Leukemias

ACUTE LEUKEMIAS

- The acute leukemias are hematologic malignancies of bone marrow precursors characterized by excessive production of immature hematopoietic cells.

- Acute leukemias are classified according to their cell of origin. Acute lymphocytic leukemia (ALL) arises from the lymphoid line. Acute nonlymphocytic leukemia (ANLL) or acute myelogenous leukemia (AML) arises from the myeloid line.

- The initial treatment for acute leukemias is called ***induction*.**

- An estimated 10,410 deaths per year, representing approximately **2%** of all cancer deaths, are caused by acute leukemias.

- The acute leukemias are the leading cause of cancer-related deaths in persons younger than age 35 years, but an uncommon cause of cancer- related death after age 35 years.

- The median age at diagnosis of patients with AML is about 65 years, whereas the median age for ALL patients is about 10 years.

- For persons younger than 20 years of age, the 5-year survival rate is 83% for ALL and 50% for AML.

- The prognosis of adult acute leukemia is generally worse than that of childhood leukemia, with only 30% to 40% of patients becoming long-term survivors.

- The current induction therapy for acute lymphocytic leukemia (ALL) typically consists of vincristine, asparaginase, and a steroid (prednisone or dexamethasone).

- The current induction therapy for acute myelogenous leukemia (AML) usually consists of a combination of cytarabine and daunorubicin, with the frequent addition of a steroid and/or an antimetabolite such as 6-thioguanine.

- ALL accounts for 75% to 80% of all cases of childhood leukemia, whereas AML accounts for no more than 20%.

Etiology:

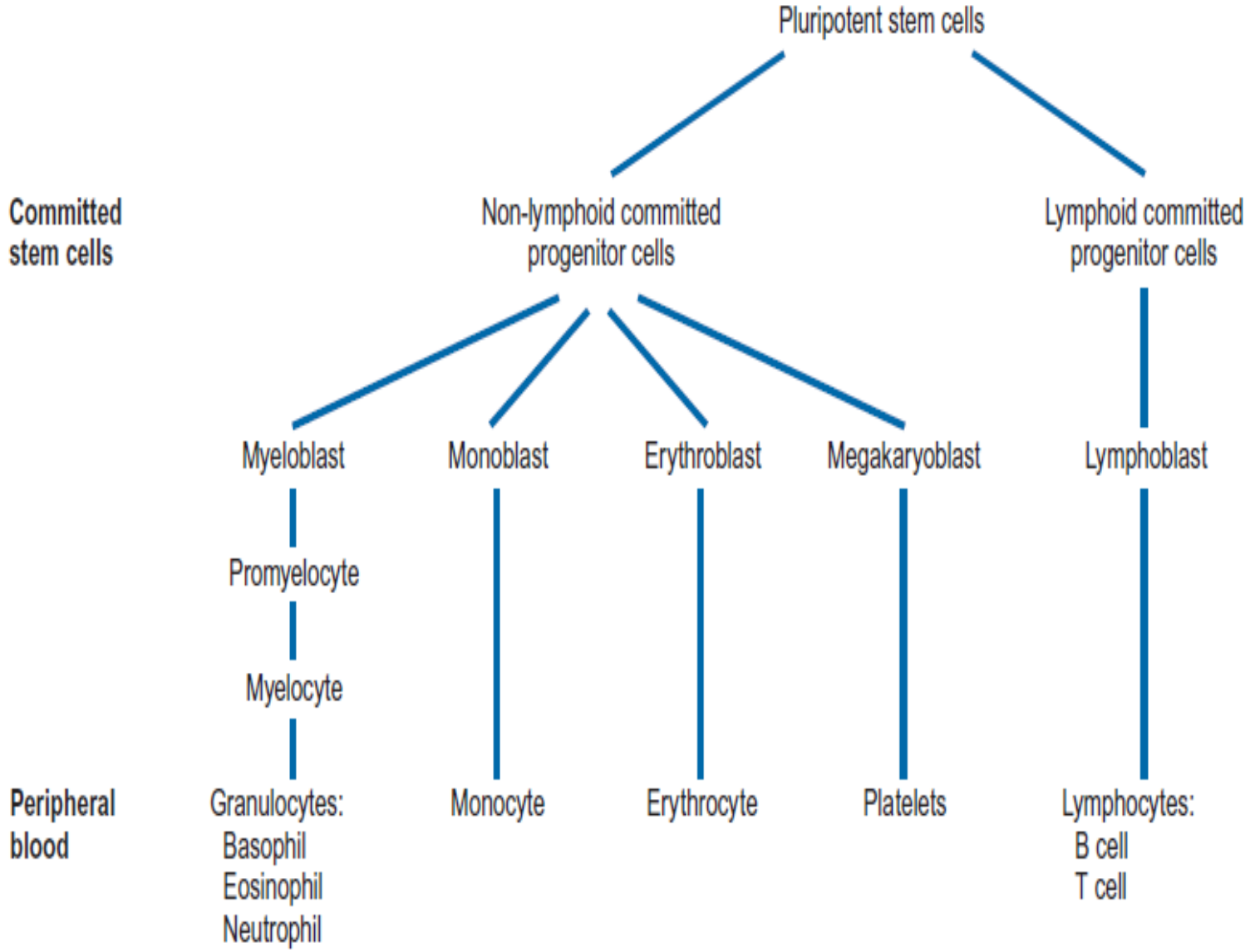
- Multifactorial: Genetics, socioeconomics, infection, environment, hematopoietic development, viruses, toxins, immunological status all may play a role.

