

2.2.4

Leukemia

2.2.4 – Leukemia

Watch the video [Leukemia Overview](#)

Leukemia is also referred to as blood cancer because the person affected will have cancer in the body's blood forming tissues including the bone marrow. Leukemia is caused by abnormalities in genes that control the regulation of blood cell growth and development or abnormalities in the negative feedback loops that keep blood cell growth within normal range. Leukemia can be caused by a problem in the myelogenous or lymphocytic variations of the hemocytoblast. It is classified as chronic or acute based on how differentiated the cell it affects is. Acute forms of leukemia involve a less differentiated cell that is closer to the original hematopoietic stem cell. Acute forms of leukemia can be seen earlier and progresses more rapidly. Leukemia that is considered chronic affects a cell that has differentiated farther.

There are four types of leukemia: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML). Acute lymphoid leukemia is the most common leukemia among adolescents. Chronic lymphoid and acute myeloid leukemia are more common in adults over the age of 20.

There are several things that we know can increase the risk for leukemia. Benzene (found in cigarette smoke), formaldehyde, radiation and chemotherapy all increase a person's risk of developing leukemia. Disruption or dysregulation of genes is another common cause.

Watch the video about the [Philadelphia Chromosome](#)

One common structural change in genes that can lead to leukemia involves the formation of the **Philadelphia chromosome**. The structural change occurs through a translocation, which is when portions of two chromosomes switch places with one another. The Philadelphia chromosome occurs when breaks at the end of chromosome 9 and 22 allow the ABL proto oncogene of chromosome 9 to be translocated to the breakpoint cluster region of chromosome 22. This translocation produces BCR-ABL gene sequence and the Philadelphia chromosome. BCR-ABL codes for a protein that allows affected cells to bypass the regulatory signals controlling normal cell growth and differentiation. This results in the malignant transformation of white blood cells to become leukemia cancer cells.

The BCR-ABL protein is a tyrosine kinase. This means it is an enzyme capable of transferring a phosphate group from ATP to a tyrosine amino acid found within a particular portion of a protein. BCR-ABL will transfer a phosphate group to a growth inducing protein and activate it. Once activated, this causes uncontrolled myeloid growth and leads to leukemia. While BCR-ABL can lead to any of the leukemias, it is most often associated with chronic myeloid leukemia. The Philadelphia chromosome is seen in 90% of those with CML.

Imatinib (Gleevec) is a drug used in the treatment of CML. It is a tyrosine kinase inhibitor that competitively inhibits the BCR-ABL protein by occupying its ATP binding site. Keeping this tyrosine kinase busy prevents it from exerting its growth promoting actions in the cell and greatly reduces the number of cancer cells.

Acute Leukemia

Watch the video on [Acute Leukemias](#)

Acute lymphocytic leukemia (ALL) starts with a problem in the lymphoid line of blood cell differentiation. 85% of cases of ALL are pre B-cell origin meaning that ALL develops from a lymphoid blast. **Acute myeloid leukemia (AML)** develops from an early cell in the myeloid line that is either a myeloid stem cell or a myeloid blast.

Manifestations of the acute forms of leukemia result from so much of the body's resources being diverted to the growth and maintenance of cancer cells. These cancer cells prevent the action of normal homeostatic mechanisms that would normally maintain proper hematopoiesis. Patients will experience a decrease in red blood cells (anemia), platelets (thrombocytopenia) and neutrophils (neutropenia). Systemic manifestations include weight loss, fever, and frequent infections. Leukostasis may also occur. **Leukostasis** is the excessive elevation of circulating aberrant hematopoietic blast cells. The high number of these circulating abnormal cells increases blood viscosity and can increase the risk of leukoblastic emboli formation. These emboli are dangerous because they can obstruct small vessels in the lungs and brain. If obstruction in the lungs occurs the patient will become short of breath and have progressive dyspnea (difficult or labored breathing). If the obstruction occurs in the brain, confusion and even coma may result. Treatment of leukostasis may include apheresis (blood drawing and filtering) to remove excess cells. This is generally followed by chemotherapy to decrease leukoblastic proliferation. Patients with acute forms of leukemia undergoing chemotherapy commonly present with gout. This is because chemotherapy causes a lot of cell death, so quite a bit of DNA and RNA must be broken down by the body. This increased breakdown creates an excessive amount of uric acid which can crystallize in the patient's joints. We will learn more about gout in a later chapter.

Diagnosis of acute leukemia can be achieved by a complete blood count (high leukocyte numbers are observed), bone marrow biopsy (examination of hematopoietic cell characteristics), cytogenetic studies (looking for chromosomal abnormalities and cell markers), lumbar puncture (assessing whether malignant white blood cells have spread to the central nervous system) and a CT scan of the chest, abdomen, and pelvis.

There are two major effective treatments for acute forms of leukemia: chemotherapy and bone marrow/stem cell transplantation. Chemotherapy greatly increases the survival rate for acute leukemia patients. In ALL the 5 year survival rate in children is 80%. In AML the overall survival rate is only 30%, but it is a less common type of acute leukemia. Bone marrow or stem cell transplantation is done when other forms of treatment have failed. The complications that can arise from a bone marrow transplant make it a risky option for older patients so it is not often recommended for patients over 50 years in age.

Chronic Leukemia

Chronic Lymphocytic Leukemia (CLL)

Chronic leukemias involve the proliferation of a more differentiated myeloid or lymphoid cell. CLL accounts for 1/3 of all leukemia cases and is found mostly in older adults. Chronic lymphocytic leukemia has two forms: indolent and aggressive. **Indolent** CLL is often asymptomatic at the time of diagnosis. In fact, patients with the indolent form often get diagnosed when blood is being analyzed for some other unrelated complaint or symptom. Indolent CLL may be simply monitored and treated symptomatically and patients often live for many years and die of unrelated illnesses before the CLL becomes lethal. **Aggressive** CLL manifests itself by a relatively quick onset of lymphadenopathy, hepatosplenomegaly, fever, abdominal pain, weight loss, progressive anemia, thrombocytopenia, and rapid rise in lymphocyte count. Hypogammaglobulinemia (decreased gamma globulins in the blood) is also common and can lead to difficulty fighting off infections. Aggressive CLL will need to be treated as other forms of leukemia are treated (chemotherapy, possible radiation and even bone marrow transplant).

The reasons behind whether CLL is indolent or aggressive have to do with the exact gene mutations that occur in the lymphoblastic line. Several laboratory tests are generally conducted to assess which mutated genes exist and this helps determine a patient's prognosis. Whether the CLL is indolent or aggressive, there are likely to be excessive numbers of immature and abnormal lymphocytes (including the NK cells as they are of the lymphocyte lineage).

Chronic Myelogenous Leukemia (CML)

CML only accounts for 10-15% of leukemia cases and is mostly found in older adults. The hallmark of CML is BCR-ABL gene products that can be detected in the peripheral blood. This is most often caused by the "Philadelphia Chromosome" discussed earlier. CML is characterized by excessive granulocytes, erythroid precursors, and megakaryocytes. There are three phases of CML. The first is the chronic phase which normally lasts around 4 years and consists of weakness and weight loss. The second phase is the short accelerated phase when the patient starts to have symptoms such as fever, night sweats and bone pain. These symptoms occur because of the sudden increase in leukocyte proliferation and the metabolism. The third phase is the terminal blast crisis phase. It normally lasts about three months and is characterized by leukostasis (extremely elevated blast cell count) which is considered to be a medical emergency.



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