A Review on Acute Lymphoblastic Leukaemia

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Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children. It makes up three quarters of all cases of leukaemia in children and 20% of all cases of leukaemia in adults. It is now curable in 60 – 70% of children but only 20-35% in case of adults. Most of the understanding of biology and treatment of ALL originates from studies in children. A systematic literature review on different aspects of ALL was carried out. Relevant information from original articles, review articles, short communications and case reports published in different national and international journals, relevant books and online publication were compiled. Immunophenotypic and cytogenetic analyses of ALL have contributed to a more rational classification of ALL. These analyses have identified subgroups with poor prognosis or with different therapeutic requirements. Innumerable research works by many authorities from different parts of the world are in progress to find out the exact aetiology, pathogenesis and methods of treatment to cure this fatal disease. Currently intensive induction and maintenance chemotherapy are associated with encouraging results in children with ALL. The results for adults are inferior but still very encouraging, provided those with appropriate experience and facilities treat them. Although chemotherapy of ALL has proved highly successful in obtaining long-term remission, even in adults, the same degree of success has not been obtained in all types of ALL. Allogeneic bone marrow transplantation is a promising method of treatment for ALL, particularly those with poor prognostic features. Although the prognosis of patients with ALL has improved markedly during the past decades, newer strategies, including more dose-intensive therapy, the searches for new drugs, more target-specific therapy, are needed to improve the current cure rates.

Key words: Acute lymphoblastic leukaemia

Introduction

The leukaemias are malignant neoplasms of the haemopoietic stem cells.1 acute leukaemia is the most common malignancy in children.2 In the United States the incidence of ALL is roughly 6000 new cases per year (as of 2009), or approximately 1 in 50,000.3 Acute lymphoblastic leukaemia makes up three quarters of all cases of leukaemia in children and 20% of all cases of leukaemia in adults,2,4 ALL has a peak age incidence between 2 to 6 years and is more common in whites than in blacks. ALL occurs more commonly in boys than in girls. In Bangladesh it is not possible to ascertain the incidence of leukaemia including ALL until an ambitious study is being undertaken. A few hospital based small studies have been made and these studies show that the incidence of leukaemia in children ranges from 44% to 80%,5,6,7 and in adults about 61.7%8 among all cancer patients. Commonest type of childhood leukaemia is ALL ranging from 50% to 90.7% among all leukaemias in this age.5,6,7 Incidence of ALL in adults ranges from17.6% to 37.5%.8

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Maximum incidence of ALL is noted in the age group 1-10 years.\textsuperscript{6,8,9} Males are more commonly affected than females.\textsuperscript{7,8,9} It is to be noted that although studies have shown that the incidence of ALL in Bangladesh does not significantly differ from those in the developed countries; these small hospital based studies may not reflect the actual magnitude of this malady in the whole community.

Although chemotherapy of ALL has proved highly successful in obtaining long term remission, even in adults, the same degree of success has not been obtained in all types of ALL.\textsuperscript{10} Bone marrow transplantation is a promising method of treatment for ALL particularly those with poor prognostic features but is still unattainable in many developing countries like ours due to its high cost and vigilant maintenance. In this review, we like to make an overall review on the aetiology, pathogenesis, management and prognosis of ALL in the light of recent advances, which have been made in this field.

**Aetiology**
The exact aetiology of leukaemia is still unknown. It may result from interaction of several different factors.

**Risk factors for leukaemia**

**Radiation** - ALL is associated with exposure to radiation. The association of radiation and leukaemia in humans clearly established in studies of victims of the Chernobyl nuclear reactor and atom bombs in Hiroshima and Nagasaki.\textsuperscript{11} Increased incidence of deaths from different cancers and leukaemia including acute lymphoblastic leukaemia have been reported by Smith and Doll in 1981 among British radiologists. Radiotherapy for ankylosing spondylitis and diagnostic X-rays of the foetus in pregnancy are also associated with development of leukaemia.\textsuperscript{12}