PATHOPHYSIOLOGY:

- Hematopoiesis is defined as the development and maturation of blood cells and their precursors.

- All blood cells are generated from a common hematopoietic precursor, or *stem cell.*

- In contrast to the ordered development of normal cells, the development of leukemia seems to represent an arrest in differentiation at an early phase in the continuum of stem cell to mature cell.



Haemopoiesis.

LEUKEMIA CLASSIFICATION:

- The French-American-British (FAB) classification system identifies eight different subtypes of AML based on granulocytic differentiation and maturation, and this system is used to determine prognosis and choice of therapy. However, it does not consider clinical characteristics, clonal cytogenetic abnormalities, immunophenotyping, or response to therapy.

- The World Health Organization and the Society of Hematopathology have proposed a new classification system for myeloid neoplasms. This new classification system incorporates not only morphologic findings, but also genetic, immunophenotypic, biologic, and clinical features. It has long been known that certain cytogenetic abnormalities have prognostic significance, but did not always correlate well with the FAB classification system.

Morphologic (FAB) Classification of Acute Myeloid Leukemia

		Frequency of FAB Subtype[a]		
		Adults	Children <2 years	Children >2 years
	Subtype	(%)	(%)	(%)
M0	Acute myeloblastic leukemia, without maturation	5	Low	Low
M1	Acute myeloblastic leukemia with minimal maturation	15	17	25
M2	Acute myeloblastic with maturation	25		27
M3	Acute promyelocytic leukemia	10		5
M4	Acute myelomonocytic leukemia	25	30	26
M5a	Acute monoblastic leukemia, poorly differentiated	5	52	16
M5b	Acute monoblastic leukemia, well differentiated	5		
M6	Acute erythroleukemia	5		2
M7	Acute megakaryoblastic leukemia	10		5–7

WHO classification of AML

Subgroup	Examples
AML with recurrent genetic abnormalities	Inversion chromosome 16 (inv 16) t(15;17) t(8;21)
AML with multilineage dysplasia	
Therapy-related AML	
AML not otherwise classified	AML without maturation AML with granulocytic maturation AML with granulocytic and monocytic differentiation AML with monocytic differentiation AML with erythroid differentiation AML with megakaryocytic differentiation

Clinical Presentation of ALL:

- The patient may present with weakness, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- *Anemia* usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Patients often present with bone pain secondary to expansion of the marrow cavity from leukemic infiltration.
- CNS involvement is common at diagnosis.
- Temperature may be elevated secondary to a low WBC count.
- Patients may present with organ involvement, such as peripheral adenopathy, hepatomegaly, and splenomegaly.

