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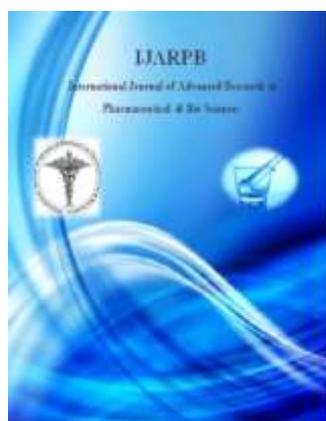
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Leukemia : A Review Article

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ABSTRACT

Hematopoiesis is characterized by a rapid, continuous turnover of cells. Normally, production of specific blood cells from their stem cell precursors is carefully regulated according to body's need. If the mechanism that controls the production of these cells is disrupted, the cells can proliferate excessively. Hematopoietic malignancies are often classified by cells involved. LEUKEMIA is a neoplastic proliferation of one particular cell type (granulocytes, monocytes, lymphocytes, or infrequently RBCs).

The defect originates in hematopoietic stem cell, the myeloid, or lymphoid cells. Leukocytosis refers to an increased level of leukocytes in circulation.

KEYWORD: Leukemia, Types of leukemia, Tumor biology, Treatment

(Review Article)**INTRODUCTION**

The hematologic system consists of blood and the sites where blood is produced, including the bone marrow and the RETICULOENDOTHELIAL

SYSTEM(RES).Blood is a specialized organ that differs from other organs in that it exists in fluid state.blood is composed of plasma and various types of cells.

Blood makes up approximately 7% to 10% of normal body weight and amounts to 5 to 6L of volume.Circulating through the vascular system and serving as a link between body organs,blood carries oxygen absorbed from lungs and nutrients absorbed from the gastrointestinal tract to the body cells for cellular metabolism.Blood also carries hormones ,antibodies ,and other substance to their sites of action.In addition, blood carries waste products produced by cellular metabolism to the lungs ,skin,liver, and kidneys,where they are transformed and eliminated from the body. By means of the hemoglobin contained in the erythrocytes, it carries oxygen to the tissues and collects the carbon dioxide (CO₂). It also conveys nutritive

substances (e.g. amino acids, sugars, mineral salts) and gathers the excreted material which will be eliminated through the renal filter. The blood also carries hormones, enzymes and vitamins. It performs the defense of the organism by mean of the phagocitic activity of the leukocytes.

Blood consists of three types of cells and cell fragments floating in a liquid called plasma. These cellular components are:

- **Red Blood Cells** ("erythrocytes," "RBCs") - oxygen-carrying cells
- **White Blood Cells** ("leukocytes," "WBCs") - cells that help make up the body' defense mechanism.Its types are:

a)Granulocytes:Neutrophil,Basophil,Eosino phil.

b)Agranulocytes:Lymphocytes,monocytes

- **Platelets** ("thrombocytes") - fragments of cells that play an important role in formation of blood clots.

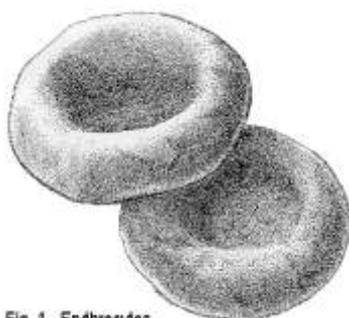


Fig. 1 - Erythrocytes

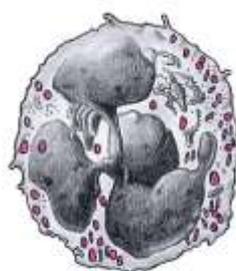


Fig. 8 - Neutrophil



Fig. 9 - Eosinophil

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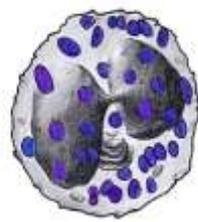


fig. 10 - Basophil



Fig. 11 - Lymphocyte



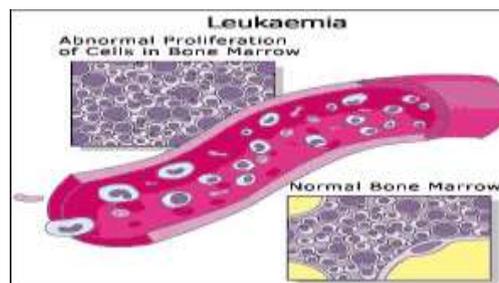
Fig. 12 - Monocyte



LEUKEMIA

leukemia /leu-ke-mia/ (loo-ke-me-ah) a progressive, malignant disease of the blood-

forming organs, marked by distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow.



