EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 5
152-159
Year: 2023

# ACUTE LYMPHOBLASTIC LEUKAEMIA

**Shivangi Nema, Shashikant Namdev, Sarvesh Jain, Saurabh Ahirwar and Megha Shrivastava***

Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

***Corresponding Author: Megha Shrivastava**
Adina Institute of Pharmaceutical Sciences, NH86A, Lahdara, Sagar, MP, 470001.

**Article Received on 06/03/2023** **Article Revised on 27/03/2023** **Article Accepted on 17/04/2023**

## ABSTRACT
Acute lymphoblastic leukaemia develops in both children and adults, with a peak incidence between 1 year and 4 years. Most acute lymphoblastic leukaemia arises in healthy individuals, and predisposing factors such as inherited genetic susceptibility or environmental exposure have been identified in only a few patients. It is characterised by chromosomal abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells. Along with response to treatment, these abnormalities are important prognostic factors. ALL accounts for approximately 2 percent of the lymphoid neoplasms in the United States and occurs slightly more frequently in males than females, and three times as frequently in Caucasians as in African-Americans. Patients typically present with symptoms related to anemia, thrombocytopenia, and neutropenia due to the replacement of the bone marrow with the tumor. Symptoms can include fatigue, easy or spontaneous bruising and/or bleeding, and infections. Additionally, B-symptoms, such as fever, night sweats, and unintentional weight loss are often present but may be mild, and hepatomegaly, splenomegaly, and lymphadenopathy can be seen in up to half of adults on presentation. Central nervous system (CNS) involvement is common and can be accompanied by cranial neuropathies or symptoms, predominantly meningeal, related to increased intracranial pressure. This activity examines when acute lymphocytic leukemia should be considered on differential diagnosis and how to properly evaluate it. This activity highlights the role of the interprofessional team in caring for patients with this condition.

**KEYWORDS:** Leukaemia, Acute Lymphoblastic Leukaemia, Lymphoid Cells.

## INTRODUCTION
Acute lymphoblastic leukaemia (ALL) is a type of leukaemia where cancerous cells build up in the bone marrow, until eventually there's no room for normal blood cells to be made there. ALL is an acute leukaemia, which means it develops quickly and needs treatment straight away. Around 800 people are diagnosed with ALL in the UK each year. It affects children more often than adults. Acute lymphocytic leukemia (ALL) is a type of cancer of the blood and bone marrow - the spongy tissue inside bones where blood cells are made. Acute lymphoblastic leukemia (ALL) comprises a group of lymphoid neoplasms that are morphologically and immunophenotypically similar to B and T lineage progenitors. The pathogenesis of ALL involves the abnormal proliferation and differentiation of clonal populations of lymphoid cells. Studies in pediatric populations have identified genetic syndromes that predispose to a small number of ALL cases, including Down's syndrome, Fanconi's anemia, Bloom's syndrome, ataxiatelangiectasia, and Nijmegen's breakdown syndrome. Acute lymphoblastic leukemia has been hailed as a major success story in pediatric oncology with the advent of dose-escalating chemotherapy and allogeneic SCT. However, the high risk of this disease and the significant toxicities associated with chemotherapy in adults make the results less promising. Because some studies have shown benefits of pediatric-inspired therapies, much uncertainty remains about how adults with ALL can best be managed.

The word "acute" in acute lymphocytic leukemia comes from the fact that the disease progresses rapidly and creates immature blood cells, rather than mature ones. The word "lymphocytic" in acute lymphocytic leukemia refers to the white blood cells called lymphocytes, which ALL affects. Acute lymphocytic leukemia is also known as acute lymphoblastic leukemia. Acute lymphocytic leukemia is the most common type of cancer in children, and treatments result in a good chance for a cure. Acute lymphocytic leukemia can also occur in adults, though the chance of a cure is greatly reduced. The main signs and symptoms you get with ALL are caused by not having enough normal blood cells, because there are too many blast cells in your bone marrow. Common signs and symptoms are Fatigue is a kind of tiredness that lasts a long time and doesn't improve with rest. It's caused by a low number of red blood cells in your blood (a low red blood cell count). The medical name for this is anaemia. Anaemia can

also make you feel breathless, even when you're resting, and lead to chest pain. This is caused by a low number of platelets in your blood (a low platelet count). Platelets are the blood cells that stop bleeding by making the blood clot. A low platelet count can mean bruising easily, bleeding from your gums or nose, bleeding from wounds, which is hard to stop, black, tarry poos or poos that are streaked with red, because of bleeding in your gut, headaches, difficulty speaking or difficulty moving parts of the body, because of bleeding into the brain. This is caused by a low number of white blood cells. A low white blood cell count can lead to infections and fevers that last for longer or happen more often than normal. This is caused by a high metabolism, which is the rate you burn energy from food. We don't completely understand why the metabolism speeds up in people with ALL.