Findings at diagnosis in leukemias

	AML	ALL	CML	CLL
WBC	↑ in 60%, may be N or ↓	↑ in 50%, may be N or ↓↓	↑↑ commonly 100×10^9–250×10^9 L^{-1}	Commonly ↑
Differential WBC	Mainly myeloblasts	Mainly lymphoblasts	Granulocytes ↑↑, especially neutrophils, myelocytes, basophils and eosinophils <10% blasts present	>5 × 10^9 L^{-1} monoclonal lymphocytes
RBC	Severe anaemia	Severe anaemia	Anaemia common	Anaemia in 50% of patients, generally mild
Platelets	↓↓	↓↓	Usually ↑, may be N or ↓	↓ in 20–30%
Bone marrow aspiration and trephine	Predominantly blasts	Predominantly blasts	Hypercellular blasts < 10%	Lymphocytic infiltration
Cytogenetic analysis	Important abnormalities detected	Important abnormalities detected	Presence of Ph chromosome	
Lymphadenopathy	Rare	Common	Rare	Common
Splenomegaly	50%	60%	Usual and severe	Usual and moderate
Other features	DIC, high urate	High urate, CNS involvement	↑ Serum uric acid	Immune paresis

N, normal; ↓, reduced; ↑, increased; WBC, white blood cells; DIC, disseminated intravascular coagulation; Ph, Philadelphia; RBC, red blood cells.

TREATMENT:

- The primary objective in treating patients with acute leukemia is to achieve a complete and continuous remission (CCR).

- **Remission** is defined as the absence of all clinical evidence of leukemia with the restoration of normal hematopoiesis.

- Failure to achieve remission in the first 7 to 14 days of therapy is highly predictive of disease recurrence.

1- Acute Lymphoblastic Leukemia (ALL):

- After a CR is achieved, the goal is to maintain the patient in continuous CR. In general, a child is considered to be "cured" after being in continuous CR for 5 to 10 years.

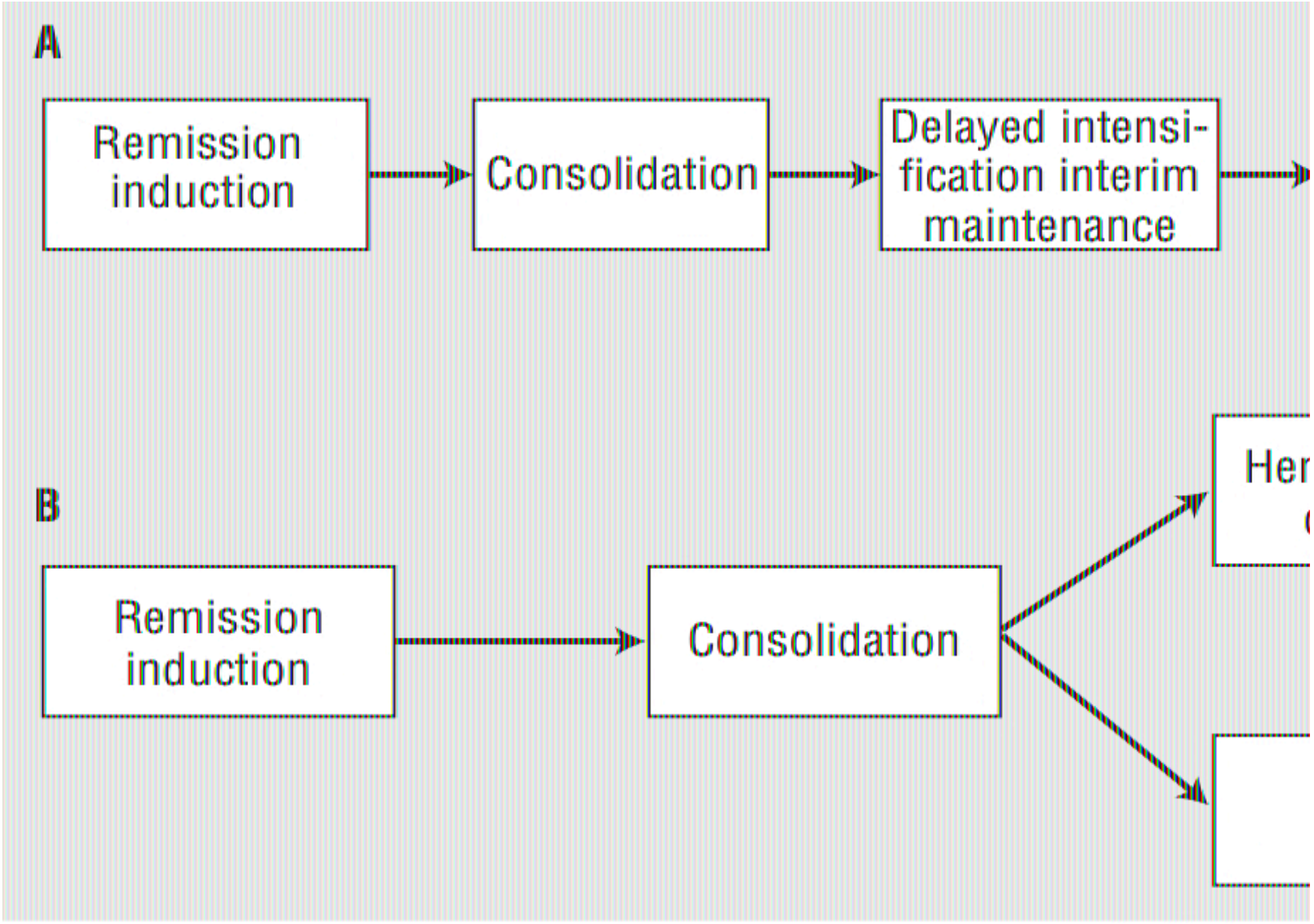
- The treatment for ALL consists of three main elements: remission induction, intensification (**consolidation**), and continuation (maintenance) phases of treatment.

