

Consensus (Narrative)

Leukemia: Up-to-Date Information from Pathogenesis to Management

The Medical Therapeutic Consensus Task Force (MTCTF)

SUMMARY

Leukemia is a type of cancer that affects bone marrow, it's characterized by presence of high number of abnormal white blood cells in the blood that affects nearly all body organs and tissue and give rise to multiple symptoms and complications. Despite the high number of research studies in the field of leukemia, it's yet not clear how the disease forms, and there's no proven mechanism that explains leukemia. Prognosis and responsiveness to treatment is better in children than in adults. There are four main types of leukemia: Acute Lymphocytic leukemia, acute myeloid leukemia, Chronic Lymphocytic leukemia, and chronic myeloid leukemia. Leukemia isn't linked to any specific preventable risk factors, and that's why it's totally unpreventable. Non-specific risk factors predisposing to leukemia include irradiation, some types of viral infections, tobacco, benzene, chloramphenicol, phenylbutazone, hair dyes, and chromosomal factors. Main symptoms of leukemia include anemia with dyspnea, thrombocytopenia with bleeding tendency, leucopenia with recurrent infections, weight loss, fever, fatigue, anorexia, lymphadenopathy, hepatosplenomegaly, night sweating, bone pain, weakness, and shortness of breath. Diagnosis of leukemia depends on complete blood picture to detect the decreased number of normal blood cells and the increased number of the abnormal leukemic cells. Also bone marrow biopsy, CSF examination, blood chemistry testing, and radiology are useful diagnostic and confirmatory methods. Supportive treatment of leukemia aims aid compensation for the decreased body functions, such as packed RBCs transfusion to compensate anemia, platelet transfusion to compensate thrombocytopenia, antibiotics to compensate for neutropenia, and allopurinol to treat gout. Specific treatment of leukemia depends mainly on chemotherapy, such as busulphan in treatment of CML. The Chinese leukemia treatment "a combination between Chinese & western medicine" is remarkably becoming a popular alternative to chemotherapy. ■

KEYWORDS

Leukemia; Pathophysiology; Mechanism; Therapy

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BOX 1. 15 INTERESTING GENERAL FACTS ABOUT LEUKEMIA

- [1] About 1 million Americans are either suffering or recovering from blood cancer.
- [2] Nearly each ten minutes, an American citizen dies from leukemia.
- [3] Approximately a combined total of 171,550 are expected to be diagnosed with one of the three Main types of blood cancer [Lymphoma, Myeloma, Leukemia] by the end of 2016.
- [4] Those who are older than 67 years are the most prone to get leukemia. However about 1/3 of Leukemia patients are kids and teens. Survival rates of leukemia are so low as it usually affects old people who have already reached The natural end of human life.
- [5] Leukemia affects male patients more than female ones.
- [6] According to rate of occurrence, leukemia type of cancer comes 10th or 11th [ranked after endometrial tumors that affect uterus]
- [7] Blood cancer as a whole accounts for a percent of 10% of newly-diagnosed cancer in USA.
- [8] The five-years survival rate of leukemia from 2005 – 2011 was about 62%.
- [9] The five-year survival rate have tripled or even quadrated in the last 50 years.
- [10] Leukemia nearly affects every important organ in the body.
- [11] Despite the high number of research studies in the field of leukemia, it's yet not clear how the Disease forms, and there's no proven mechanism that explains leukemia.
- [12] Many researches have shown that there is no clear connection between any groups of risk Factors and suffering from leukemia, that's why leukemia is nearly 100% unpreventable.
- [13] About \$70-\$90 million are spent every year on leukemia researches.
- [14] The Chinese leukemia treatment "a combination between Chinese & western medicine "is remarkably becoming a popular alternative to chemotherapy.
- [15] It's believed that leukemia wasn't discovered until the 18th century.

DIFFERENT TYPES OF LEUKEMIA

Acute means the disease progresses rapidly, and the symptoms are more sever.