Acute lymphocytic leukemia occurs when a bone marrow cell develops changes (mutations) in its genetic material or DNA. A cell's DNA contains the instructions that tell a cell what to do. Normally, the DNA tells the cell to grow at a set rate and to die at a set time. In acute lymphocytic leukemia, the mutations tell the bone marrow cell to continue growing and dividing. Factors that may increase the risk of acute lymphocytic leukemia include are Children and adults who've had certain types of chemotherapy and radiation therapy for other kinds of cancer may have an increased risk of developing acute lymphocytic leukemia. People exposed to very high levels of radiation, such as survivors of a nuclear reactor accident, have an increased risk of developing acute lymphocytic leukemia. Certain genetic disorders, such as Down syndrome, are associated with an increased risk of acute lymphocytic leukemia. When this happens, blood cell production becomes out of control. The bone marrow produces immature cells that develop into leukemic white blood cells called lymphoblasts. These abnormal cells are unable to function properly, and they can build up and crowd out healthy cells. It's not clear what causes the DNA mutations that can lead to acute lymphocytic leukemia.

Leukemia is a cancer of the blood and bone marrow. Bone marrow is the spongy tissue in the center of most bones where blood cells are formed. Leukemia begins in one of the immature cells in the bone marrow. One or more changes (mutations) occur in the cell's DNA, causing it to become a type of cancer cell called a "leukemic cell." Leukemic cells do not mature into healthy, functioning blood cells. They grow faster and live longer than normal blood cells. They divide and copy themselves to create more and more leukemia cells. Over time, the leukemia cells prevent or suppress the development of normal, healthy blood cells in the bone marrow. These cells enter the bloodstream from the bone marrow and can spread to organs such as the liver and spleen. There are many different types of leukemia, divided mainly by whether the leukemia is acute (rapidly growing) or chronic (slow-growing) and whether it begins in myeloid or lymphoid cells. Knowing the specific type of leukemia can help doctors better predict an individual's prognosis (outlook) and select the best treatment. There are four main types of leukemia, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML). There are three main types of blood cells: red blood cells, white blood cells, and platelets. Red blood cells carry oxygen throughout the body. White blood cells help fight infections. Platelets help stop bleeding by clumping (clotting) at the site of injury. Blood cells begin as hematopoietic stem cells in the bone marrow. Hematopoietic stem cells are immature (underdeveloped) blood cells . In healthy bone marrow, these hematopoietic stem cells ultimately develop into red blood cells, white blood cells, and platelets through a process called 'differentiation' (National Cancer Institute, 1975). In patients with ALL, a mutation or series of mutations in the DNA (genetic material) of lymphoid stem cells (or "lymphoblasts") leads to the formation of leukemic cells. Leukemia cells are immature cells stuck in early cellular development. These leukemia cells, also known as ALL blasts, fail to mature into fully functional leukocytes. Due to genetic errors in mutated cells, cells continue to grow and divide, while healthy cells usually stop dividing and eventually die. All cells emerging from the original leukemia blast also have mutated DNA. When leukemic cells grow uncontrollably and accumulate rapidly in the bone marrow, production of normal, healthy red blood cells, white blood cells, and platelets slows or stops. The result is too many immature leukemic blasts that are unable to fight infection and too few mature, functional red blood cells and white blood cells and platelets.

**Pathogenesis**

The pathogenesis of ALL involves the abnormal proliferation and differentiation of a clonal population of lymphoid cells.[1] Studies in the pediatric population have identified genetic syndromes that predispose to a minority of cases of ALL, such as Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia and Nijmegen breakdown syndrome.Other predisposing factors include exposure to ionizing radiation, pesticides, certain solvents or viruses such as Epstein-Barr Virus and Human Immunodeficiency Virus.[2] However, in the majority of cases, it appears as a de novo malignancy in previously healthy individuals. Chromosomal aberrations are the hallmark of ALL, but are not sufficient to generate leukemia. Characteristic translocations include t(12;21) [ETV6-RUNX1], t(1;19) [TCF3-PBX1], t(9;22) [BCR-ABL1] and rearrangement of MLL. More recently, a variant with a similar gene expression profile to (Philadelphia) Ph-positive ALL but without the BCR-ABL1 rearrangement has been identified. In more than 80% of cases of this so-called Ph-like ALL, the variant possesses deletions in key transcription factors involved in B-cell development including IKAROS family zinc

finger 1 (IKZF1), transcription factor 3 (E2A), early B-cell factor 1 (EBF1) and paired box 5 (PAX5).

