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Original Research Paper

Oncopathology

B-ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT ALL is a kind of B or T lymphoblastic cancer defined by uncontrolled growth of aberrant, immature lymphocytes and their progenitors, which eventually leads to the replacement of bone marrow and other lymphoid organs, resulting in a distinct disease pattern. Because the tumor has replaced the bone marrow, patients usually have symptoms like anemia, thrombocytopenia, and neutropenia. Fatigue, easy or spontaneous bruising and/or bleeding, and infections are all possible symptoms. Furthermore, B-symptoms such as fever, night sweats, and unintended weight loss are common but mild, and hepatomegaly, splenomegaly, and lymphadenopathy can be found in up to half of adults at the time of presentation. Involvement of the central nervous system (CNS) is prevalent, and it might be followed by cranial neuropathies. This activity looks at when acute lymphocytic leukemia should be evaluated on the differential diagnosis list and how to evaluate it effectively. The function of the interprofessional team in caring for patients with this condition is highlighted in this exercise.

KEYWORDS : Acute B-lymphoblastic leukemia

INTRODUCTION:

ALL, or acute lymphoblastic leukemia, is the most prevalent type of cancer in children, attacking the immune system's B and T cells. Blood stem cells (immature cells) mature into myeloid stem cells or lymphoid stem cells in the bone marrow of a healthy child.

- A myeloid stem cell develops into Myeloblast cell that develops into one of three types of adult blood cells:
- Red blood cells deliver oxygen and other substances throughout the body's tissues.
- Granulocytes, which are white blood cells that fight infection and disease and include neutrophils, eosinophils, and basophils.
- Monocytes are a type of agranular white blood cell that phagocytizes foreign materials.
- A lymphoid stem cell transforms into a lymphoblast cell, which then differentiates into one of three types of lymphocytes (agranular white blood cells):
- B lymphocytes, which produce antibodies to aid in the battle against infection.
- T cells assist B lymphocytes in the production of antibodies that aid in the fight against infection.

Cancer-fighting cells and viruses are attacked by natural killer cells.

OBJECTIVE

Learn about the epidemiology of acute lymphocytic leukaemia. Describe the typical exam findings in patients with acute lymphocytic leukaemia. Examine the treatment options for acute lymphocytic leukaemia.

Acute B-lymphoblastic leukemia (B-ALL):

ALL is characterized by a clonal growth of lymphoid blasts in the bone marrow, blood, or other organs. ALL can be of T or B ancestry. The expansion of blasts from the B lineage is known as pre-B ALL. Too many stem cells turn into lymphoblasts, B lymphocytes, or T lymphocytes in a child with ALL. These leukemia cells do not function like normal lymphocytes and are unable to effectively fight infection. In addition, when the number of leukemia cells in the blood and bone marrow rises, there is less room in the blood and bone marrow for healthy white blood cells, red blood cells, and platelets.

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The following are some of the possible risk factors for ALL:

- Being subjected to x-rays prior to delivery.
- Being subjected to ionizing radiation.
- Chemotherapy treatment in the past.
- Having a family history of certain genetic disorders, such as Down syndrome.

Type 1 neurofibromatosis

- Bloom's disease.
- Fanconi anemia is a kind of anemia caused by a mutation in the Fanconi gene
- Ataxia-telangiectasia.
- Li-Fraumeni syndrome (Li-Fraumeni syndrome).
- A deficit in the healing of constitutional mismatches (mutations in certain genes that stop DNA from repairing itself, which leads to the growth of cancers at an early age).
- Having certain chromosome or gene alterations.

Epidemiology:

The occurrence of Acute leukemia affects roughly 4 people per 100,000 each year. All of these make up 30% of the total. ALL is a common occurrence in youngsters. The majority of occurrences occur in youngsters under the age of six. In the United States, about 3200 instances of ALL are diagnosed each year; 80-85 percent of them are precursor B-ALL, while the rest are precursor T-ALL. Children have an overall cure rate of 85 percent, and roughly half of adults have long-term disease-free survival.

