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Pathophysiology and Treatment or Management of Acute lymphocytic Leukemia

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Introduction

Acute lymphoblastic leukemia (ALL) is a kind of leukemia that affects lymphoid progenitor cells in the bone marrow, blood, and extramedullary locations. While 80 percent of ALL cases occur in youngsters, it is a life-threatening condition in adults. The incidence of ALL in the United States is estimated to be 1.6 per 100,000 people. In 2016, an estimated 6590 new cases of ALL were detected, with over 1400 fatalities as a result of the disease (American Cancer Society). ALL has a bimodal incidence pattern, with the first peak occurring in childhood and the second peak happening around the age of 50 [1].

Pathophysiology

The aberrant proliferation and differentiation of a clonal population of lymphoid cells is involved in the pathogenesis of ALL. Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, and Nijmegen breakdown syndrome have all been discovered as hereditary abnormalities that predispose to a small percentage of ALL cases in children. Ionizing radiation, pesticides, some solvents, and viruses like the Epstein - Barr virus and the Human Immunodeficiency Virus are all predisposing factors. ALL is characterized by chromosomal abnormalities, although they are insufficient to cause leukemia. t(12;21) (ETV6-RUNX1), t(1;19) (TCF3-PBX1), t(9;22) (BCR-ABL1), and MLL rearrangement are all common translocations. A variation with a gene expression profile identical to (Philadelphia) Ph-positive ALL but without the BCR-ABL1 rearrangement has just been discovered. The variation has deletions in critical 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 in more than 80% of patients of this so-called Ph-like ALL (PAX5) [2].

Kinase-activating mutations are also found in 90% of Ph-like ALL cases. Rearrangements involving ABL1, JAK2, PDGFRB, CRLF2 and EPOR, activating mutations of IL7R and FLT3, and loss of SH2B3, which encodes the JAK2-negative regulator LNK, are among the most prevalent. This has important therapeutic implications since it implies that Ph-like ALL, which has a poor prognosis, could react to kinase inhibitors. In vitro and in vivo human xenograft models, cell lines and human leukemic cells expressing ABL1, ABL2, CSF1R, and PDGFRB were sensitive to second-generation TKIs (for example, dasatinib); those with EPOR and JAK2 rearrangements were sensitive to JAK kinase inhibitors (for example, ruxolitinib); and those with ETV6-NTRK3 fusion were sensitive to ALK inhibitors crizotinib.

The increase of malignant, poorly differentiated lymphoid cells in the bone marrow, peripheral blood, and extramedullary locations is the most common clinical presentation of ALL. With a mix of constitutional symptoms and indicators of bone marrow loss, the presentation might be vague (anemia, thrombocytopenia, and leukopenia). 'B symptoms' (fever, weight loss, night sweats), easy bleeding or bruising, weariness, dyspnea, and infection are also common symptoms. Extramedullary involvement is prevalent, and in 20% of cases, lymphadenopathy, splenomegaly, or hepatomegaly might result. At the time of diagnosis, 5–8% of individuals have CNS involvement, which most usually manifests as cranial nerve impairments or meningismus. A mediastinal mass is another symptom of T-cell ALL [3].

The presence of 20% or more lymphoblast's in the bone marrow or peripheral blood confirms the diagnosis. Both for validating the diagnosis and risk stratification, morphology, flow cytometry, immune phenotyping, and cytogenetic tests are useful. At the time of diagnosis, lumbar puncture with CSF analysis is standard of treatment to assess for CNS involvement. A brain MRI should be conducted if the CNS is implicated. Complete blood count with differential and smear to assess various hematopoietic cell lines, coagulation profiles, and serum chemistries are among the other tests performed. To monitor for tumor lysis syndrome, baseline uric acid, calcium, phosphate, and lactate dehydrogenase should be documented.

Treatment / Management

Children who have been diagnosed with Acute Lymphocytic Leukemia should be sent to a paediatric cancer centre for examination and treatment. Induction treatment for children with Acute Lymphocytic Leukemia includes anthracycline, vincristine, 1-asparaginase, and a corticosteroid. Consolidation therapy, which includes treatment with a range of chemotherapeutic agents, is now commonly utilized and has shown to be effective.

Oral 6-mercaptopurine or methotrexate is given once a week or once a month as maintenance treatment. A multidrug regimen separated into various phases (i.e., induction, consolidation, and maintenance) is used to treat children with Acute Lymphocytic Leukemia. It also includes therapy focused at the central nervous system (CNS). The majority of therapy plans last two to three years. Intrathecal prophylaxis is used for CNS prophylaxis. In most cases, patients will require 8-16 intrathecal treatments. If the patient has Ph-chromosome positive ALL, the current therapy includes imatinib, nilotinib, dasatinib, or ponatinib, which are tyrosine kinase inhibitors [4].

Stem cell transplantation is a treatment that involves replacing a patient's usual supply of blood cells (bone marrow) with healthy young blood cells (stem cells) from a healthy well-matched donor. However, as chemotherapy advances, the role of transplantation in ALL is diminishing.

CAR-T cell therapy has recently been studied in ALL with promising outcomes. Several studies have found high remission rates. Unfortunately, CART is linked to significant side effects including as cerebral edoema and cytokine release syndrome, both of which are potentially lethal.

To avoid transfusion-related graft vs host disease, which is always lethal, all blood products must be irradiated prior to transfusion. Acute Lymphocytic Leukemia seldom necessitates splenectomy. Splenectomy can assist increase platelet count; however it has little effect on the prognosis of leukemia. Splenectomy is used to address severe symptoms that do not respond to chemotherapy, such as stomach discomfort. In most situations of an enlarged spleen, radiation can be used to try to shrink the size of the spleen. Tumor lysis syndrome is a potentially fatal complication that can develop in chemotherapy patients. Hyperuricemia, potassium and phosphate elevations, and calcium deficiency are all symptoms. The presence of renal failure is unavoidable [5].

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