- Therapy to eradicate subclinical CNS leukemia is also an integral part of therapy for ALL.

- Induction consists of a standard three-drug regimen: glucocorticoid (prednisone or dexamethasone), vincristine, and asparaginase or pegylated asparaginase.

- *For patients with high risk ALL, daunorubicin is added to the standard three-drug regimen.*

Treatment algorithm for *(A)* acute lymphoblastic leukemia and *(B)* acute myeloid leukemia.



- The availability of imatinib mesylate, a signal transduction inhibitor that inhibits BCR-ABL kinase, has stimulated much research to try and improve responses in the 10% to 20% of children who are Ph+ and refractory to a four- drug induction.

- Imatinib is currently incorporated into childhood treatment trials for Ph+ ALL in Europe and the United States.

- After completion of induction and restoration of normal hematopoiesis, patients begin intensification **(consolidation)**.

- The goal of intensification is to administer dose-intensive chemotherapy in an effort to further reduce the burden of residual leukemic cells.

- The purpose of maintenance therapy is to further eliminate leukemic cells and produce an enduring CCR.

- Standard consolidation lasts 4 weeks and usually consists of vincristine, mercaptopurine, and intrathecal methotrexate.

- The two most important agents in maintenance chemotherapy are a combination of oral methotrexate and 6-mercaptopurine.

- Consolidation may be intensified for slow early responders or high-risk patients to include cyclophosphamide, low-dose cytarabine, and pegaspargase.

- Children with Ph+ ALL or infants with t(4;11) mixed lineage leukemia (MLL), or children who only achieve a partial remission may receive a HSCT in first remission if a suitable donor is available.

- One or two delayed intensification phases separated by low-intensity interim maintenance cycles have been added to maintain remission and to decrease cumulative toxicity.

- Delayed intensification usually consists of dexamethasone, vincristine, doxorubicin, pegaspargase, cyclophosphamide, thioguanine or mercaptopurine, low-dose cytarabine, and intrathecal methotrexate.

- *CNS prophylaxis* relies on intrathecal chemotherapy (e.g., methotrexate, cytarabine, and corticosteroids), systemic chemotherapy with dexamethasone and high-dose methotrexate.

- The use of granulocyte colony-stimulating factor colony-stimu- lating factor in children and adults administered during, after, or between courses has been shown to shorten the duration of neutro- penia by 2 to 10 days.

2- *Acute Myelogenous Leukemia:*

- As with ALL, the primary aim in treating patients with AML is to induce remission and thereafter prevent relapse.

- Despite several strategies to increase the intensity of therapy, the overall survival rate has reached a plateau at 50% to 60%.

CLINICAL PRESENTATION of AML:

- The patient may present with weakness, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- Anemia usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Disseminated intravascular coagulation is common in AML M3 and is associated with generalized bleeding or hemorrhage.
- Lymphadenopathy, massive **hepatosplenomegaly**, and bone pain are not as common in AML as in ALL.
- Temperature may be elevated secondary to a low WBC count.

Laboratory Tests:

- Complete blood count with differential is performed.
- The anemia is usually **normochromic** and **normocytic.**
- Approximately 50% of children present with platelet counts of less than 50 × 103/μL (50 × 109/L).
- The WBC count may be normal, decreased, or high.
- Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.
- ***Electrolytes:*** Potassium and phosphorus are often elevated. Calcium is usually low.
- *Coagulation disorders:* Elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia.
- The presence of greater than 20% blasts in the bone marrow is diagnostic for AML.