COUNTRIES WITH HIGHEST INCIDENCE OF LEUKEMIA CANCER

	Country	Incidence per 100,000 individuals
1	<u>Denmark</u>	29
2	<u>Luxembourg</u>	28.7
3	<u>Italy</u>	28.4
4	<u>Belgium</u>	27
5	<u>France</u>	26.8
6	<u>Croatia</u>	26.6
7	<u>Latvia</u>	26.4
8	<u>Germany</u>	26
9	<u>New Zealand</u>	26
10	<u>Australia</u>	25.3

(Review Article)**WHAT ARE RISK FACTORS FOR LEUKEMIA?**

Although the cause of leukemia in most patients is unknown, several factors are associated with increased risk of developing the disease. Factors that influence risk of developing leukemia include:

- Age
- Prior Chemotherapy
- Ethnicity/Gender
- Inherited Syndromes (such as Down Syndrome)
- Ionizing Radiation
- Infection by certain viruses
- Cigarette smoking

The relative effects of these and other risk factors in any given case of cancer is variable. Some of these and other risk factors are discussed on the following pages.

Age

The risk of developing most types of leukemia increases steadily with age. The curve for acute lymphoblastic leukemia (ALL) incidence, however, is U-shaped: highest between the ages of 3-7 and rising again after the age of 40. The reason for this peak in early childhood ALL remains uncertain.

Chemotherapy

There is a subset of acute myeloid leukemia (AML), known as "secondary AML" or "therapy-related myeloid leukemia," which can develop following treatment with chemotherapy. Although a causal relationship is implied by the name, the exact mechanism remains unknown. Prognosis for secondary AML is generally unfavorable compared to primary AML.

Ethnicity/Gender

With the exception of chronic myeloid leukemia (CML), which has a similar incidence in whites and blacks, leukemia occurs more commonly in those of white ancestry compared to those of Asian, Hispanic and black ancestry. Leukemia also occurs more frequently in males than females.

Inherited Syndromes

Children with Down syndrome (DS) have a roughly 20-fold increased risk of developing childhood leukemia compared to children without DS. Approximately 10% of children with DS are born with a "transient leukemia" that resolves spontaneously within months of birth. One to two percent, however, develop a malignant acute leukemia requiring chemotherapy by the age of 4. While several hypotheses have been proposed, the reason for this increased risk remains uncertain.

Other inherited syndromes that increase risk of leukemia include:

- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi syndrome
- Klinefelter syndrome
- Neurofibromatosis

Ionizing Radiation

An increase in leukemia has been observed in survivors of the atomic bombing of Japanese cities. Although the risk associated with exposure to lower level radiation is not clear, studies have shown an increase in leukemia following the use of radiotherapy for ankylosing

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spondylitis (a form of arthritis) and exposure to diagnostic X-rays of the fetus during pregnancy.

Viruses

Infection with Human T-cell Lymphotropic Virus-1 (HTLV-I) is linked to the development of Adult T-cell Leukemia/Lymphoma (ATLL), a cancer of activated mature T lymphocytes.

HTLV-I and ATLL are widespread in certain regions of the world, such as the Caribbean basin, Japan, and parts of South America and Africa, while very rare in others. Most people who are infected with HTLV-I do not develop leukemia. Data from cancer registries in Japan suggest the lifetime risk of developing ATLL among those infected is 2.1% for females and 6.6% for males.

TYPES OF LEUKEMIA:

Leukemias are classified into 4 main categories, based on the type of white blood cell affected (lymphoid vs. myeloid) and characteristics of the disease (acute vs. chronic):

Based on characteristics of disease classified as:

- a) ACUTE LEUKEMIA
- b) CHRONIC LEUKEMIA

Based on types of WBCs affected classified as:

- a) MYELOGENOUS LEUKEMIA
- b) LYMPHOCYTIC LEUKEMIA

Acute Leukemias

Acute leukemia develop from early cells, called "blasts". Blasts are young cells, that divide

frequently. In acute leukemia cells, they don't stop dividing like their normal counterparts do.

Chronic Leukemias

In chronic leukemia, the leukemia cells come from mature, abnormal cells. The cells thrive for too long and accumulate. The cells grow slowly.

Myelogenous Leukemia

Myelogenous leukemia develops from myeloid cells. The disease can either be chronic or acute, referred as chronic myelogenous leukemia (CML), or acute myelogenous leukemia (AML).

Lymphocytic Leukemia

Lymphocytic leukemia develops from cells called lymphoblasts or lymphocytes in the blood marrow. The disease can be acute or chronic, referred as chronic lymphocytic leukemia (CLL), or acute lymphocytic leukemia (ALL).