Pathophysiology:

B-ALL is thought to be caused by a series of gene mutations that begin in the pluripotent stem cell stage and progress through clonal expansion, differentiation, cell proliferation, and dysregulated cell apoptosis, with the end result being the replacement of normal lymphoid cells by malignant cells and uncontrolled growth and spread throughout the body (2).

Splenomegaly and hepatomegaly are caused by platelet and lymphocyte sequestration in the spleen and liver. Because these white blood cells are abnormal, the spleen reacts by attempting to remove them from the bloodstream (3,4,5).

Clinical Features:

The following are clinical characteristics:

- Fever.
- Bruising and bleeding are easy to come by.
- Petechiae is a type of plant (flat, pinpoint, dark-red spots under the skin caused by bleeding).
- Weakness, fatigue, or a pale appearance.
- Joint or bone pain.
- Excessive gasping for air.
- Swollen lymph nodes in the neck, underarm, stomach, or groin that aren't painful.
- A feeling of fullness or pain below the ribs.
- Anorexia nervosa (anorexia nervos

Laboratory Diagnosis:

- B- ALL is diagnosed through tests that check the blood and bone marrow.
- Physical examination and medical history: An examination of the body to check for general signs of health, as well as signs of disease, such as tumors or anything else that seems out of the ordinary. A medical history of the patient's health habits, as well as previous illnesses and treatments, is obtained.
- Complete blood count (CBC) with differential: A test that involves drawing a sample of blood and counting the number of red blood cells, platelets, number and type of white blood cells, and the amount of haemoglobin (the oxygen-carrying molecule) in the red blood cells.
- Blood chemistry studies: A test that measures the level of various chemicals in a sample of blood**.** Electrolytes (such as sodium, potassium, and chloride), lipids, proteins, glucose (sugar), and enzymes are among these compounds. Blood chemistry tests are used to determine how well a person's kidneys, liver, and other organs are functioning. A high level of a chemical in the blood can indicate a sickness or be a side effect of treatment.
- Bone marrow aspiration and biopsy: A hollow needle is inserted into the hipbone or breastbone to remove bone marrow and a small piece of bone. Under a microscope, a pathologist examines the bone marrow and bone for symptoms of malignancy.

Classification:

World Health Organization

- The World Health Organization classification of acute lymphoblastic leukemia was created in 2008 in an attempt to provide a more clinically relevant categorization system that could lead to meaningful prognostic and therapeutic decisions. Through cytogenetic and molecular diagnostics tests, this approach discovered differences in genetic, immunophenotype, molecular, and morphological aspects. This subtyping aids in determining the prognosis and best treatment for each individual instance of ALL.
- The following WHO subtypes are associated with ALL:
- Not otherwise specified B-lymphoblastic leukemia/ lymphoma (NOS)with recurrent genetic abnormal it with t(9;22)(q34.1;q11.2);*BCR-ABL1* With t(v;11q23.3);*KMT2A* rearranged
- with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
- with t(5;14)(q31.1;q32.3) *IL3-IGH*
- with t(1;19)(q23;p13.3);*TCF3-PBX1*
- with hyperdiploidy
- with hypodiploidy

Immunophenotyping is a laboratory technique that uses antibodies to identify cancer cells based on the antigens or markers found on their surfaces. This test aids in the diagnosis of some kinds of leukemia. The cancer cells, for example, are examined to discover if they are B lymphocytes or T lymphocytes.

Cytogenetic analysis is a laboratory test that counts and examines the chromosomes of cells in a blood or bone marrow sample for any abnormalities, such as damaged, missing, altered, or additional chromosomes. Changes in particular chromosomes could indicate the presence of cancer. Part of one chromosome swaps places with part of another chromosome in Philadelphia chromosome–positive ALL, for example. The "Philadelphia chromosome" is what it's called. Cytogenetic analysis is used to aid in the diagnosis of cancer, treatment planning, and monitoring the effectiveness of treatment.

