cell ALL, but not AML or T-cell ALL [37].

Several studies have linked leukemia to pesticides. One large recent study of 491 children with ALL found that risk was increased by home use of some kinds of pesticides and by use of multiple different pesticides. Herbicide use during pregnancy was associated with 50% increase in risk. A study of nearly 2,000 children found that the risk of acute lymphoblastic leukemia was increased if the children's mothers were exposed to solvents, paints, or thinners before conception or during pregnancy or to plastics after birth. The father's exposure to plastics before conception was associated with greater risk. This study reported that the timing of exposure was an important factor [38]. Several studies have found that exposure to electro magnetic field (EMFs) increases risk of leukemia for children [37]. It was found that children living near high voltage power installations were more likely to be found to have leukemia than other children [39]. One recent study found that risk of leukemia was elevated when exposure to EMFs was consistent over the term of the pregnancy and in cases where the design of the water system in the home led to 'ground currents' from connections between plumbing pipes and the grounding for the electricity [40]. Only one environmental risk factor (ionizing radiation) has been significantly linked with either ALL or AML; most environmental risk factors [e.g., electromagnetic fields (EMFs), cigarette smoking] have been weakly or

inconsistently associated with either form of childhood leukemia [41].

Some genetic diseases have also association with acute lymphocytic leukemia. Children with trisomy 21 (i.e., Down syndrome) are up to 15 times more likely to develop leukemia than normal children. Other less common pre-existing chromosomal abnormalities have been linked to leukemia, included are Klinefelter's syndrome, Bloom syndrome, and Fanconi's anemia. Lymphoid malignancies, with a predominance of T-ALL, have been reported in patients with ataxia-telangiectasia (AT), an autosomal recessive disorder characterized by increased chromosomal fragility [42, 43, 44, 45]. Literature supports the hypothesis that an infection is involved in the etiogy of acute lymphocytic leukemia in children, particulrily those cases occuring in children between 2 and 5 years of age [9, 46, 47]. Viruses have also been linked to some forms of leukemia. Assosiation of human T-cell lymphotrophic virus type 1 with adult T-cell leukemia, of epstein-Barr virus with mature B-cell ALL and of human imunodeficiency virus (HIV) with lymphoproliferative disorders have been described [48, 49].

Many cases of ALL that develop in children have a prenatal origin. Evidence in support of this comes from the observation that the immunoglobulin or T-cell receptor antigen rearrangements that are unique to each patient's leukemia cells can be detected in blood samples obtained at birth. Similarly, there are data that patients with ALL characterized by specific chromosomal abnormalities had blood cells carrying the abnormalities at the time of birth [50, 51, 52]. Genetic studies of identical twins with concordant leukemia further support the prenatal origin of some leukemia [52]. The emerging association between certain combinations of dermatoglyphic traits and specific chromosome aberrations quickly established a useful diagnostic and an integral part of the medical diagnostic [50]. In pediatric leukemia, data have indicated that most chromosome translocations and preleukemic clones arise in utero during fetal hematopoiesis with secondary genetic events that occur postnatally [33]. There is little indication that propensity for ALL is passed on from parents to children.

Immunophenotyping:

Numerous immunophenotypic features have been examined for their potential prognostic value. Flow cytometry is the preferred method of diagnosis and immunophenotyping acute lymphoblastic leukemia. ALL presumably arises from malignant transformation of B- or T-cell progenitor cells. B-cell leukemia occurs more frequently than T-cell leukemia. The ALL arise from B-cell in 85% patients and from T-cell in 15% cases. B-cell is more commonly seen in children, but can occur at any age. It is the most common type of leukemia found in children (nearly 75% of cases occur in children under six years of age), although it affects both children and adults [53]. In children, B-cell ALL accounts for 60-80% cases whereas T-cell comprises only 11-20% (**Fig. 2**) [15]. T-cell ALL represents approximately 15% to 20% of all cases of ALL in Western countries [54, 55]. The stages of ALL include Early pre-B ALL, Common ALL, Pre-B-cell ALL, Mature B-cell ALL (Burkitt leukemia), Pre-T-cell ALL and Mature T-cell ALL [56]. B- and T-cell lymphoblastic leukemia cells express surface antigens that parallel their respective lineage developments. Precursor B-cell ALL cells typically express CD10, CD19, and CD34 on their surface along, with nuclear terminal deoxynucleotide transferase (TdT), while precursor T-cell ALL cells commonly express CD2, CD3, CD7, CD34, and TdT [57]. In a study by Bayram et al the most frequently detected five antigens were I2, CD10, CD41, CD2 and CD7/CD19 at the time of diagnosis and CD41, I2, CD10, CD19 and CD2 at the time of relapse. Flow cytometric investigations revealed that antigen levels determined at the time of diagnosis increased or decreased by 10% at the time of relapse [58]. CD19 is also expressed on the earliest B-precursor lymphocytes that are malignantly transformed in ALL. Therefore, B-lineage ALL seems to be most suitable for a bispecific approach aimed at CD19 [59].