Most of the clinical manifestations of ALL reflect the accumulation of malignant, poorly differentiated lymphoid cells within the bone marrow, peripheral blood, and, extramedullary sites.[8] Presentation can be nonspecific, with a combination of constitutional symptoms and signs of bone marrow failure (anemia, thrombocytopenia, leukopenia).[3] Common symptoms include 'B symptoms' (fever, weight loss, night sweats), easy bleeding or bruising, fatigue, dyspnea and infection. Involvement of extramedullary sites commonly occurs and can cause lymphadenopathy, splenomegaly or hepatomegaly in 20% of patients. CNS involvement at time of diagnosis occurs in 5–8% of patients and present most commonly as cranial nerve deficits or meningismus. T-cell ALL also may present with a mediastinal mass.[4]

Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood. Evaluation for morphology, flow cytometry, Immunophenotyping and cytogenetic testing is valuable both for confirming the diagnosis and risk stratification. Lumbar puncture with CSF analysis is standard of care at the time of diagnosis to evaluate for CNS involvement.[5] If the CNS is involved, brain MRI should be performed. Other evaluation includes complete blood count with differential and smear to evaluate the other hematopoietic cell lines, coagulation profiles and serum chemistries. Baseline uric acid, calcium, phosphate and lactate dehydrogenase should be recorded to monitor for tumor lysis syndrome.[6]

**Classification**

The first attempt at classifying ALL was the French American British (FAB) morphological criteria that divided ALL into 3 subtypes (L1, L2 and L3) based on cell size, cytoplasm, nucleoli, vacuolation and basophilia.[7] In 1997, the World Health Organization proposed a composite classification in attempt to account for morphology and cytogenetic profile of the leukemic blasts and identified three types of ALL: B lymphoblastic, T lymphoblastic and Burkitt-cell Leukemia. Later revised in 2008, Burkitt-cell Leukemia was eliminated as it is no longer seen as a separate entity from Burkitt Lymphoma, and B-lymphoblastic leukemia was divided into two subtypes: B-ALL with recurrent genetic abnormalities and B-ALL not otherwise specified. B-ALL with recurrent genetic abnormalities is further delineated based on the specific chromosomal rearrangement present. In 2016, two new provisional entities were added to the list of recurrent genetic abnormalities and the hypodiploid was redefined as either low hypodiploid or hypodiploid with TP53 mutations. In adults, B-cell ALL accounts for ~75% of cases while T-cell ALL comprises the remaining case.[8]

**Treatment for ALL**

**Monoclonal antibodies**

CD22 is a B-lineage differentiation antigen expressed in B-cell ALL in 50–100% of adults and 90% of children. Upon binding of an antibody, CD22 is rapidly internalized, thus making it an attractive target for delivering immunotoxin to leukemic cells.[9]

**Epratuzumab**

Epratuzumab is an unconjugated monoclonal antibody targeting CD22 that has been studied in pediatric and adult relapsed/refractory ALL. Epratuzumab was evaluated in 15 pediatric patients as part of a salvage therapy regimen. The antibody was administered as a single-agent followed by the antibody in combination with standard re-induction chemotherapy.[10]

**Inotuzumab ozogamicin**

Inotuzumab ozogamicin (InO) is a monoclonal antibody against CD22 that is conjugated to calicheamicin, a potent cytotoxic compound that induces double-strand DNA breaks.[11] Upon internalization of the immunoconjugate, calicheamicin binds DNA and causes double-stranded DNA breaks, which induces apoptosis. Preclinical studies showed that calicheamicin conjugated to an anti-CD22 antibody resulted in potent cytotoxicity leading to regression of B-cell lymphoma and prevention of xenograft establishment at picomolar concentrations Phase 1 studies in non-hodgkin lymphoma (NHL) established a maximum tolerated dose of 1.8 $mg/m^2$ InO given intravenously every 3 to 4 weeks. Subsequently, InO was studied in adults with relapsed/refractory ALL. In this phase 2 trial, 90 patients were treated with either a single infusion every 3 to 4 weeks or weekly InO infusions. InO has also been studied in frontline therapy in combination with low-intensity HCVAD for elderly patients >60 years. These patients are prone to adverse events from chemotherapy and have poorer outcomes than their younger counterparts. In attempt to reduce toxicity, doxorubicin was eliminated from induction therapy, and cyclophosphamide, prednisone, methotrexate and cytarabine were given at reduced doses. InO was given during each of the first four courses. The regimen was well tolerated and produced superior 1-year OS as compared to historical data among similar patient population (78 vs 60%).[12,13]