**Chemicals** - Among the chemical agents Benzene\textsuperscript{13} and other aromatic hydrocarbons have been implicated in the causation of acute leukaemias.\textsuperscript{14} Aksoy et al (1974) in a study among shoe workers in Istanbul noted an incidence of leukaemia of 13 per 100,000. Among all the cases, ALL constituted 11.5 percent.\textsuperscript{13}

**Drugs** - Leukaemia also occurs more commonly in subjects who have taken cytotoxic agents which produce an increase in the incidence of chromosome breakage. Drugs most commonly implicated are alkylating agents, such as cyclophosphamide, chlorambucil, melphalan, procarbazine etoposide and nitrosoureas. However, most common type of leukaemia is AML.

**Chromosomal abnormality** - Children with trisomy 21 (Down’s syndrome or Mongolism) have approximately 15 times the risk of developing acute leukaemia than have children in the general population.\textsuperscript{2} Acute lymphoblastic leukaemia is the most common type of leukaemia among mongoloids.

A number of other constitutional disorders have also been found to be associated with an increased incidence of acute leukaemia. These are Fanconi’s aplastic anaemia, ataxia telangiectasia, congenital agamaglobulinaemia, Bloom’s syndrome and the Wiskott-Aldrich syndrome.\textsuperscript{15} Several investigators have found that children with Bloom’s syndrome\textsuperscript{16} and Ataxia telangiectasia\textsuperscript{2,16} are at an increased risk of developing acute lymphoblastic leukaemia.

**Twin studies** - At the greatest risk thus far known is the child whose identical twin has developed leukaemia. Among monozygotic twins the concordance rate for ALL is about 20%.\textsuperscript{16,17}
Viruses - Viruses are a well-known cause of lymphoid leukaemia in several species including rodents, birds, cows, and subhuman primates. Most common are the RNA tumour viruses (retroviruses), which typically induce thymic or B-cell leukaemias or lymphomas. One rare form of T-cell leukaemia/lymphoma appears to be associated with a retrovirus (HTLV-1) similar to the virus causing leukaemia in cats and cattle. Patients were usually young to middle aged men. However HTLV has not been identified in any form of childhood leukaemia.

In addition to retroviruses, the role of DNA viruses in lymphoid malignancy has been studied, particularly the Epstein-Barr virus (EBV). It has been found that, infection with the virus is extremely widespread and the virus has a propensity for growing in lymphoid cells and in no other cells. EBV has a clear association with Burkitt’s lymphoma and therefore may be related to ALL of L3 subtype (so called Burkitt’s leukaemia).

Pathogenesis and molecular epidemiology
The precise pathogenetic events leading to the development of ALL are still unknown, but they are likely to affect genes that control lymphoid cell homeostasis, resulting in dysregulated clonal expansion of immature progenitor cells. The prenatal origin of some leukaemias was established through genetic studies of identical twins with concordant leukaemia and backtracking of leukaemia-specific fusion-gene sequences (e.g. MLL-AF4, TEL-AML1) to neonatal blood spots. The t(4;11) and MLL-AF4 fusion sequence has high concordance rate in identical twins (25-100%) and a very brief latency period (a few weeks to a few months), which suggests that this fusion per se be sufficient for leukaemogenesis or at the very least, may be able to provoke a secondary change leading to leukaemia development. Deficiency of glutathione-S-transferase (GST-MT and GST-T1), enzymes that detoxify electrophilic metabolites by catalyzing their conjugation to glutathione, has been associated with infant leukaemias without MLL rearrangements and ALL in black children. Continued molecular epidemiological studies should provide further insights into the underlying mechanisms of leukaemogenesis and may lead to the development of effective preventive measures.