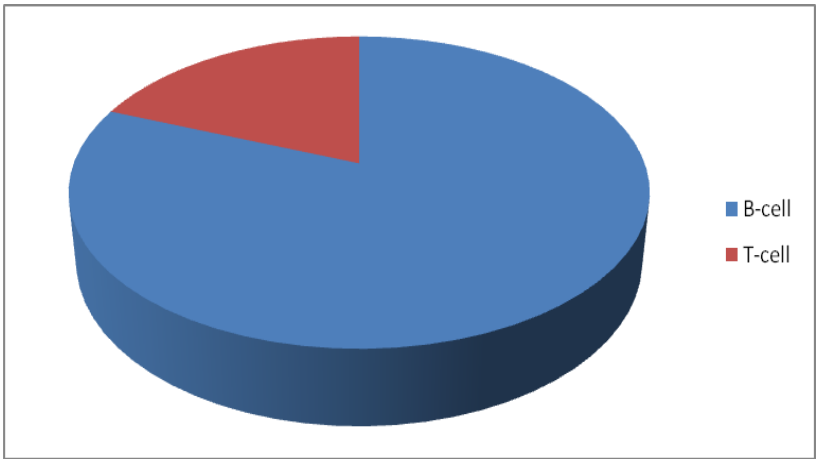

Figure 2: Percentage Frequency of Cell Type in Children of Acute Lymphocytic Leukemia.

Cytogenetics:

There have been many technical difficulties which make it difficult to gain information for chromosomal findings in ALL. Chromosome studies in ALL exhibit poor morphology; chromosomes tend to spread poorly, and appear blurred and fuzzy with indistinct margins, making banding studies challenging or even impossible [60, 61]. Williams et al used a direct technique of bone marrow (BM) chromosomal analysis by using specific flaming techniques and modified G-banding has been developed by Williams et al [61]. They identified clonal karyotypic abnormalities in 94% to 98% of cases of ALL. Such improved techniques also detected randomly occurring cytogenetic abnormalities in cases with hyperdiploid chromosome numbers (>50) that had previously been classified as normal in karyotype [61]. These results showed a high prevalence of clonal chromosomal abnormalities in ALL, as was shown for acute non lymphoblastic leukemias by Yunis, who used high-resolution banding techniques [62]. The majority of cases of ALL demonstrate an abnormal karyotype, either in chromosome number (ploidy) or as structural changes such as translocations, inversions, or deletions. These changes were detected in only half of ALL patients in the first banding studies [63]. Improvements in spreading and banding techniques have resulted in higher rates of detection, and most studies now report chromosomal changes in 60% to 85% of ALL cases [64, 65, 66, 67]. The third International Workshop on Chromosomes in Leukemia (TIWCL) found the majority of cytogenetic changes in cases of B precursor ALL, with only 39% occurring in T-cell ALL [64, 66].

Most studies on karyotypic abnormalities and their clinical significance have been performed in childhood ALL. Adult ALL showed nonrandom chromosomal abnormalities similar to those found in childhood ALL, but their distribution and their biological significance were different. However, in adult ALL the role of cytogenetics in patient management has largely been centered on the presence of the Philadelphia (Ph) chromosome which usually arises from t(9;22)(q34;q11.2) and results in *BCR-ABL* fusion [68]. Among the several changes, ploidy distribution and recurrent translocation associated with specific morphology and immunphenotype are well recognized in ALL. Numerical chromosomal abnormalities alone are less common in adult ALL, possibly reflecting a fundamental difference in the pathogenesis between childhood and adult ALL [69]. Among adults, patients with normal karyotype and those with isolated 9p/*CDKN2A-CDKN2B* deletions had a relatively favorable (standard) prognosis, whereas those with 6q deletions, miscellaneous, and hyperdiploid karyotype had an intermediate prognosis, and patients with t(9;22)/*BCR/ ABL1*,t(4;11)/*MLL/AF4*, t(1;19)/*TCF3/PBX1* constituted the unfavorable prognosis group [70]. In childhood ALL numerous good and high-risk cytogenetic subgroups have been

identified which are regularly used to stratify patients to particular therapies [71].

Diagnosis:

ALL is diagnosis with a medical history, physical examination, complete blood count, blood smears, cytogenetics and immunophenotyping. The higher the white blood cell counts the worse the prognosis [72]. Blast cells are seen on blood smear in majority of cases. Pathological examination, cytogenetics (in particular the presence of Philadelphia chromosome), and immunophenotyping establish whether myeloblastic (neutrophils, eosinophils, or basophils) or lymphoblastic (B lymphocytes or T lymphocytes) cells are the problem. RNA testing can establish how aggressive the disease is; different mutations have been associated with shorter or longer survival. Medical imaging can find invasion of other organs commonly the lung, liver, spleen, lymph nodes, brain, kidneys, and reproductive organs [73, 74]. ALL lymphoblasts were classified using the French-American-British (FAB) criteria as having L1, L2 and L3 morphology. Most cases of ALL that show L3 morphology express surface immunoglobulin (Ig) and have a *C-MYC* gene translocation identical to that seen in Burkitt lymphoma i.e. t(8;14). On the bases of Immunophenotype the World Health Organization (WHO) classifies ALL as either B or T lymphoblastic leukemia. B lymphoblastic leukemia is subdivided by the presence or absence of specific recurrent genetic abnormalities i.e. t(9;22), MLL rearrangement, t(12;21), hyperdiploidy, hypodiploidy, t(5;14), and t(1;19).