A third anti-CD22 monoclonal antibody, moxetumomab, is currently in development for treatment of pediatric and adult ALL. Moxetumomab is a reformulation of an older study drug, BL22, which was composed the variable region ($F_v$) of an anti-CD22 monoclonal antibody fused to Pseudomonas aeruginosa exotoxin A. BL22 was shown to be highly active against Hairy Cell Leukemia in a phase 2 trial In a phase 1 trial of children with relapsed/refractory ALL, BL22 was well tolerated and exhibited anti-leukemic activity at all doses, but clinical benefits were transient and modest.[14,15] Therefore, BL22 was reformulated as moxetumomab to contain a $F_v$ fragment with greater affinity for CD22. In phase 1

trials, moxetumomab showed an overall activity rate of 70% in children with relapsed/refractory ALL. Enrollment is ongoing for a phase 1/2 trial of moxetumomab pasudodotox for treatment of relapsed/refractory ALL in adults.[16,17]

Combotox is a combination immunotoxin that contains a 1:1 mixture of anti-CD19 and anti-CD22 antibodies, both conjugated to the cytotoxin deglycosylated ricin-A chain. In pediatric patients with relapsed/refractory ALL, combotox led to a CR in 3 of 17 patients. In addition, six additional patients experienced a >95% reduction in peripheral blasts. In adults with relapsed/refractory disease, combotox led to reduction of peripheral blasts in all patients; however, a durable response was not seen as blast count rebounded quickly after the final dose of combotox. A phase I trial is recruiting patients to evaluate combotox in combination with cytarabine for adults with relapsed/refractory.[18]

Ofatumumab is a second-generation anti-CD20 antibody with a distinct binding site from that of rituximab. Ofatumumab was first showed to have benefit in fludarabine-refractory chronic lymphocytic leukemia, irrespective of prior rituximab exposure. Ofatumumab induces higher levels of complement-dependent cytotoxicity (CDC) and has a slower dissociation rate than rituximab, and thus holds promise for CD20+ lymphoid malignancies both as frontline therapy and as salvage for rituximab-refractory disease.[19] In a phase 2 study, ofatumumab was used in combination with HCVAD in patients with either newly diagnosed pre-B CD20+ ALL or those who had completed a single course of chemotherapy.

Another novel anti-CD20 monoclonal antibody, obinutuzumab, has shown promise in preclinical trials for CD20-positive B-ALL. Obinutuzumab was engineered to have enhanced affinity for the FcγRIIIa receptor on effector cells and thus enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). This compromises the ability of obinutuzumab to activate complement and predictably, CDC was inferior to that of rituximab and ofatumumab in vitro. However, obinutuzumab induced direct cell death and ADCC more rapidly and effectively. When all three mechanisms of cell death were evaluated together in B-cell depletion assays, obinutuzumab was more effective than either rituximab or ofatumumab achieving higher maximal depletion and lower $EC_{50}$. Furthermore, obinutuzumab was superior in inhibiting growth in NHL xenograft models. Awasthi et al. compared obinutuzumab to ritixumab in pre-B-ALL cell lines and found obinutuzumab to be superior in inducing cell death and ADCC. In a pre-B-ALL xenograft model, overall survival was improved with obinutuzumab compared to ritixumab. In clinical trials, obinutuzumab has been added to chlorambucil for treatment of adults with CLL and shown to prolong progression-free survival and improve complete response rate when compared to rituximab and chlorambucil. Taken together, these results suggest a role for obinutuzumab in CD20+ pre-B-ALL.[20]

**REGN1979**

REGN1979 is a biallelic monoclonal antibody targeting CD20 and CD3. The theory of REGN1979 is similar to that of blinatumumab, to engage T cells and B-cells thus resulting in activation of T-cell immune response against B-cells. REGN1979 prevented the establishment of lymphoma xenografts and led to complete tumor regression in murine models.In addition, in a primate model, REGN1979 led to a complete and durable depletion of B-cells. When compared to treatment with rituximab, treatment with REGN1979 led to significantly more profound depletion of B-cells. The safety of REGN1979 was established in a phase 1 trial of 25 patients with NHL and CLL. Dose-dependent antitumor activity was observed. The most significant adverse events include cytokine release syndrome (CRS) and hypotension. A phase 2 trial of REGN1979 in relapsed/refractory ALL is currently open for recruitment.

