A Look at Acute Lymphoblastic Leukemia in Children

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Acute lymphoblastic leukemia (ALL) is the most common malignancy found in the pediatric population. This type of cancer occurs in children in 2/3 of cases, with a current cure rate of almost 80% in children. In comparison, only 30 to 40 percent of adults with ALL are cured, likely due to the higher association of unfavourable genetic abnormalities in adults’ leukemic lymphoblasts. Usually occurring at approximately 2 to 9 years of age (Sather), ALL presents with fever, fatigue, pallor and pain. At least half of patients with ALL present with fever, often induced by pyrogenic cytokines released from leukemic cells or due to infection. In contrast, acute myeloid leukemia (AML) is less common than ALL, with an unclear etiology and similar presentation. A discussion of the diagnosis, treatment and outcomes for ALL is presented, with a particular emphasis on childhood ALL.

This article has been reviewed by Dr. Sam Yoshida.

Introduction, Characterization and Diagnosis

ALL can result from the blockage of any lymphoid cell at a point of development, and a diagnosis of ALL is dependent on immunophenotyping. The diagnosis of ALL can be obtained by a bone marrow aspiration.

The French-American-British (FAB) classification is based on morphology and simple cytochemical stains. There are three major subgroups. By this system, FAB L1 is the most common, with small cells, small nucleoli, and little cytoplasm. FAB L2 includes large cells, a clefted nucleus, large nucleoli, and abundant cytoplasm. FAB L3 includes large cells, a homogenous nucleus, many nucleoli, abundant cytoplasm, and prominent vacuoles. This system is effective, although cytogenetics and immunophenotyping have been suggested to add further to diagnostic accuracy in some cases.

Immunoflow cytometry determines the B cell expression of CD19 or CD10 or cALLa (common/childhood ALL antigen), a historical marker that is obsolete. TdT (terminal deoxynucleotidyl transferase) is a marker for B cell leukemia, as well, but has been suggested to have both a low sensitivity and specificity for prediction of relapse. T cell markers such as CD7, CD2, CD4 and CD8 can assist in determining different treatments and survivals. On the basis of such immunophenotypic analyses alone, firm diagnoses can be made in virtually all cases.

Cytogenetic analyses look for hyperdiploidy and translocations. Patients with hyperdiploidy with more than 50 chromosomes often have other clinical features that suggest a good prognosis. B cell translocations include t(4,11), t(9,22), t(8,14), and t(1,19) which give poor prognoses. In contrast, patients with t(12,21) generally have a favourable prognosis.

T cell translocations, for example, include t(11,14). These patients are often young males, often with associated unfavourable clinical characteristics. In addition, children with Philadelphia chromosome-positive ALL have been found to have a poor prognosis, with no consensus on the best treatment for this variant.

Associated Clinical Features, Treatments and Outcomes

The primary goal of therapy is to induce complete remission and to restore normal haematopoiesis. Therapy for ALL is based on risk, wherein factors such as age, white blood cell count, patient gender and cytogenetics must be accounted for. The presence of a mediastinal mass or central nervous system leukemia also predicts a relatively poor prognosis. The inclusion of race or ethnicity as a part of race-adapted therapy, thereby allocating black and Hispanic children to more aggressive protocols, remains debatable. Differences in clinically determined prognostic indicators are likely a result of the presence or absence of genetic abnormalities.
Patients between the ages of 2 to 9 years with a white blood count of less than 50,000 microL are considered to be at standard risk, with a high 4-year event-free survival of 80%. In turn, patients greater than 10 years of age with a white blood count of greater than 50,000 microL are considered to be at high risk, with a 4-year event-free survival of approximately 65%. However, patients at less than 1 year of age with a white blood count of over 100,000 microL with associated poor cytogenetics — such as the unfavourable MLL translocations — are at very high risk. These patients have a reported survival of up to 50% with a sibling-donated bone marrow transplant and less than 30% survival with a matched unrelated donor. With such a poor prognosis, infants with ALL are treated with multiple drugs at high dosages and with no cranial irradiation.

As therapy for ALL improves, reported survival rates have increased over the years — with a cure rate from less than 30% overall to 80% overall since 1970. Most standard risk and high-risk patients should receive chemotherapy alone. Intensive chemotherapy includes fractionated high-dose cyclophosphamide, high-dose methotrexate and cytarabine.

Furthermore, male patients require a longer duration of therapy compared to female patients, as a result of sanctuary sites. It has been reported that female patients have a better event free survival period even when treated with less therapy. High risk patients with sanctuary site involvement, such as in the central nervous system or testicles, should also receive radiation. However, since cranial irradiation can result in significant neurotoxicity and predisposes to a risk of brain tumours, as well as to neuropsychological deficits and endocrinopathy leading to short stature, obesity, precocious puberty and osteoporosis, many physicians choose to administer intensive systemic chemotherapy early on, and ultimately give patients growth hormone therapy to avoid negative endocrine-related effects. In addition, high risk patients receive chemotherapy and consideration for bone marrow transplants. Flow cytometry can be used as a prognostic indicator, as children with ALL who achieve a profound clearance of leukemic cells after 2 to 3 weeks of remission-induction chemotherapy have been reported to have excellent outcomes. It is an important challenge to integrate new data in the literature with modern methods of assigning risk-based therapy.

Supportive care for patients with ALL includes the administration of broad-spectrum antibiotic therapy for patients presenting with fever. At most centres, patients are treated prophylactically for Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole at 3 days per week. Since hyperuricemia, hyperkalemia and hyperphosphatemia with secondary hypocalcemia are common in patients with a great burden of leukemic cells, patients should also be hydrated intravenously and treated for these associated conditions.

It should be noted that the third most common malignancy in children is relapsed ALL. For these patients, therapy remains controversial, with debates over the benefits and risks of chemotherapy alone, sibling bone marrow transplants, matched unrelated donor bone marrow transplants, with respect to the optimal timing of bone marrow transplants, and the suggestion of no therapy at all. Conventional intensive chemotherapy can cure up to 30% of children who have relapsed, and similar results have been reported with autologous bone marrow transplantation.

Conclusion

ALL is a serious disease, often occurring in children, and should be treated according to risk stratification. However, despite major improvements in risk-assignment in recent decades, unknown mechanisms still account for the successes and failures of therapy in individual patients. Efforts are underway to identify new drugs and therapeutic approaches which may lead to options that are more specific and less toxic compared to standard chemotherapy. It is promising to note that in the past few decades, remarkable advances have been made in the cure rates of childhood ALL, and novel strategies of treatment may ultimately result in better treatment options.

References

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