ACUTE MYELOID LEUKEMIA

Acute myeloid **leukemia** (AML) is a cancer of the blood and bone marrow. It usually progresses quickly if it is not treated. The disease accounts for about 10,600 new cases of leukemia each year, and it occurs in both adults and children.

Other names for AML include:

- Acute myelogenous leukemia
- Acute myeloblastic leukemia
- Acute granulocytic leukemia
- Acute non-lymphocytic leukemia.

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Normally, the body produces bone marrow stem cells (immature cells) that develop into mature blood cells.

The three types of mature blood cells include:

- Red blood cells that carry oxygen and other materials to all tissues of the body
- White blood cells that fight infection and disease
- Platelets that help prevent bleeding by causing blood clots to form.

In AML:

- The stem cells usually develop into a type of white blood cell called myeloblasts (or myeloid blasts)
- The myeloblasts (or **leukemia cells**) are abnormal and do not mature into healthy white blood cells
- Leukemia cells are unable to do their usual work and can build up in the blood and bone marrow so there is less room for healthy white blood cells, red blood cells, and platelets.

This may lead to infection, anemia, or easy bleeding. The leukemia cells can spread outside the blood to other parts of the body, including the central nervous system (brain and spinal cord), skin, and gums.

ACUTE LYMPHOCYTIC LEUKEMIA

Acute lymphocytic **leukemia** (ALL) is a type of cancer in which the bone marrow makes too many lymphocytes, which is a type of white blood cell. Acute lymphocytic leukemia, which is also called acute lymphoblastic leukemia, accounts for about 3,800 new cases of leukemia each year. Although acute lymphocytic leukemia is the most common type of leukemia in young children, it can also affect adults.

The three types of lymphocytes include:

- B lymphocytes that make antibodies to help fight infection
- T lymphocytes that help B lymphocytes make the antibodies that help fight infection
- Natural killer cells that attack cancer cells and viruses.

In acute lymphocytic leukemia:

- The lymphocytes are not able to fight infection very well
- The number of lymphocytes increases in the blood and bone marrow
- There is less room for healthy white blood cells, red blood cells, and platelets.

This may cause infection, anemia, and easy bleeding. Acute lymphocytic leukemia can also spread to the central nervous system (brain and spinal cord).

CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia is a form of cancer in which the bone marrow makes too many white blood cells. In most cases, the cause involves a genetic mutation called the

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Philadelphia chromosome. Common symptoms of this condition include tiredness, night sweats, and fever.

- **CML**
- Chronic myeloid leukemia
- Chronic granulocytic leukemia.

Chronic myelogenous leukemia usually occurs during or after middle age, and rarely occurs in children. It accounts for approximately 4,400 new cases of leukemia each year.

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic **leukemia** (also known as **CLL**) is a type of cancer in which the bone marrow makes too many lymphocytes (a type of white blood cell). Also known as chronic lymphoblastic leukemia, this is the second most common type of leukemia seen in adults, accounting for about 7,000 new cases of leukemia each year.

In chronic lymphocytic leukemia, too many stem cells develop into a type of white blood cell called lymphocytes. The three types of lymphocytes include:

- B lymphocytes that make antibodies to help fight infection
- T lymphocytes that help B lymphocytes make antibodies to fight infection
- Natural killer cells that attack cancer cells and viruses.

With chronic lymphocytic leukemia, the lymphocytes are not able to fight infection very well, and as the amount of lymphocytes increases in the blood and bone marrow, there is less room for healthy white blood cells, red

blood cells, and platelets. This may result in infection, anemia, and easy bleeding.

TUMOR BIOLOGY

Genetic changes that occur in cancer include mutation of key regulatory genes, changes in protein products, and changes in the amount of product produced by genes (gene expression). As changes accumulate, cells become more abnormal and cancer progresses.

The Philadelphia Chromosome

Translocations involve chromosome breakage and exchange of chromosome fragments. One such translocation, found in over 95% of chronic myeloid leukemias (CML) as well as some acute lymphoblastic leukemias (ALL), occurs between chromosomes 9 and 22. Part of the proto-oncogene *abl* is removed from chromosome 9 and joined to the *bcr* gene on chromosome 22. Similarly, part of chromosome 22 is removed and relocated to chromosome 9. The exchange leads to the creation of a shortened form of chromosome 22, called the Philadelphia chromosome (after the location of its discovery).