**C-CD19**

CD19 is the most widely expressed B-lineage specific antigen, expressed during all stages of differentiation, but lost on maturation to plasma cells. CD19 serves as a co-receptor for the B-cell surface immunoglobulin and its activation triggers a phosphorylation cascade involving src-family kinases and PI3K as well as the activation of c-myc, leading to proliferation and differentiation. CD19 is expressed in nearly all B-cell leukemias, and is rapidly internalized upon binding of an antibody, making it an ideal candidate for immunoconjugate therapy.[21]

**Coltuximab ravtansine (SAR3419)**

Coltuximab ravtansine is an anti-CD19 humanized monoclonal antibody conjugated to a semisynthetic maytansinoid compound, an anti-tubulin molecule similar to vincristine. Maytansinoids are more potent than vinca alkaloids, and thus have been of limited use in systemic therapy due to unacceptable toxicity. However, this potency makes them attractive candidates for targeted delivery. In preclinical studies, SAR3419 monotherapy delayed progression in pre-B-ALL xenografts and provided objective response. When used in combination with a chemotherapy regimen that mimicked pediatric induction protocols, SAR3419 was effective at prolonging the duration of remission.SAR3419 was then evaluated in a Phase 1 clinical trial with CD19+ B-cell lymphoma. Dose-limiting toxicities were reversible blurred vision and neuropathy.[22] A maximum tolerated dose (MTD) of 160 $mg/m^2$ administered once every three weeks was established. Reduction of tumor size was seen in 74% of patients, including 47% of patients with rituximab-resistant disease. An initial phase 2 clinical trial was terminated early due to low response rate of 25%.[23]

**Denintuzumab mafodotin (SGN-CD19A)**

A second anti-CD19 conjugated monoclonal antibody, denintuzumab mafodotin, is currently in development. In this case, the antibody is linked to the microtubule-disrupting agent monomethyl auristatin F (MMAF). In a phase 1 study of patients with relapsed/refractory B-ALL or aggressive B-cell lymphomas, a complete response rate of 35% was observed. Dosing interval of 3 weeks was shown to be superior to weekly dosing. An MTD was identified at 5 mg/kg q3wk. Interestingly, among Ph-positive B-ALL, the response rate was 63%, leading to recruitment of Ph-positive patients for an expansion cohort.[24] These results warrant further evaluation of denintuzumab mafodotin for relapsed/refractory ALL.

**ADCT-402**

ADCT-402 is the newest anti-CD19 monoclonal antibody to enter development. It is a humanized monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD). PBDs are a class of natural antibiotics derived from actinomycetes bacteria that inhibit cell division by binding in the minor groove of DNA and cross-linking strands of DNA. In vivo studies show superior antitumor activity of ADCT-402 against CD19-positive lymphoma than maytansinoid or auristatin based therapy. A phase 1 trial of ADCT-402 for relapsed/refractory ALL is underway (NCT02669264).

**D-CD25**

CD25 is a cell surface antigen and component of the Interleukin-2 receptor (IL-2 R) heterotrimer. Binding of IL-2 R by its ligand activates JAK/STAT, MAP kinase and phosphoinositide 3-kinase (PI3K) signaling pathways, leading to cell proliferation. IL-2 R is rapidly recycled upon binding of its ligand. The IL-2 R signaling pathway is particularly activated in T-cell immune response, and has thus been an attractive target for post-transplant immunosuppression. In some studies, CD25 expression has been as high as 30% of pre-B-ALL lymphoblasts, including 100% expression among the Ph-positive subset.[25]

**JAK inhibitor (Ruxolitinib)**

The JAK/STAT signaling pathway has been identified as a significant mechanism by which leukemic cells bypass normal growth and proliferation restrictions. In particular, Ph-like ALL appears to be dependent on JAK signaling. The most common rearrangements in Ph-like ALL involve the transmembrane receptor CRLF2, which signals through downstream JAK kinases. Many cytokine receptors, including IL-7 R, act through JAK kinases as well. In addition, JAK1 and JAK2 mutations are found in approximately half of CRLF2-rearranged Ph-like ALL. Preclinical studies have suggested benefit of ruxolitinib for the treatment of Ph-like ALL and CRLF2-rearranged ALL. In addition, ruxolitinib inhibited tumor growth in in vitro and in vivo models of T-ALL with a gain of function in IL-7 R-alpha subunit.A phase 2 trial of ruxolitinib with standard multi-agent chemotherapy is currently open for recruitment of children, adolescents and adults with newly diagnosed high-risk B-ALL with CRLF2 rearrangements (NCT02723994).