Cytogenetics
Cytogenetic translocations associated with specific molecular genetic abnormalities in ALL is shown in the Table 1.
Table 1. Cytogenetic translocations associated with specific molecular genetic abnormalities in ALL

<table>
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<tr>
<th>Cytogenetic translocations</th>
<th>Molecular genetic abnormalities</th>
<th>%</th>
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<tbody>
<tr>
<td>Cryptic t(12;21)</td>
<td>TEL-AML1 fusion</td>
<td>25.4%</td>
</tr>
<tr>
<td>t(1;19)(q23;p13)</td>
<td>E2A-PBX(PBX1) fusion</td>
<td>4.8%</td>
</tr>
<tr>
<td>t(9;22)(q34;q11)</td>
<td>BCR-ABL fusion(P185)</td>
<td>1.6%</td>
</tr>
<tr>
<td>t(4;11)(q21;q23)</td>
<td>MLL-AF4 fusion</td>
<td>1.6%</td>
</tr>
<tr>
<td>t(8;14)(q24;q32)</td>
<td>IGH-MYC fusion</td>
<td></td>
</tr>
<tr>
<td>t(11;14)(p13;q11)</td>
<td>TCR-RBTN2 fusion</td>
<td></td>
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The most common translocation is 12;21 and portends a good prognosis. Translocation 4;11 is the most common in children under 12 months and portends a poor prognosis.

Classification
The FAB classification
- ALL-L1; small uniform cells
- ALL-L2 large varied cells
- ALL-L3 large varied cells with vacuoles (bubble-like features)

Each subtype is then further classified by determining the surface markers of the abnormal lymphocytes, called immunophenotyping. There are two main immunologic types: pre-B cell and pre-T cell. The mature B-cell ALL (L3) is now classified as Burkitt’s lymphoma/leukaemia.

Who proposed classification of acute lymphoblastic leukaemia
The recent WHO international panel on ALL recommends that the FAB classification be abandoned, since the morphological classification has no clinical or prognostic relevance. It instead advocates the use of the immunophenotypic classification mentioned below.

1. Acute lymphoblastic leukaemia/lymphoma. Synonyms: Former FAB L1/L2

Treatment
The earlier acute lymphoblastic leukaemia is detected, the more effective the treatment. Treatment of acute leukaemia can include chemotherapy, steroids, radiation therapy, intensive combined treatments (including bone marrow or stem cell transplants), and growth factors.

Chemotherapy
Chemotherapy for ALL consists of three phases: remission induction, consolidation/intensification, and maintenance therapy.

Remission induction - The aim of remission induction is to rapidly kill most tumour cells and get the patient into remission. This is defined as the presence of less than 5% leukaemic blasts in the bone marrow, normal blood cells and absence of tumour cells from the blood and absence of other signs and symptoms of the disease. CNS prophylaxis should begin during this phase of treatment and continue during the consolidation/intensification period. The rationale is based on the presence of CNS involvement in 10-40% of adult patients at diagnosis.
Combination of prednisolone or dexamethasone, vincristine, asparaginase and daunorubicin (used in adult ALL) is used to induce remission. Those patients with Philadelphia chromosome positive ALL (or bcr-abl plus ALL) should have imatinib (dasatinib) added to their initial chemotherapy.24

Consolidation/Intensification - Intensification uses high doses of intravenous multidrug chemotherapy to further reduce tumour burden. Since ALL cells sometimes penetrate the CNS, most protocols include delivery of chemotherapy into the CSF. Typical intensification protocols use vincristine, cyclophosphamide, cytarabine, daunorubicin, etoposide, thioguanine or mercaptopurine given as blocks in different combinations. For CNS protection, intrathecal methotrexate or cytarabine is usually used combined with or without cranio-spinal irradiation. Central nervous system relapse is treated with intrathecal administration of hydrocortisone, methotrexate and cytarabine.