The normal ABL protein functions as a tyrosine kinase. Tyrosine kinases are enzymes that transfer phosphate groups from ATP to other molecules. Activation of key regulatory enzymes in this manner leads to a cascade of events that ultimately results in cell division. The newly created *bcr-abl* fusion gene located on the Philadelphia chromosome codes for a protein that has increased tyrosine kinase activity, and therefore leads to increased stimulation of cell division, compared to the normal ABL protein.

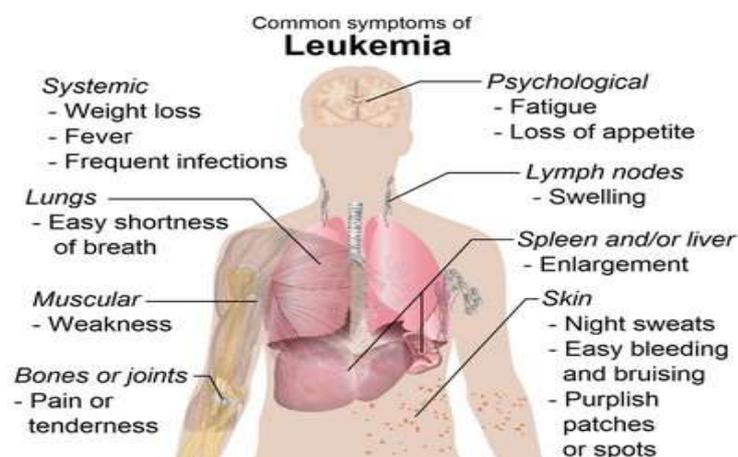
(Review Article)**WHAT ARE THE CLINICAL FEATURES SHOWN BY THE PATIENT?**

In many cases, the first signs and symptoms of leukemia are nonspecific (vague). Early signs also may occur with other types of cancer or with other medical conditions. Although leukemia signs and symptoms vary depending on the type of disease, there are some general features. Broad symptoms of leukemia include the following:

- Fatigue

- Malaise (vague feeling of bodily discomfort)
- Abnormal bleeding
- Excessive bruising
- Weakness
- Reduced exercise tolerance
- Weight loss
- Bone or joint pain
- Infection and fever
- Abdominal pain or "fullness"

Enlarged spleen, lymph nodes and liver

**HOW THE DISEASE CAN BE DIAGNOSED?**

Physical Exam During a physical exam, a doctor may look for lumps, other abnormalities, or symptoms of leukemia. A thorough medical history will be taken and the patient can report a history of leukemia or any symptoms or risk factors.

Blood Tests Blood tests, like a CBC (complete blood count) can detect leukemia. A CBC determines the number of red blood cells, white blood cells, and platelets. It also can count the number of red blood cells that make up the blood sample and the amount of hemoglobin in the blood.

A peripheral blood smear may also be done. A peripheral blood smear determines the presence of blast cells and reveals the type and quantity of white blood cells.

Cytogenetic analysis is a blood test in which a sample of blood is examined to check for changes in the chromosomes of the lymphocytes. This blood test may also be ordered.

Biopsy A biopsy is a procedure in which a sample of cells are removed from the body to be examined for cancer. Bone marrow aspiration is a type of biopsy used to diagnose leukemia. A fine needle is inserted into the hip

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or breast bone and a sample of the bone and bone marrow is removed. It is then examined by a pathologist. Lymph node biopsy is also done.

Lumbar Puncture/Spinal Tap A lumbar puncture or spinal tap may be done to diagnose leukemia. Under an anesthetic, a small amount of spinal fluid is removed from the spaces between the vertebrae in the spine. The fluid is then examined by a pathologist.

Other Medical Tests and Procedures Used to Diagnose Leukemia Other procedures like CT scans, X-Rays, MRI's, and ultrasounds may be used to diagnose leukemia.

TREATMENT

Leukemia is not a single disease. Instead, the term leukemia refers to a number of related cancers that start in the blood-forming cells of the bone marrow. There are both acute and chronic forms of leukemia, each with many subtypes that

- vary in their response to treatment. Therefore, In general, there are five major approaches to the treatment of leukemia :
- Surgery
- Radiation Therapy
- Chemotherapy
- Immunotherapy
- Stem Cell Transplantation

SURGERY

surgery to remove an enlarged spleen or to install a venous access device (large plastic tube) to give medications and withdraw blood samples.

RADIATION THERAPY

Radiation therapy is one of the many tools used to combat cancers. Radiation treatments utilize high-energy waves such as x-rays to kill cancer cells. Radiation can be used alone or in conjunction with other treatments (e.g. chemotherapy and surgery) to cure or stabilize cancer.