Acute Lymphocytic Leukemia [ALL]

Also Called: Acute lymphoblastic leukemia or acute lymphoid leukemia.

Incidence: can occur at any age, but most commonly occurs under the age of 15 [Teens] Or above the age of 65, and characterized by formation of Thymic Mass.

Pathology: Build-up and accumulation of lymphoblastic cells in bone marrow
[present in the shaft of long bone, and responsible for synthesis of different blood cells]

► Those abnormal cells cannot differentiate into neither T-Cells [the immune cells that kills the infected cells, preventing spread of the pathogen to the healthy cells], Nor B-Cells [the immune cells that are responsible for producing the antibodies which give our bodies protection against re-infection with the same pathogen again]

► Also, those abnormal malignant cells limits the bone marrowability to produce

Other types of blood cells, for example:

↓ Red Blood Cells Synthesis → Anemia → Fatigue.

↓ Platelets → Thrombocytopenia → Bleeding tendency.

↓ Immune Cells → ↓ Resistance to microbes → Recurrent infections

Standard treatment : Chemotherapy and radiology

Survival Rate : 85% in children & 50% in adults

Subtypes: B-lymphoblastic leukemia T-lymphoblastic leukemia Burkett's leukemia Acute Bi-phenotypic leukemia

Acute Myeloid Leukemia [AML]

Also Called : Acute myelogenous leukemia or acute myeloblastic leukemia.

Prevalence : It's the most common type of leukemia

Incidence : adults aging from 50 – 60 years

Mechanism : Build-up and accumulation of myeloblastic cells in bone marrow

► Those abnormal cells cannot differentiate into neither Red Blood Cells [the cells that carry hemoglobin and play a very important role in respiration and gas.

► Also, those abnormal malignant cells migrate to different organs and tissues where they develop and replicate causing the characteristic clinical symptoms.

Standard treatment: Unfortunately, it's incurable, but there are many effective supportive treatment.

Survival : the 5-years survival rate is 40%

Subtypes : Acute myeloblastic leukemia Acute megakaryocytic leukemia Acute Monocytic leukemia Acute promyelocytic leukemia [90% Survival]

Chronic Lymphocytic Leukemia[CLL]

Incidence : adults above the age of 55 "almost never affects kids"

Survival : the 5-years survival rate is 75%

Subtype : B-cell prolymphocytic leukemia [more aggressive]

Chronic Myeloid Leukemia [CML]

Incidence : usually affects adults [children can be affected, but this's rare]

Standard treatment : treated with imatinib (under the name of Gleevec in USA, Glivec in Europe)

Survival : the 5-years survival rate is 90%

Subtype : chronic myelomonocytic leukemia.

OTHER TYPES OF LEUKEMIA

Hairy cell leukemia
T-cell prolymphocytic leukemia
Large granular lymphocytic leukemia
Adult T-cell leukemia.

CAUSES OF LEUKEMIA

Genetic “chromosomal” factors

Philadelphia Chromosome : in CML, Congenital Diseases with abnormalities : such as Down’s syndrome, Fanconi anemia, Klinefelter syndrome.

Radiation

Retroviruses
HTLV-1 [Human T-cell Leukemia Virus-1]
EBV [Epstein-Barr Virus]

Viruses

Retroviruses
HTLV-1 [Human T-cell Leukemia Virus-1]
EBV [Epstein-Barr Virus]

Chemical and Drugs

Hydrocarbons [Benzene]. Alkylating agents.
Chloramphenicol. Phenylbutazone.
Tobacco. Hair dyes.

Mother to fetus transmission

Only a few cases has been of sick babies to sick moms have been reported.

CLINICAL MANIFESTATIONS OF LEUKEMIA

Bone Marrow Failure

Overcrowding of the bone marrow with abnormal leukemia cells, significantly diminishes The ability of bone marrow to synthesize other blood cells, leading to :

Anemia

The total hemoglobin level becomes below 12 g/dl in ♀ or 14 g/dl in ♂ .