- With recent advances in chemotherapy and supportive care, 65% to 85% of all patients with AML achieve a CR, and 20% to 40% become long-term survivors.

- Overall, the median duration of remission is 1 to 2 years. In patients older than 60 years of age, the percentage of patients achieving a CR is lower (39% to 64%), and the median duration of remission is shorter than 1 year.

- In contrast to ALL, effective therapies used in AML cause severe and often prolonged myelosuppression, with the exception of tretinoin. As a result, patients with AML, particularly patients older than 60 years of age, are at greater risk for treatment-related fatal infectious and bleeding complications.

- The combination of an anthracycline (e.g., daunorubicin, doxorubicin, or idarubicin) and the antimetabolite cytarabine forms the backbone of AML induction therapy.

- Once an initial remission is achieved, further intensive therapy is imperative to prevent relapse.

- Three options available for patients include high dose chemotherapy, allogeneic bone marrow transplantation from an HLA-matched related or unrelated donor, and autologous bone marrow transplantation.

- In most cases, intrathecal cytarabine with or without methotrexate and systemic high-dose cytarabine provide adequate CNS prophylaxis in pediatric population.

- One reason for the lower CR rate in AML as compared to ALL is the inability to give optimal doses of chemo- therapy because of marrow toxicity.

- Strategies evaluated as postremission therapy include (a) low- dose, prolonged maintenance therapy, (b) short-course intensive chemotherapy-alone regimens, and (c) high-dose chemotherapy with or without radiation therapy followed by alloHSCT or autolo- gous HSCT (autoHSCT).

- It is not clear whether the same agents (cytarabine and an anthracycline) given for remission induction should be used for postremission therapy in higher doses, or whether different agents should be given.

- If leukemic relapse is caused by a resistant cell line, then the use of different agents that are non–cross-resistant with drugs used in induction might be beneficial.

Treatment of Relapsed Leukemias:

- Relapse is the recurrence of leukemic cells at any site after remission has been achieved.
- Bone marrow relapse predicts a poor outcome for most patients.
- **Factors predicting a relapse** and poor prognosis for children with ALL are short initial remission, T-cell immunophenotype, high leukocyte count at relapse.
- Once a patient has obtained a second remission with conventional chemotherapy, allogeneic HSCT is the therapy of choice.

Complications of Treatment:

1- Tumor Lysis Syndrome:

- Tumor lysis syndrome (TLS) is an oncologic emergency that is characterized by metabolic abnormalities resulting from the death of blast cells and the release of large amounts of purines, pyrimidines, and intracellular potassium and phosphorus.

- Measures to prevent TLS include aggressive hydration, alkalinization to help solubulize uric acid, allopurinol.

2- **Infection:**

- Infection is a primary cause of death in acute leukemia patients.

- Currently, the most commonly used initial antibiotic agent is cefipime, a fourth-generation cephalosporin.

- ✓ After the appropriate postremission therapy has been completed, the patient may return monthly for 1 year, and then every 3 months, to check hematologic values.

- ✓ If no evidence of disease exists after 5 years from the diagnosis and the patient has been in continuous CR, the patient is considered cured.

- ✓ Pharmacists need to be involved in checking drug doses and any dose modifications for organ dysfunction or prior toxicity. Pharmacists are often in the best position to recognize the potential for medication errors and drug interaction and to help avoid them. Similarly, pharmacists are often able to identify the possibility that patient problems are secondary to drug treatments.

CHRONIC LEUKEMIAS:

- Chronic leukemia consists of a number of disorders, including chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL).

- Chronic leukemia differ from acute leukemia in that its clinical course is indolent. Most patients with chronic leukemia survive for several years after their initial diagno- sis, even without treatment.

- Conversely, most patients with acute leukemia die of their disease within weeks to months if not treated.

CHRONIC MYELOGENOUS LEUKEMIA:

- CML is a hematologic cancer that results from an abnormal proliferation of an early myeloid **progenitor** cell.

- This leads to abnormal proliferation and accumulation of progenitor and mature myeloid cells in the bone marrow and peripheral blood.