**ADCT-301**

ADCT-301 is a monoclonal antibody against CD25 conjugated to a PBD. In preclinical studies, ADCT-301 has been shown to be potently cytotoxic to CD25-positive anaplastic large cell lymphoma and Hodgkin lymphoma cell lines. In vivo, ADCT-301 exhibited antitumor activity in xenograft and disseminated mouse models. A phase 1 trial is recruiting participants for ADCT-301 in relapsed/refractory AML and ALL (NCT02588092).[26]

**Proteasome inhibitor (Bortezomib)**

Bortezomib, a proteasome inhibitor, was first approved for the treatment of multiple myeloma. Preclinical studies have suggested a synergistic role of bortezomib with dexamethasone and additive effects to standard chemotherapy agents in acute leukemias. As a single agent, bortezomib did not produce durable responses in patients with relapsed/refractory ALL, despite demonstrable proteasomal inhibition. However, in a phase 2 study, bortezomib in combination with vincristine, dexamethasone, pegylated asparaginase and doxorubicin produced a response rate of 80% in children with relapsed/refractory pre-B-ALL. In a recent phase 2 COG trial, re-induction chemotherapy plus bortezomib resulted in a complete response in 68% of children with relapsed pre-B-ALL. Due to it's ability to inhibit the NF-κB and NOTCH1 signaling pathways, bortezomib is being studied as frontline therapy in T-cell ALL. Recruitment is ongoing for a phase 3 trial of standard chemotherapy with or without bortezomib in children and young adults (age 2–30) with newly diagnosed T-cell ALL or T-cell lymphoblastic lymphoma (NCT02112916). In adults, recruitment has begun for a phase 2 trial of bortezomib with combination chemotherapy in relapsed/refractory ALL (NCT01769209).[27]

**PI3K/mTOR Inhibitors**

The phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and mammalian target of rapamycin (mTOR) pathways are shown to be constitutively activated in 50–75% of T-ALL. Preclinical studies suggest that inhibition of the PI3K/AKT/mTOR pathways may be an effective treatment for T-ALL A dual PI3K/mTOR inhibitor, NVP-BEZ235, potently inhibited the proliferation ALL cells in vitro, causing $G_0/G_1$ arrest. Moreover, inhibition of proliferation was synergistic when NVP-BEZ235 was combined with cytotoxic agents.On the basis of this promising preclinical data, several clinical trials are underway to evaluate the use of mTOR and PI3K inhibitors in combination with multi-agent chemotherapy in the frontline and relapsed/refractory setting

(NCT01756118, NCT02484430, NCT01523977, NCT01 403415, NCT01614197 and NCT01184885).

**Chimeric antigen receptor (CAR) T cells**

Chimeric antigen receptor-modified (CAR) T cells are genetically engineered T cells that express the antigen-binding domain of an immunoglobulin linked via transmembrane domains to the intracellular T-cell receptor signaling moieties. This allows the T cells to recognize unprocessed antigens and to be activated in a major histocompatibility complex (MHC)-independent manner. First generation CAR-Ts contain intracellular signaling moieties derived only from the T-cell receptor/CD3 complex. In contrast, second- and third-generation CAR-Ts include co-stimulatory signals in the CAR gene constructs. More recently, fourth-generation CAR-Ts have been engineered to include a cytokine-expressing cassette.

The process of CAR T-cell therapy involves collecting T cells, introducing the CAR construct, and then an autologous transplant of the modified T cells back into the patient. Options for gene delivery methods include viral vectors and RNA-based methods. Using a viral vector has the benefit of inducing permanent gene expression and thus offering antitumor activity for as long as the transduced T cells persist. As no DNA is inserted into the genome of the T-cell, this eliminates the risk of malignant transformation.[28] Given the high replicative potential of these T cells, this methods also offers the advantage of a profound antitumor response. However, the effects of direct mRNA insertion are transient and antitumor activity rarely persists beyond 7 days. Preclinical studies have suggested a role for RNA-based methods with multiple infusions; however, all current clinical trials utilize a viral vector to deliver the CAR construct.