Anemia decreases the blood ability to carry oxygen leading to fatigue, weakness.

Dyspnea, shortness of breath, tiredness and decreased ability to exercise.

In severe cases other symptoms like confusion and unconsciousness may occur.

Also the heart may try to compensate the decreased tissue oxygenation by ↑

COP [Cardiac output] through increasing both contractility force and rate, which

Can lead to palpitation, murmurs, angina, ventricular hypertrophy or heart failure.

Thrombocytopenia

Due to decreased number of platelets below 150.000 / μ l. The decrease in the number of thrombocytes, hinders the body ability to stop

Bleeding from injured blood vessels, which can manifest as bleeding gums, nose Bleed, purpura, or petechia.

Also, it may manifest by heavier longer periods or breakthrough bleeding in female leukemic patients

Granulocytopenia & Lymphocytopenia:

The abnormal immature leucocytes cannot differentiate into the useful functional

Types of wbc, which leads to :

↓ T-lymphocytes → ↓ Ability to control viral infections & mutated cells.

↓ B-lymphocytes → ↓ Ability to form antibodies → recurrent infections.

↓ pmnls [polymorph-Nuclear Lymphocytes] → ↓ Body resistance to Infections, and generalized lowered body immunity. May manifest as throat and mouth ulcers, enlarged cervical lymph nodes, Parotiditis, pneumonia, cellulitis, or even bacteremia [Bacteria invade the blood]. Manifestations due to infiltration of body organs by leukemia cells When the abnormal leukemia cells are disseminated into blood, they migrate to Several tissues and organs giving rise to several symptoms that differ according To the affected organ .

Central Nervous System “CNS”

Symptoms include ↑ ICT [increased Intra-Cranial Tension] which can lead to nausea, headache, tremors, cranial nerve palsy, or spinal compression.

Lungs

Symptoms include parenchymal infiltration, pleural effusion [presence of excess fluid around the lungs which impairs lung expansion], dyspnea, shortness of breath, or mediastinal syndrome

Reticulo-Endothelial System

Leukemia causes generalized lymphadenopathy [inflammation of lymph nodes And lymph vessels], for example :- Enlarged mediastinal lymph nodes → Mediastinal Syndrome :

- Obstructed Superior Vena Cava
- Severe edema
- Cough and headache

Enlarged porta hepatitis lymph nodes → obstructive jaundice

Due to obstruction of bile outflow, that leads abnormal yellowish

Discoloration of skin and mucous membranes (e.g.: whiteness of eye),

Together with dark urine, dark stool, and severe itching.

S Hepato – Splenomegaly [enlarged liver and spleen] → Nausea and pain.

Gastro-intestinal Tract

Hypertrophy of gums, mouth ulcers, pain, diarrhea, colic and hemorrhage.

Kidney and genital system

Hematuria [presence of blood in urine], UTI [Urinary Tract Infection], Ureteric Obstruction [By urate stones], Testicular Swelling [in ALL].

Musculo-skeletal

Sub-periosteal infiltration [the abnormal leukemia cells infiltrates under the Membrane that covers the outer surface of the bone “Periosteum”] causing Bone and joint pain, together with tenderness and muscle weakness.

General Manifestations

Fever : due to opportunistic bacterial infection enhanced by lowered body immunity together
With tissue destruction and increased metabolic rate “hypermetabolism” Weight loss
Prostration & Asthenia

Other Manifestations

Other clinical disorders caused by leukemia may include :
Gout : due to increased serum uric acid.
Hypokalemia [decreased blood Potassium Level] : due to renal tubular dysfunction.
Hyponatremia : due to ↑ ADH [Syndrome of Inappropriate Anti-Diuretic Hormone].
Mickulicz’s Syndrome : enlarged salivary & lacrimal glands.
Chloroma : Soft tissue masses occurring at any site
Leukostasis : due to excess blasts which lead to obstruction of blood capillaries, with
Subsequent ischemia or rupture of those obstructed capillaries

DIAGNOSIS & INVESTIGATIONS OF LEUKEMIA**Diagnosis of Acute Leukemia**

(1) Complete Blood Count [CBC]
2 Red Blood Cells : severe normocytic normochromic anemia [may require BM transplant]
Low hemoglobin levels below 12 g/dl in male or 14 g/dl in female.
2 Platelets : thrombocytopenia with low platelets level below 150.000 / µl.