- The clinical course of CML has three phases: chronic phase, acceler- ated phase, and blast crisis.

- It is estimated that new cases of CML representing 15% of all leukemias. CML patients have a median age at diagnosis of 67 years.

- For most newly diagnosed cases of CML, the etiology is unclear. Ionizing radiation and heavy occupational exposure to benzene are known risk factors.

- The increased risk of CML from radiation exposure was evident in atomic bomb survivors and in patients who received radiation therapy for ankylosing spondylitis.

- CML is not associated with any known oncogenic viruses.

- Chronic myelogenous leukemia (CML) is characterized by the presence of the Philadelphia chromosome (Ph), a transloca- tion between chromosomes 9 and 22.

- The resulting abnormal fusion protein, p210 *BCR-ABL*, phosphorylates tyrosine kinase residues and is constitutively active, resulting in uncontrolled cell proliferation.

- The Ph can be found in both myeloid and lymphoid cells, which suggests that the transformed cell of CML is a pluripotent stem cell.

- Granulocytosis, usually present in CML, results from the increased growth rate of the transformed clone and disruption of normal hematopoietic cell maturation.

- Later in the clinical course of CML, cytopenias may occur in association with fibrotic changes in the bone marrow.

- Chemotherapy can be used to control CML in the chronic phase, but as the disease progresses, the cancer may no longer respond to treatment.

- CML arises from a defect in an early progenitor cell. Several cell lines may be affected, including myeloid, erythroid, megakaryocyte.

- The loss of control of tyrosine kinase activity causes abnormal cellular proliferation and inhibition of apoptosis.

Clinical Presentation:

- Approximately 50% of patients are asymptomatic at diagnosis.
- Symptoms may include fatigue, fever, weight loss, and bleeding.
- Organomegaly consisting of splenomegaly and hepatomegaly is common.

Diagnostic Procedures

Peripheral blood smear

- Bone marrow biopsy (required for diagnosis)
- Cytogenetic studies

Laboratory Findings

Peripheral blood smear

- Leukocytosis (WBC count greater than 100 × 103/μL,
- or 100 × 109/L)
- Thrombocytosis (approximately 50% of patients in chronic phase)
- Anemia
- Presence of blasts

Bone marrow

- Hypercellularity with presence of blast.

Newly Proposed System for Defining Phase of Chronic Myelogenous Leukemia

Chronic Phase	Accelerated Phase	Blast
• <10% blasts in peripheral blood or bone marrow	• 10–29% blasts in peripheral blood or bone marrow • Platelets <100,000 cells/mm^3 or >1,000,000 cells/mm^3 Additional findings • Cytogenetic evolution • Progressive Splenomegaly	• >30 eral mar • Larg on biop • Pres ulla Additi • • •

Treatment:

- An early goal of therapy is to achieve *hematologic complete remission* or to normalize peripheral blood.
- Nearly all patients with CML are treated initially with imatinib.
- Hydroxyurea may be used after diagnosis to rapidly reduce high white blood cell (WBC) counts and to prevent complications associated with large numbers of circulating neutrophils.
- Interferon-alfa is not used in newly diagnosed patients and is used largely in patients who do not respond to imatinib therapy.