Maintenance therapy - The aim of maintenance therapy is to kill any residual cell that was not killed by remission induction and consolidation. For this purpose, daily oral mercaptopurine, once weekly oral methotrexate, once monthly 5-day course of intravenous vincristine and oral corticosteroids are usually used. The length of maintenance therapy is 3 years for boys, 2 years for girls and adults.25

Subclinical treatment of CNS - Cranial irradiation is the most effective CNS-directed therapy. However, the concern that it can cause substantial neurotoxicity and occasional brain tumours, has prompted most leukaemia therapists to use intensive intrathecal and systemic chemotherapy for 80-90% of patients. This approach, in combination with cranial irradiation for selected high or very high-risk cases, has lowered the CNS relapse to less than 5% in most studies.25 Therefore, cranial irradiation is now reserved for salvage therapy, thus sparing most patients from its toxic effects. While this approach is under study, most clinical trials still specify cranial irradiation for patients at particularly high risk of CNS relapse, e.g. those with CNS 3 status or T-cell with high leucocyte count.

Allogenic haemopoietic stem-cell transplantation - Many advances have been made in transplantation, such as prevention of graft-versus-host disease, expansion of the pool of suitable unrelated or related donors, acceleration of engraftment, enhancement of the graft-versus-leukaemia effect, and supportive care. Because improvements in transplantation and chemotherapy are occurring in parallel, the indications for transplantation in newly diagnosed and relapsed patients should be subjected to periodic re-evaluation. At present, Philadelphia-chromosome positive ALL and early haematological relapse are clear indications for transplantation.27 However, transplantation has not been shown to improve outcome in other types of very high-risk leukaemia, including infant ALL with MLL rearrangement.

Prognosis The survival rate has improved from zero four decades ago, to 20-75 percent currently, largely due to clinical trials on new chemotherapeutic agents and improvement in stem cell transplantation (SCT) technology. The prognosis for ALL differs between individuals depending on a variety of factors: Sex - females tend to fare better than males.16
Ethnicity - Caucasians are more likely to develop acute leukaemia than African-Americans, Asians and Hispanics and tend to have a better prognosis than non-Caucasians. Age at diagnosis - children between 1-10 years of age have better prognosis. Age <1 year or >10 years have poorer prognosis. White blood cell count at diagnosis - >50,000/µl is associated with poor outcome. Initial presentation with CNS - leukaemia carries a worse prognosis. Characteristics of leukaemia cells - FAB L3 subtype is at highest risk. Those with B-cell ALL have worst prognosis. Cytogenetics - is an important predictor of outcome. Some cytogenetic subtypes have a worse prognosis than others. These subtypes are shown in the Table II.

Table II: Cytogenetic subtypes and their predictors

<table>
<thead>
<tr>
<th>Cytogenetic change</th>
<th>Risk category</th>
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<tr>
<td>Philadelphia chromosome (20% of adult &amp; 5% of paediatric) t(4;11)(q21;q23)</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>t(8;14)(q24.1;q32)</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Complex karyotype (more than four abnormalities)</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Low hypodiploidy or near triploidy</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>High hyperdiploidy (&gt;50 chromosomes)(trisomy 4,10,17) del(9p)</td>
<td>Good prognosis</td>
</tr>
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Conclusion
The prognosis of patients with ALL has improved markedly during the past decades, though not equally in all types. However newer strategies, including more dose intensive therapy, the searches for new drugs, more target specific therapy are needed to improve the current cure rates. Of the new agents being tested, GW-506U78 is particularly effective in patients with T-lineage ALL but is associated with significant neurological toxic effects. STI-571 (known as Gleevec) selectively inhibits BCR-ABL tyrosine kinase. In a recent study, this agent induced a response rate of 70%, with 20% complete response (albeit transient) in patients with BCR-ABL positive ALL in relapse. Other promising agents include antibodies conjugated to toxins, eliciting complement activation and cell toxicity, or triggering signals that inhibit cell growth; molecular agents that increase the susceptibility of leukaemic cells to apoptosis, such as BCL2 antisense oligonucleotides and proteasome inhibitors, genetically manipulated cytokines that induce apoptosis in ALL cells. Several research works are in progress to find out the best method for treating this once highly killing disease. However, time has not yet come to make any comment on their effectiveness, yet we are in a hope that it will not be very far when like many other diseases ALL will essentially become a curable disease.

References