Recently, the application of CAR-T cells has been expanded to CD22-positive B-ALL. Early preclinical studies have showed antitumor activity of CD22-directed CAR-Ts in in vitro and in vivo models that approximates that of CD19-directed CAR-Ts. Based on these findings, phase 1 trials using CD22-directed CAR-Ts are in the recruiting stages (NCT02650414). Preliminary results of nine patients have demonstrated that therapy is well tolerated and produced a sustained remission at 3 months in all three patients treated with a dose level of $1 \times 10^6$ transduced T cells/kg.

**Hematopoietic cell transplantation**

After achieving complete response, treatment options include consolidation and maintenance chemotherapy or Allo-SCT for eligible patients. For high-risk patients and patients with relapsed/refractory disease, Allo-SCT has long been considered the standard of care and best chance for a durable response.[29] While criteria differ between studies, in general high-risk disease is defined as Ph-positive ALL, elevated WBC count, CNS disease, high-risk gene rearrangements, or hypodiploidy. The LALA-94 and City of Hope and Stanford University series have shown a benefit of Allo-SCT over standard chemotherapy in these high-risk patients. It is therefore recommended that all high-risk young adults with an available donor undergo Allo-SCT during their first CR (CR1).

Allo-SCT also should be considered in all patients that relapse, optimally after achieving a second CR (CR2). The LALA-94 trial showed a 5-year OS of 33% in patients who were able to undergo Allo-SCT during CR2 compared to 8% in patients who underwent Allo-SCT during active relapse. Patients who are unable to achieve CR2 by conventional methods should be considered for clinical trials with novel agents as a bridge to Allo-SCT. In the MRC/ECOG 2993 study, 5-year survival was highest in the group receiving a sibling donor Allo-SCT compared to unmatched donor or chemotherapy alone (23%, 16% and 4%, respectively).[30]

**CONCLUSION**

Leukemias like ALL primarily affect the bone marrow and blood, whereas lymphomas primarily affect the lymph nodes or other organs (but can also affect the bone marrow). It may be difficult to tell whether lymphocytic cancer is leukemia or lymphoma. When at least 20% of the bone marrow is composed of cancerous lymphocytes called lymphoblasts or simply "blasts," the disease is usually considered leukemia. Acute lymphoblastic leukemia is heralded as a major success story in pediatric oncology with the advent of dosescaling chemotherapy and allogeneic SCT. However, because of the high-risk nature of the disease and the significant toxicities associated with chemotherapy in adults, the results are not very encouraging. Because some studies have shown benefits of pediatric-inspired therapies, much uncertainty remains about how adults with ALL can best be treated. Acute lymphoblastic leukemia has been touted as a major success story in pediatric oncology through the implementation of dose-intensification chemotherapy and Allo-SCT. However, due to high-risk disease characteristics and significant toxicity associated with chemotherapy in adults, outcomes are far less encouraging. There remains much uncertainty about how best to treat adults with ALL, as some studies have shown benefit of pediatric-inspired regimens. However, not all adults are able to tolerate such dose intensification and the exact subset of patients who are likely to benefit has not clearly been defined. The successes from tyrosine kinase inhibition in CML have been translated to Ph-positive ALL, and second and third generation TKIs are being studied for use in high-risk Ph-like disease. Other signaling pathways, such as PI3K/AKT/mTOR pathway, are also promising targets for small molecule inhibition. In addition to targeting intracellular pathways, monoclonal antibodies recognize cell surface antigens. Immunoconjugates, such as inotuzumab ozogamicin, bind to leukemic cells, are internalized and release a cytotoxin that kills the leukemic cell; whereas dual-specific antibodies, such as blinatumumab, cause the

direct activation of T cells against blasts. CAR-Ts involve a similar mechanism, in which a patient's own T cells are genetically programmed to recognize leukemic cells, inducing an anti-leukemic immune response. Finally, existing agents, such as bortezomib, decitabine and ruxolitinib that are well tolerated in the treatment of various malignancies are now being studied for application in ALL. As the role of these novel agents is further defined and integrated into new treatment strategies, adult ALL may follow pediatric ALL as a major success story in the near future.