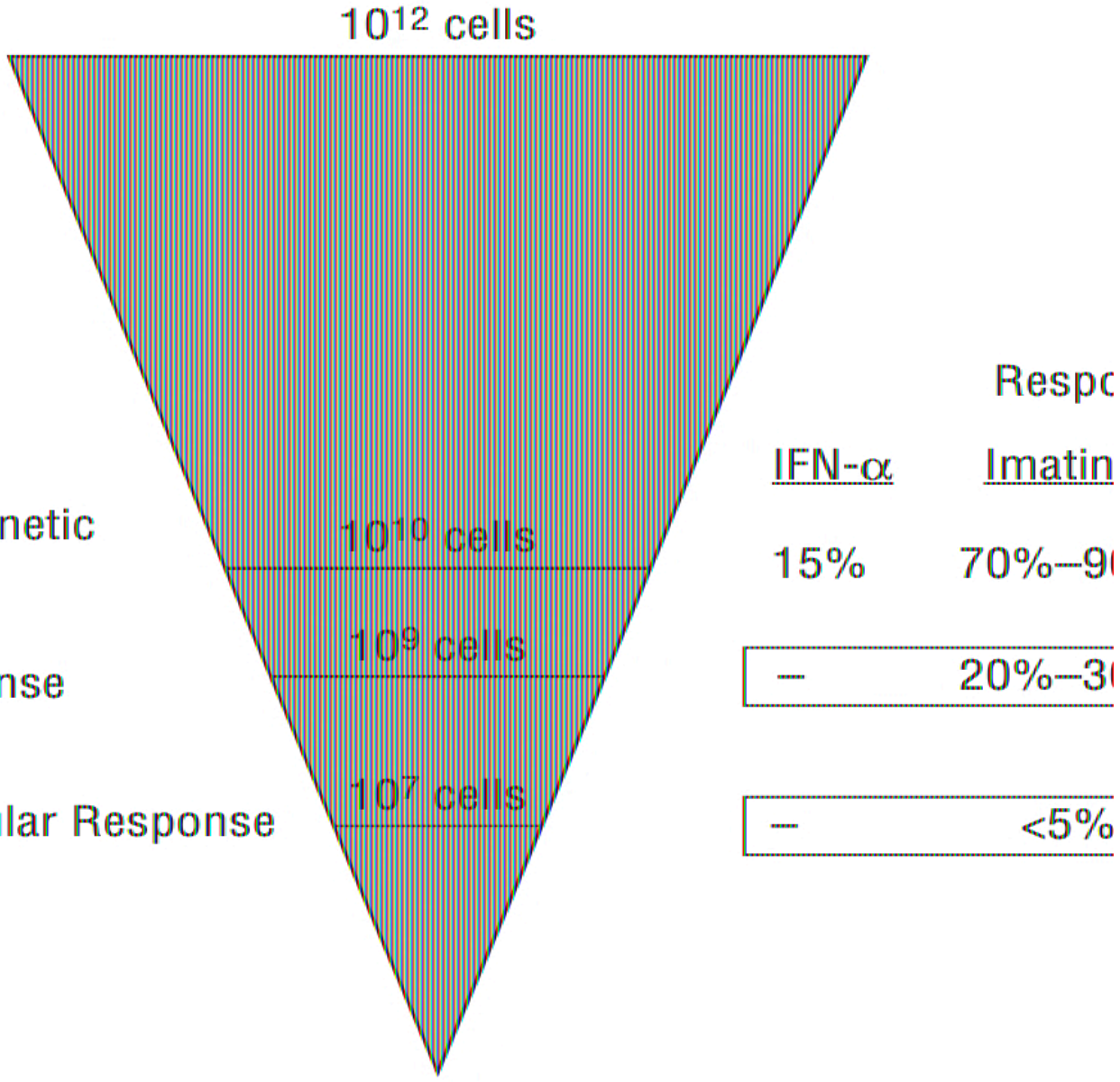
- **Allogeneic** stem cell transplantation is the only curative therapy for CML and is used in younger patients with a matched donor.

- A small percentage of patients will choose allogeneic hematopoietic stem cell transplantation (HSCT), which is the only treatment shown to permanently eliminate the Ph-positive malignant clone.

- Imatinib mesylate is a tyrosine kinase inhibitor used as first-line therapy in the majority of patients with CML.

- Prior to the introduction of imatinib, the combination of interferon-alfa and low dose cytarabine was the nontransplant treatment of choice for patients in chronic phase CML.

Therapy	5-Year Survival (%)	Med (Mo
Busulfan[25]	30–40	40–5
Hydroxyurea[25]	40–50	50–6
IFN-α[1]	50–70	60–8
IFN-α + ara-C[1]	60–80	NR
Allogeneic transplantation		
Matched sibling[1,55]	60–80	NR
Matched unrelated[1,7]	40–70	NR
Imatinib[21]	89	NR


Chronic Phase
(Diagnosis)
10^{12} cells
10^{10} cells
10^{9} cells
10^{7} cells
Complete Cytogenetic
Response
Molecular Response
Complete Molecular Response
Respc
IFN-α
Imatin
15%
70%–9
–
20%–3
–
<5%

2- CHRONIC LYMPHOCYTIC LEUKEMIA:

- CLL is a cancer that results in the accumulation of functionally incompetent B lymphocytes.

- CLL is a disease of the elderly, with a median age of onset between 65 and 75 years, although 20% to 30% of CLL occurs in patients who are younger than 55 years of age.3 Etiologic factors have not been identified in CLL, and there is no data supporting either radiation or viral oncogenesis.1

- CLL is considered an indolent, incurable disease in which treatment should be initiated when patients have symptoms.