2 Leucocytes [Leucocytosis] :
Total Leucocytic Count [TLC] : abnormally increased and may exceed 100.000/mm³
Predominant blast cells consists 30-90% (normally 1-3%), [maybe lympho or myeloblas].

2 Sub-leukemic Leukemia : TLC is normal or subnormal with presence of Blast

2 Aleukemic leukemia : TLC is normal or subnormal with absence of Blast

In this case, blood tests cannot reveal that a person has leukemia despite Having clear leukemia clinical picture.

This occurs mainly during early stages or remission.

This case can be diagnosed only by bone marrow examination.

Differentiation between leukemic cells is important, and can be done by :

Morphology

Surface markers : immunophenotyping

Cytoplasmic markers

Myeloblasts are Myeloperoxidase + Ve

Lymphoblasts are PAS + Ve

(2) Bone Marrow Examination

Bone marrow is hyper-cellular, full of abnormal blast cells [30 - 90 % or even 100% of BM]

Very important in diagnosis of aleukemic leukemia.

(3) Lymph Node Biopsy

Lymph Node Biopsy is used to diagnose specific types of leukemia under certain conditions

(4) Cerbro – Spinal Fluid Examination [CSF exam.]

Used for detection of abnormal leukemic cells

(5) Radiology

2 X-ray : reveals bone osteoporosis, periosteal elevation, and exclude mediastinal mass.

2 MRI : reveals the extent of brain and nervous damage due to leukemia.

2 Ultrasound : For organs in abdominal cavity, e.g.: kidney, liver, and spleen.

2 CT : rarely used to check mediastinal [chest] lymph nodes.

(6) Blood Chemistry Tests

Used for checking the degree of liver & kidney damage caused by leukemia.

Can also be used to check the effect of chemotherapy on patients.

Blood Shows :

[↑ Uric acid level [may lead to gout][↑ LDH [Lactate Dehydrogenase level]

[↓ K⁺ level [Hypokalemia] [↓ Na⁺ level [Hyponatremia]

(7) FAB classification

[French – British – American classification of Acute Leukemia :

Myeloid Lymphoid
M1 → M7 L1 → L3

(8) Leukemoid Reaction [Leukemoid Blood Picture]
It's a condition characterized by marked leukocytosis (< 25.000 /mm³)
± immature forms, either :
Lymphatic Leukemoid Reaction

Viral : infectious mononucleosis, herpes simples, hepatitis, and HIV

Bacterial : Pertussis “whooping cough”, TB, and brucellosis

Protozoal : Toxoplasmosis

Myeloid Leukemoid Reaction

2 Ch.Ch. By ↑ wbc < 50.000 /mm³, and/or presence of immature leukocytes.

2 Occurs in :-

Bone Marrow overstimulation [Hyperactive BM] :-

Occurs in acute hemolysis, acute hemorrhage, and acute hypoxia.

Bone Marrow infiltration [Leucoerythroplastic Anemia]

Presence of both immature rbc & immature wbc

Diagnosis of Chronic Leukemia

(1) Complete Blood Count [CBC]

2 Red Blood Cells : early increased, but later on → normocytic normochromic anemia.

2 Platelets : early increased, but later on → thrombocytopenia with low platelets level.

2 Leucocytes [Leucocytosis]

Total Leucocytic Count [TLC] : ranges between 100.000/mm³ – 500.000/mm³

P Neutrophils mainly ↑, but also eosinophils and basophils can ↑.

