

# The Adult Leukemias - Part 1: Acute Lymphocytic Leukemia

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## Abstract

Acute lymphocytic leukemia (ALL) is a malignant clonal proliferation of lymphoid precursors with arrested maturation. It is one of the first malignancies that responded to chemotherapy and one of the first to be cured in a large percentage of affected children.

## EPIDEMIOLOGY

ALL is the most common childhood malignancy, accounting for about 80% of all childhood leukemias, but only about 20% of adult leukemias are ALL.<sup>1</sup> A slight male predominance exists in the United States, and more whites and Latin Americans are afflicted than any other ethnicity. ALL represents approximately 1-2% of all cancers, with 3000 - 5000 new cases diagnosed each year in the US.<sup>1</sup> There is a bimodal distribution, with the first peak around 3-5 years of age, the second around 50 years of age, and increasing incidence up to 2 cases per 100,000 in persons greater than 65 years old.<sup>2</sup> The ratio of incidence of acute myeloid leukemia (AML) to ALL is 6:1.<sup>3</sup>

The etiology of ALL is unknown, however, many studies have attempted to determine risk factors without any definite conclusions being reached. Some associations continue to present themselves, such as genetic and environmental correlations. ALL risk is significantly increased among identical twins of ALL patients. In addition, siblings of patients with ALL have a four-fold increased risk of developing the disease when compared to the general population.<sup>1</sup> Certain congenital disorders have been associated with an increased risk of leukemia. High dose radiation exposure is a definite risk for ALL, especially if exposure is in utero.<sup>1</sup> Japanese atomic bomb survivors have had a 20 fold increased risk of ALL.<sup>1</sup> Chemical exposure, especially to benzene, has been associated with an increased

risk of acute leukemia, but only 1/3 of cases are ALL. Clusters of increased incidence exist, suggesting an infectious cause of the disease, however this is difficult to substantiate. Viruses are considered mutagens capable of inducing the clonal malignancy associated with leukemia. Human T cell lymphotropic virus (HTLV-1) is a known viral cause of human T-cell leukemia and suggests that other viruses, specifically Epstein-Barr virus (EBV), may contribute to the onset of ALL.<sup>2,4</sup>

## PRESENTATION

Expansion of the leukemic clone in the bone marrow with impairment of normal hematopoiesis manifests itself in signs and symptoms of ALL. The most common presentation is the abrupt onset of malaise, fatigue, bone pain, bleeding/bruising, weight loss, and possibly fevers. Often fever is without obvious infectious cause, but rather due to the leukemia itself.<sup>1</sup> These symptoms are frequently misdiagnosed initially and attributed to an infectious process rather than a malignancy. About 10% of patients feel well and are asymptomatic.<sup>3</sup> Clinically, many ALL patients have lymphadenopathy (20-60%) with painless, mobile nodes. Approximately 75% of patients present with hepatomegaly with or without splenomegaly, although liver function is usually preserved.<sup>1</sup> The degree of lymphadenopathy and hepatosplenomegaly correlates with the tumor burden, so when present, portends a worse prognosis. Occasionally, other organs may be involved, including the kidneys, lungs, heart, eyes, GI tract, and skin. Central nervous system (CNS) involvement, although present in only 10% initially, will eventually occur in 50% to 75% of patients if CNS prophylaxis is not given as part of therapy.<sup>5</sup> Prophylaxis for CNS disease consists of methotrexate and cytosine arabinoside given intrathecally. CNS leukemia manifests itself with signs and symptoms of increased intracranial

pressure, such as headaches worse when supine, papilledema, nausea, vomiting, irritability, and lethargy. Meningismus is common, and usually affects cranial nerves III, IV, VI, VII.<sup>1</sup> Testicular involvement occurs frequently in children (25%), but is rare in adults. Mediastinal masses are noted with the leukemic stage of lymphoblastic lymphoma, or T-cell ALL, while bulky abdominal nodes, CNS involvement, and facial neuropathies suggest Burkitt's lymphoma or other forms of mature B-cell ALL.<sup>1</sup>