- CLL is characterized by small, relatively incompetent B lymphocytes that accumulate in the blood and bone marrow over time.

- The exact cell of origin is controversial but has been described as an antigen-activated B lymphocyte.

Clinical Presentation:

Signs and Symptoms

- Fatigue, chills, bleeding, and lymphadenopathy
- Chronic infections owing to immature lymphocytes
- Organomegaly consisting of splenomegaly and hepatomegaly

Diagnostic Procedures

Peripheral blood smear

- Bone marrow biopsy
- Cytogenetic studies
- Molecular testing

Laboratory Findings

Peripheral blood

- Leukocytosis
- Anemia
- Thrombocytopenia

Treatment:

- The primary goals in the treatment of CLL are to provide palliation of symptoms and to improve overall survival.
- Because CLL is considered to be an incurable disease, the primary goals of treatment are to improve quality and duration of life.
- The management of patients with CLL is highly variable, with some patients receiving therapy immediately and delaying therapy in others.
- A response to therapy can be evaluated by a resolution of lymphadenopathy and organomegaly, normalization of peripheral blood counts, and elimination of lymphoblasts in the bone marrow.
- Today, a fludarbine- based chemotherapy is used as first-line therapy for younger patients with CLL.

- In stages III and IV disease, treatment is required, with the goal of achieving a partial or complete remission.

- Survival is improved in those patients who achieve a complete remission and is longest in those who become minimal residual disease negative.

- Orally administered alkylating agents such as chlorambucil and cyclo- phosphamide can be used as primary treatment for CLL.
-
- Some patients who don't respond to chlorambucil do respond to single-agent cyclophosphamide.

- Fludarabine-based therapy is a common initial treatment in CLL. It is particularly useful in younger patients and in those patients who can tolerate immunosuppressive chemotherapy.

- Fludarabine, along with the other purine analogs, 2-chlorodeoxyadenosine (cladribine) and 2-deoxycoformycin (pentostatin), is highly active in CLL, with fludarabine being the most widely studied purine analog in the treatment of CLL.

- **Rituximab** is a chimeric monoclonal antibody directed against the CD20 molecule on B lymphocytes.

- *Combination therapy may provide improvement in long term disease-free survival*. The combination of fludarabine, cyclophosphamide, and rituximab improves CR rates compared with fludarabine alone.

- Alemtuzumab is a monoclonal antibody that targets the CD52 antigen found on B and T lymphocytes.

- Alemtuzumab is primarily used as second-line therapy for CLL after failing combination-based therapy.

Treatment for Newly Diagnosed and Previously Treated Chronic Lymphocytic Leukemia

Treatment	Overall Response
Chlorambucil	
Untreated	37%
Fludarabine alone	
Untreated	60–80%
Previously treated	13–59%
Fludarabine + cyclophosphamide	
Untreated	80–90%
Previously treated	60–70%
Rituximab alone	
Untreated	50–60%
Previously treated	80–90%
Fludarabine + rituximab	
Untreated	80–100%
Previously treated	80–90%
Fludarabine + cyclophosphamide + rituximab	
Untreated	95%
Previously treated	73%
Alemtuzumab alone	
Untreated	80–90%
Previously treated	30–50%
Alemtuzumab + fludarabine	
Previously treated	83%

- The treatments used for CML and CLL are vastly different with tyrosine kinase inhibitors used in CML and biologics playing an increasingly important role in CLL.

- For the vast majority of patients with chronic-phase CML, imatinib is used as initial therapy.

- In patients who do not achieve an adequate response, dose escalation of imatinib, allogeneic HSCT, other tyrosine kinase inhibitors, or clinical studies should be considered.

- Allogeneic HSCT still remains the only curative therapy for CML.

- ✓ The goal in the treatment of CLL is to optimize quality of life rather than to use aggressive, toxic therapy.

- ✓ Observation is appropriate in asymptomatic patients with low-risk disease characteristics.

- ✓ Treatment should be reserved for patients with symptomatic or high-risk disease. In the older patient, the use of chlorambucil may still be preferred over fludarabine because of the lower infectious risk and ease of administration.

- ✓ The combination of fludarabine, cyclophos- phamide, and rituximab has reported the highest response rates in CLL.