P Myelocytes range from 20-50%

P Leukocyte alkaline phosphatase is low [may reach zero]

(2) Bone Marrow Examination

Bone marrow is hyper-cellular, full of abnormal myelocytes & myeloblasts.

BM examination can also demonstrate Philadelphia Chromosome

Philadelphia Chromosome

Specific chromosomal abnormality in myeloid cells found in 80-90 % Of Chronic Myeloid Leukemia Cases.

Philadelphia +Ve patients tend to have better prognosis & response to treatment.

(3) Blood Chemistry Tests

Lymph Node Biopsy is used to diagnose specific types of leukemia under certain conditions

[↑ Uric acid level [↑ Transcobalamin II [↑ Vitamin B12]

(4) Rai's staging of Chronic Lymphocytic Leukemia [Prognostic]

Stage 0 Absolute Lymphocytosis – Normal Hb & platelets

Stage 1 Stage 0 + Lymphadenopathy

Stage 2 Stage 0 + Lymphadenopathy + Hepatosplenomegaly

Stage 3 Stage 0, 1, or 2+Anemia (Hb > 11 g/dl)

Stage 4 Stage 0,1, or 2+Thrombocytopenia (Platelets > 100.000/mm³).

TREATMENT OF LEUKEMIA

Supportive Treatment of Leukemia

Anemia : packed rbc transfusion.

Bleeding : platelets transfusion.

Infections : granulocyte transfusion, antibiotics, antifungal, or antiviral.

Gout : Allopurinol.

Leukostasis : removal of leukemia cell from blood by leukopheresis.

Prevention of acute tumor lysis syndrome “that follows chemotherapy”, by :-

Adequate hydration, allopurinol, and dialysis.

Supportive Treatment of Leukemia

Aim : sensitization of immune system to enable it to detect and remove tumor cells.

2 Methods : Bacillus-Calmette-Guerin vaccine, levimazol, monoclonal abs,

Subcutaneous irradiated allogeneic leukemic cells.

Oncotherapy of ALL

(1) Remission induction [4-6 w]

Prednisone [orally] Vincristin [IV]

Criteria of Remission:-

- Absent clinical manifestations

- Bone Marrow : Lymphoblast > 5 %

- Blood : Absent blast, PNL < 5.000/mm³,

Platelets < 75.000/mm³.

(2) CNS Prophylaxis [2-5 w]

Cranial irradiation ± Spinal irradiation + Methotrexate [intrathecal]

(3) Consolidation

Similar to remission induction.

(4) Maintenance for 2 years at least

Prednisone / Vincristin [every 3 months]

(5) Follow up via clinical symptoms and hematological exams

Testicular biopsy for men may be needed.

Oncotherapy of AML

(1) Remission induction

Either : 6-Mercaptopurine + Methotrexate + Cyclophosphamide

Or : Cytosine arabinoside + 6-thioguanine + Doxorubicin

(2) CNS Prophylaxis [usually not used]

(3) Consolidation [7-10 months]

Usually not useful.

Bone Marrow transplantation usually needed.

(4) Bone Marrow Transplantation

Especially in patients > 45 years

Treatment of CML

(1) Chemotherapy

Busulphan [Myleran].

Hydroxyurea [Hydrea].

(2) X-ray total or local radiotherapy

(3) Recent approaches

Early splenectomy followed by aggressive chemotherapy

alpha-interferon – Imatinib mesylate

Bone marrow transplantation.

Treatment of CLL

It's delayed till appearance of symptoms, as it's believed that drugs doesn't affect mortality

(1) Chemotherapy

Chlorambucil [Leukeran].

Prednisone.

Alternative treatment includes :

Combined Chemotherapy. Cyclophosphamide [endoxan].

Fludarabine. Monoclonal Antibodies.

(2) Lymph Node & Spleen Radiotherapy. ■

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