### **LABORATORY STUDIES**

The WBC is usually high, and may be  $>100 \times 10^9/L$ , frequently with a large number of circulating lymphoblasts. These blasts may be difficult to distinguish morphologically from myeloblasts in 20-30% of cases; histochemical staining for terminal deoxynucleotidyl transferase activity (TdT) is imperative for diagnosis. The absolute neutrophil count is frequently low despite the high total WBC. Symptoms of leukocytosis are seldom seen, as lymphoblasts are small and do not readily sludge in vessels. Normochromic, normocytic anemia is nearly universal, and thrombocytopenia is the rule, with two thirds of patients presenting with platelet counts less than  $50 \times 10^9/L$ . As with other leukemias, uric acid and lactic dehydrogenase may be elevated and reflect the large tumor burden. Clinical coagulopathies are uncommon, while chemical DIC is frequent. A bone marrow that contains more than 30% lymphoblasts, of which at least 30% stain positive for TdT and less than 3% positive for myeloperoxidase, is diagnostic of ALL.<sup>6</sup> Because the defect is a maturation arrest and accumulation of immature cells, the bone marrow biopsy is most often hypercellular.

Immunophenotyping has become important not only in distinguishing B versus T cell lineage, but also in determining the level of differentiation present, which may be important for optimal therapeutic decision-making. In ALL of B cell origin (85%) immunophenotyping is positive for CD19 and CD20; when CD10 (CALLA) is positive, it is referred to as CALLA+ ALL. Mature B cell ALL expresses surface immunoglobulin (SIg) positivity and clonal kappa or lambda immunophenotype. In contrast, T cell ALL (15% of cases) is positive for at least two of the T cell markers (CD1 to CD8). Immunophenotyping is essential for diagnostic subtyping as well as for prognostication and appropriate tailoring of therapy. For example, T cell ALL patients have had improved prognosis with cytoxan/ara-C therapy, while

mature B cell ALL requires short term, dose intensive therapy but no maintenance is necessary.

### **DIFFERENTIAL DIAGNOSIS**

ALL can initially be confused with infectious causes or other malignancies that cause lymphocytosis and lymphadenopathy. Infectious causes that must be ruled out include toxoplasmosis, cytomegalovirus infection, and mononucleosis.<sup>7</sup> The bone marrow will be normal with infection, not in ALL. Other malignancies that must be ruled out include acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML) in lymphoid blast phase, non-Hodgkin's lymphoma in leukemic phase, small cell lung cancer, and Ewing's sarcoma.<sup>7</sup> The diagnosis is fairly straightforward once a bone marrow is performed and analyzed.

### **TREATMENT**

Treatment is modeled after childhood ALL treatment regimens since they resulted in a favorable response. Approximately 75% of treated adults achieve a complete remission, however only 30-40% are cured. Childhood ALL has a higher cure rate (about 80%) than adult ALL. At the University of Texas M. D. Anderson Cancer Center a combination of drugs is used in an alternating regimen. Vincristine, anthracycline/adriamycin, hyperfractionated cyclophosphamide, and dexamethasone are alternated with high doses of methotrexate and cytarabine for 8 courses, ideally spanning a 6 month period. Dexamethasone is used rather than prednisone because of its increased CNS penetration. Depending on the patient's predicted CNS relapse risk, 4, 8, or 16 intrathecal are given with methotrexate alternating with cytarabine. CNS prophylaxis reduces the risk of CNS relapse to  $<5\%$ .<sup>4</sup> The duration of neutropenia is shortened with the use of growth factors such as G-CSF or GM-CSF. Prophylactic antibiotic use may prevent opportunistic infections during neutropenic periods. Maintenance consists of 2 years of vincristine, methotrexate, mercaptopurine, and prednisone, and is not necessary in mature B cell ALL (Burkitt's). Allogeneic bone marrow transplant in first remission remains controversial, but should be pursued in patients with a poor prognosis, such as those with Philadelphia chromosome positive ALL. If an HLA-identical sibling exists, optimal timing of bone marrow

transplant is in first remission if high risk ALL, or in the event of leukemia relapse while on chemotherapy in other patients.<sup>1</sup> Autologous bone marrow transplant is not recommended, as relapse rates have been high.

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