Prognosis:

Four main treatment elements can be generally recognized in chemotherapy protocols adopted by international cooperative groups: induction with the aim of complete remission, CNS preventive therapy, consolidation and maintenance therapy. ALL treated with chemotherapy and the cases with poor prognosis are also with stem cell transplantation. The form and intensity of the treatment are determined based on the risk group. Patients with good or standard risk may be given less intensive conventional chemotherapy in order to minimize the side effects of the treatment, whereas patients with high risk may receive intensive treatment including stem cell transplantation. Therefore the differences in the overall outcomes between the different risk groups have reduced in recent years. The first aim of the treatment is to reach remission, a condition in which the clinical symptoms have disappeared and no leukemic cells can be detected by conventional methods. The treatment of childhood ALL takes 2-2.5 years. The treatment results have significantly improved during the past two decades, and at present up to 80% of the childhood patients' recovered [75]. The rate is much higher than adults with ALL, of whom only 30-40% patients were cured [71].

ALL is the most common childhood malignancy; dramatic advances in its treatment over the past three decades have changed it from a universally fatal to an almost curable disease in 85% of cases. As pediatric oncologists have become more successful at treating ALL, much of the clinical research efforts have focused on stratifying patients into various risk groups based on known prognostic features, so that patients with lower-risk disease could be treated less intensively with much less side effects and toxicities, while patients with a higher risk of treatment failure could be targeted for more aggressive therapies [76]. In the risk classification of ALL, not only cytogenetic alterations, but also many other factors are taken into account. These include, for example, white blood cell count (WBC) at diagnosis, age, response to primary therapy and the phenotype of the blasts (precursor-B cell / immature B cell / T cell) [77]. The groups of patients formed according to the existing criteria however, quite heterogeneous as regards the outcome of the patients, leading to excessive treatment of some patients and failure of treatment in others.

Remission and Survival:

The leukemia karyotype has emerged as one of the most important factors in both childhood and adult ALL. The cytogenetic abnormalities confer important prognostic information in ALL was first reported by Secker-Walker et al in 1982 in a series of

childhood ALL [78]. Complete remission (CR) rates, remission durations, as well as disease-free-survivals (DFS) were significantly affected by the karyotypic abnormalities [64]. Cytogenetic studies in childhood ALL have associated a better prognosis with hyperdiploid karyotype and a worse prognosis with balanced translocation [78, 79]. Among adult patients the highest likelihood of cure (21% to 30%) was projected in patients with chromosome numbers of >50, or 47 to 50, with 6q2, or with a normal karyotype [80].

The importance of cytogenetics, as the single most important prognostic factor in adult ALL, has been reported previously by the *CALGB* and by the *GIMEMA and MRC UKALLXII/ECOG* study groups [67, 70, 81, 82, 83]. The correlation of the karyotype in ALL with other recognized prognostic factor is an independent prognostic not only in childhood [81] but also in adult patients [82]. Based on clinical risk criteria as well as modern laboratory investigation including cytogenetics, patients can be divided into prognostic and assigned to risk-adjusted treatment protocols. The clinical outcome of patients with hyperdiploidy varies in different series, being more favorable in children than in adults, where a poor outcome has been repeatedly reported [65, 82]. ALL is a biologically heterogeneous disorder, so that morphologic, immunologic, cytogenetic, and molecular genetic characterizations of leukemia lymphoblasts are needed to establish the diagnosis or to exclude other possible causes of bone marrow failure and, finally, to classify ALL subtypes. The survival rate for children younger than 15 years of age reaches about 75%, but, despite the significant improvement of outcome during the last decades, still roughly 25% of patients suffer from a relapse of the disease [83]. Even if the management of relapse remains largely controversial, an increasing use of high dose chemotherapy blocks and stem cell transplantation is adopted in most cases. With the need to stratify patients in risk groups and to provide risk-adapted therapy, treatment requires high levels of organization, expertise and knowledge.

CONCLUSION

The present study has identified several risk factors of developing ALL so general awareness can be made in society to reduce the load of disease. Cytogenetic abnormalities were found associated with clinical and prognostic factors so further investigation may help to know mechanism behind this. With identification of risk categories on the basis of cytogenetic groups, patients with low risk may be given less intensive conventional chemotherapy avoiding the toxic effect of treatment whereas patients with high risk may receive intensive treatment including stem cell transplantation. Improvements in cytogenetic techniques have yielded significant insight as to the importance of cytogenetic abnormalities in the pathophysiology and prognosis of hematological malignancies.

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