Lumbar puncture:

A method for extracting a sample of cerebrospinal fluid (CSF) from the spine. A needle is inserted between two bones in the spine and into the CSF surrounding the spinal cord, and a sample of the fluid is taken. Under a microscope, a sample of CSF is examined for symptoms of leukemia cells spreading to the brain and spinal cord. This operation is also known as a spinal tap or LP.

After leukemia has been detected, this procedure is used to see if the cancer cells have progressed to the brain and spinal cord. After the sample of fluid is evacuated, intrathecal chemotherapy is given to treat any leukaemia cells that have spread to the brain and spinal cord.

A chest x-ray shows the organs and bones within the chest. An x-ray is a form of high-energy radiation that may pass through the body and onto film, producing images of internal organs that can be used to diagnose disease. A chest x-ray is used to determine whether leukemia cells have developed a mass in the center of the chest.

Treatment:

ALL is typically treated in three stages. The goal of treatment is to achieve a long-term remission, which is defined as the absence of cancer cells in the body (usually less than 5 percent blast cells in the bone marrow).

Over the last few decades, progress has been made in improving the efficacy of treatment regimens, which has resulted in higher survival rates.

Chemotherapy, steroids, radiation therapy, rigorous combined treatments (including bone marrow or stem cell transplants), targeted therapy, and/or growth hormones are all options for treating acute leukemia.

Chemotherapy

Chemotherapy is the first line of treatment, and most people with ALL are given a drugs. Because the cancerous cells have spread throughout the body, there are no surgical choices. In general, cytotoxic chemotherapy for ALL consists of a combination of antileukemic medicines that are individually customized to each patient. Remission induction, intensification, and maintenance therapy are the three phases of ALL chemotherapy.

Induction of remission:

This is the first stage of treatment. Leukemia cells in the blood and bone marrow must be killed. This brings the leukemia to a halt.

Consolidation/intensification:

This is the treatment's second step. It starts after the leukemia has gone into remission. Consolidation/intensification therapy aims to eliminate any remaining leukemia cells in the body that could lead to a relapse.

Maintenance:

The third part of treatment is maintenance. The goal is to eliminate any leftover leukemia cells that could recur and lead to a relapse. During the remission induction and consolidation/intensification stages, cancer treatments are

frequently administered in lower doses than during the remission induction and consolidation/intensification phases. During maintenance therapy, failing to take medications as prescribed by your doctor raises the risk of cancer recurrence. This is also known as the maintenance therapy period.

- Because CNS involvement is present in 10–40% of adults with ALL when they are diagnosed, most physicians begin CNS prophylaxis and treatment during the induction phase and maintain it during the consolidation/ intensification phase.
- Adult chemotherapy regimens are similar to those used in children with ALL; however, chemotherapy alone is connected to a higher risk of illness relapse. When it comes to determining a suitable treatment regimen for adults with ALL, it's important to keep in mind that two subtypes of ALL (B-cell ALL and T-cell ALL) require specific consideration. B-cell ALL is frequently accompanied with cytogenetic abnormalities (particularly, t(8;14), t(8;14), t(8;14), t(8;14), t(8;14), t(8;14), t (2;8), and t(8;22)), which necessitate vigorous treatment with short, high-intensity regimens. Cyclophosphamide-containing treatments had the greatest effect on T-cell ALL.
- Because chemotherapy can be severe and long-term, many people have an intravenous catheter inserted into a large vein (also known as a Hickman line) or a Portacath, which is commonly implanted around the collar bone, to reduce infection risks and ensure the device's long-term survival. Because the testicles might operate as a cancer reservoir, males normally have to go through more treatment than females.