**REFERENCE**


1. National Cancer Institute. SEER cancer statistics review, 1975-2013: Leukemia, annual incidence rates (acute lymphocytic leukemia).
2. Paul S, Kantarjian H, Jabbour EJ. Adult Acute Lymphoblastic Leukemia. *Mayo Clin Proc*, 2016; 91: 1645–1666.
3. Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. *Cancer*, 2015; 121: 2517–2528.
4. Shah A, John BM, Sondhi V. Acute lymphoblastic leukemia with treatment—naive Fanconi anemia. *Indian Pediatr*, 2013; 50: 508–510.
5. German J. Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet*, 1997; 93: 100–106.
6. Bielorai B, Fisher T, Waldman D, Lerenthal Y, Nissenkorn A, Tohami T et al. Acute lymphoblastic leukemia in early childhood as the presenting sign of ataxia-telangiectasia variant. *Pediatr Hematol Oncol*, 2013; 30: 574–582.
7. Chessells J, Harrison G, Richards S, Bailey C, Hill F, Gibson B et al. Down's syndrome and acute lymphoblastic leukaemia: clinical features and response to treatment. *Arch Dis Child*, 2001; 85: 321–325.
8. Purohit A, Jain S, Nema P, Vishwakarma H, Jain PK. Intelligent or smart polymers: advance in novel drug delivery. Journal of Drug Delivery and Therapeutics, Sep 15, 2022; 12(5): 208-16.
9. Sehgal S, Mujtaba S, Gupta D, Aggarwal R, Marwaha RK. High incidence of Epstein Barr virus infection in childhood acute lymphocytic leukemia: a preliminary study. *Indian J Pathol Microbiol*, 2010; 53: 63–67.
10. Geriniere L, Bastion Y, Dumontet C, Salles G, Espinouse D, Coiffier B. Heterogeneity of acute lymphoblastic leukemia in HIV-seropositive patients. *Ann Oncol*, 1994; 5: 437–440.
11. Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin ML, Liu W, Zhang J et al. Rearrangement of CRLF2 in B-progenitor and down syndrome associated acute lymphoblastic leukemia. *Nat Genet*, 2009; 41: 1243–1246.
12. Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. *Nature*, 2007; 446: 758–764.
13. Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. *Cancer Cell*, 2012; 22: 153–166.
14. Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Pei D et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med.*, 2014; 371: 1005–1015.
15. Jain S, Purohit A, Nema P, Vishwakarma H, Qureshi A, kumar Jain P. Pathways of Targeted Therapy for Colorectal Cancer. Journal of Drug Delivery and Therapeutics, Sep 14, 2022; 12(5): 217-21.
16. Alvarnas JC, Brown PA, Aoun P, Ballen KK, Barta SK, Borate U et al. Acute lymphoid leukemia (version 2.2015). *Natl Comprehens Cancer Netw*, 2015; 13: 1240–1279.
17. Jabbour EJ, Faderl S, Kantarjian HM. Adult acute lymphoblastic leukemia. *Mayo Clin Proc*, 2005; 80: 1517–1527.
18. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*, 1976; 33: 451–458.
19. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*, 1999; 17: 3835–3849.
20. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*, 2009; 114: 937–951.
21. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.*, 2016; 127: 2391–2405.
22. Purohit A, Jain S, Nema P, Jain DK, Vishwakarma H, Jain PK. A comprehensive review on tailoring an herbal approach for treatment of poly cystic ovarian syndrome. Asian Journal of Dental and Health Sciences, Mar 15, 2022; 2(1): 27-32.
23. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*, 2005; 106: 3760–3767.
24. Faderl, S HM Kantarjian, et al, T.U.o.T.M.D.A.C.C. Department of Leukemia, Houston, Texas, T.U.o.T.M.D.A.C.C. Department of Leukemia, P.O. Box 428, 1515 Holcombe Blvd., Houston, TX

77030, S. Jeha, T.U.o.T.M.D.A.C.C. Department of Leukemia, Houston, Texas, The biology and therapy of adult acute lymphoblastic leukemia. Cancer, 2017; 98: 1337–1354.

25. Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*, 2007; 109: 3189–3197.
26. Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. *Blood.*, 2008; 111: 2563–2572.
27. Hunger SP, Mullighan CG. Redefining ALL classification: toward detecting high-risk ALL and implementing precision medicine. *Blood*, 2015; 125: 3977–3987.
28. Dongen JJMv, v.d. Velden VHJ, Brüggemann M, Orfao A. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. *Blood.*, 2015; 125: 3996–4009.
29. Bruggemann M, Raff T, Flohr T, Gokbuget N, Nakao M, Droese J et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood*, 2006; 107: 1116–1123.
30. Jacquy C, Delepaut B, Van Daele S, Vaerman JL, Zenebergh A, Brichard B et al. A prospective study of minimal residual disease in childhood B-lineage acute lymphoblastic leukaemia: MRD level at the end of induction is a strong predictive factor of relapse. *Br J Haematol*, 1997; 98: 140–146.