CHEMOTHERAPY

The term chemotherapy, or chemo., refers to a wide range of drugs used to treat cancer. These drugs usually work by killing dividing cells. Since cancer cells have lost many of the regulatory functions present in normal cells, they will continue to attempt to divide when other cells do not. This trait makes cancer cells susceptible to a wide range of cellular poisons.

A few different types of chemotherapy drugs are briefly described below.

Antimetabolites: Drugs that interfere with the formation of key bio-molecules within the cell including nucleotides, the building blocks of DNA. These drugs ultimately interfere with DNA replication and therefore cell division. Examples are mercaptopurine, methotrexate, etc.

Genotoxic Drugs: Drugs that damage DNA. By causing DNA damage, these agents interfere with DNA replication and cell division. The genotoxic chemotherapy treatments include:

Alkylating agents: The first class of chemotherapy agents used. These drugs modify the bases of DNA, interfering with DNA replication and transcription and leading to mutations. Examples are Busulfan, carboplatin, etc.

Intercalating agents: These drugs wedge themselves into the spaces

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between the nucleotides in the DNA double helix. They interfere with transcription, replication and induce mutations. Examples are Doxorubicin, Idarubicin.

Enzyme inhibitors: These drugs inhibit key enzymes, such as topoisomerases, involved in DNA replication inducing DNA damage. Examples are Etoposide, Topotecan.

Spindle Inhibitors: These agents prevent proper cell division by interfering with the cytoskeletal components that enable one cell to divide into two.

Example: Vinca alkaloids, Docetaxel, Paclitaxel, Etc

IMMUNOTHERAPY

The purpose of cancer vaccines is to stimulate the body's defenses against cancer by increasing the response of the immune system. Our immune system provides a dynamic protective system against disease from foreign pathogens and from abnormal body cells. Cancer cells are, in essence, normal body cells that have sustained mutations and no longer function properly.

Tumor vaccines usually contain proteins found on or produced by cancer cells. By administering forms of these proteins and other agents that affect the immune system, the vaccine treatment aims to involve the patient's own defenses in the fight to eliminate cancer cells. Immunotherapy is a new field in cancer treatment and prevention, and many strategies are being examined in clinical trials. Interferons are a class of proteins that are

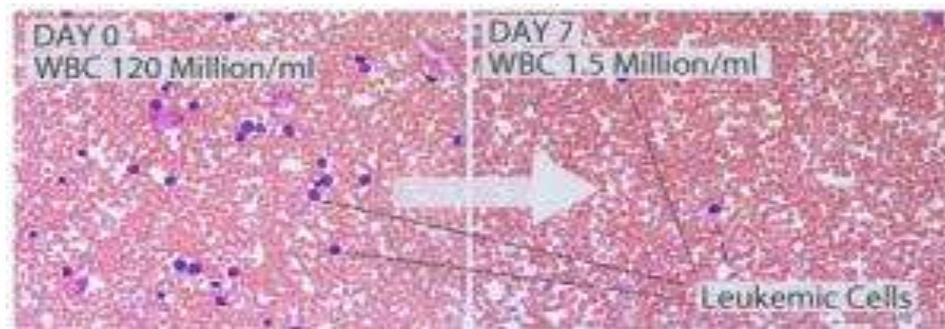
released by virus-infected cells. They help normal cells to make antiviral proteins. Interferons also help the body to reduce leukemia cell proliferation (growth and reproduction), while strengthening the body's immune response.

STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplantation (HSCT) is the transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood. It is a medical procedure in the fields of hematology and oncology, most often performed for patients with certain cancers of the blood or bone marrow, such as multiple myeloma or leukemia. In these cases, the recipient's immune system is usually destroyed with radiation or chemotherapy before the transplantation. Graft-versus-host disease is a major complication of HSCT.

RECENT NEW FINDINGS IN LEUKEMIA

ScienceDaily (Apr. 16, 2012) — Columbia University Medical Center (CUMC) scientists have demonstrated that two related enzymes -- phosphoinositide-3 kinase (PI3K) gamma and delta -- play a key role in the development of T-cell acute lymphoblastic leukemia (T-ALL), a highly aggressive childhood leukemia that is difficult to treat. The study also showed that a dual PI3K gamma/delta inhibitor can significantly prolong survival in a mouse model of the disease. Further, the dual inhibitor was shown to prevent proliferation and to reduce the survival rate of human T-ALL cells in laboratory cultures, setting the stage for clinical trials.

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- Researchers showed that a dual PI3K gamma/delta inhibitor can significantly prolong survival in a mouse model of a highly aggressive childhood leukemia. (Credit: Image courtesy of Columbia University Medical Center)

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