Radiation therapy:

Radiation treatment (or radiotherapy) is used to treat painful bony regions, high disease loads, and as part of the bone marrow transplant preparation process (total body irradiation). Physicians used whole-brain radiation for central nervous system prophylaxis in the past to prevent the occurrence and/or recurrence of leukaemia in the brain. CNS treatment, according to recent studies, produced similar benefits but with less developmental side effects. As a result, whole-brain radiation has become less common. Most adult leukemia specialists have stopped utilizing radiation therapy for CNS prophylaxis in favor of intrathecal chemotherapy.

Biological therapy:

Clinical trials for improving the effects of ALL treatment could result from the selection of biological targets based on their combinatorial effects on leukemic lymphoblasts. Tyrosine-kinase inhibitors (TKIs), such as imatinib, are frequently used in the treatment of Bcr-Abl1+ (Ph+) ALL patients. However, because this subtype of ALL is typically resistant to chemotherapy and TKIs, allogeneic stem cell transplantation is frequently advised in the event of relapse.

Immunotherapy:

CARs (chimeric antigen receptors) have been developed as a potential ALL immunotherapy. As a way of treating ALL, this technology uses a single chain variable fragment (scFv) intended to identify the cell surface marker Cd19.

CD19 is a marker found on all B-cells that can be utilized to identify the B-cell population that is potentially cancerous. Mice are inoculated with the CD19 antigen and develop anti-CD19 antibodies in this therapy. Hybridomas derived from mouse spleen cells fused to a myeloma cell line can be employed to generate the CD19 specific antibody's cDNA. The cDNA is sequenced, and the sequence encoding the heavy and light variables is identified. A short peptide linker is used to clone the varied light chains of these antibodies together. The scFv is encoded by this sequence. This can be cloned into a transgene, which will encode the CAR's end domain. The end domain is made up of a variety of subunits, but it usually includes the hinge region that attaches to the scFv, a transmembrane area, the intracellular portion of a co stimulatory protein like CD28, and the intracellular domain of CD3-zeta that contains ITAM repeats. 4-1bb and OX40 are two more sequences that are regularly used. The scFv and endodomain sequences of the final transgenic sequence are then introduced into immune effector cells taken from the person and grown in vitro. These have been used in experiments as a type of Inserting the DNA into the effectors cell can be accomplished by several methods. Pseudotyped, self-inactivating lentiviruses are an effective method for the stable insertion of a desired transgene into the target cell.

The gene-modified effector cells are subsequently reintroduced into the individual. This procedure is usually combined with a conditioning regimen like cyclo phosphamide, which has been found to enhance the effects of injected T-cells. This impact is thought to be caused by the creation of an immune space in which the cells can populate. The entire process results in an effector cell, usually a T-cell, that can recognize a tumor cell antigen without the help of the major histocompatibility complex and trigger a lethal response.

The FDA approved tisagenlecleucel as a CAR-T therapy for persons with acute B-cell lymphoblastic leukemia who had not responded to prior treatments or had relapsed in 2017. The "drug" undergoes a 22-day process. T cells purified from each person are modified by a virus that inserts genes that encode a chimeric antigen receptor into their DNA, one that recognizes leukemia cells.

Gene therapy:

In October 2021, Tecartus (brexucabtagene autoleucel) was approved for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Each dose of brexucabtagene autoleucel is a unique treatment that relies on the immune system of the patient to fight lymphoma. T cells, a kind of white blood cell, from the patient are collected and genetically engineered to add a new gene that makes it easier to target and destroy lymphoma cells. The recipient receives these modified T cells, which are then pumped back into them.

CONCLUSION:

ALL does not have any specific symptoms. Early identification of ALL is aided by reporting any symptoms to a medical expert, early screening tests, and laboratory studies. In roughly a month after treatment, up to 98 percent of children with ALL go into remission, and 9 out of 10 can be cured. However, because there is always a potential that the cancer can return, it is critical to keep in touch with the cancer care team as needed.

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