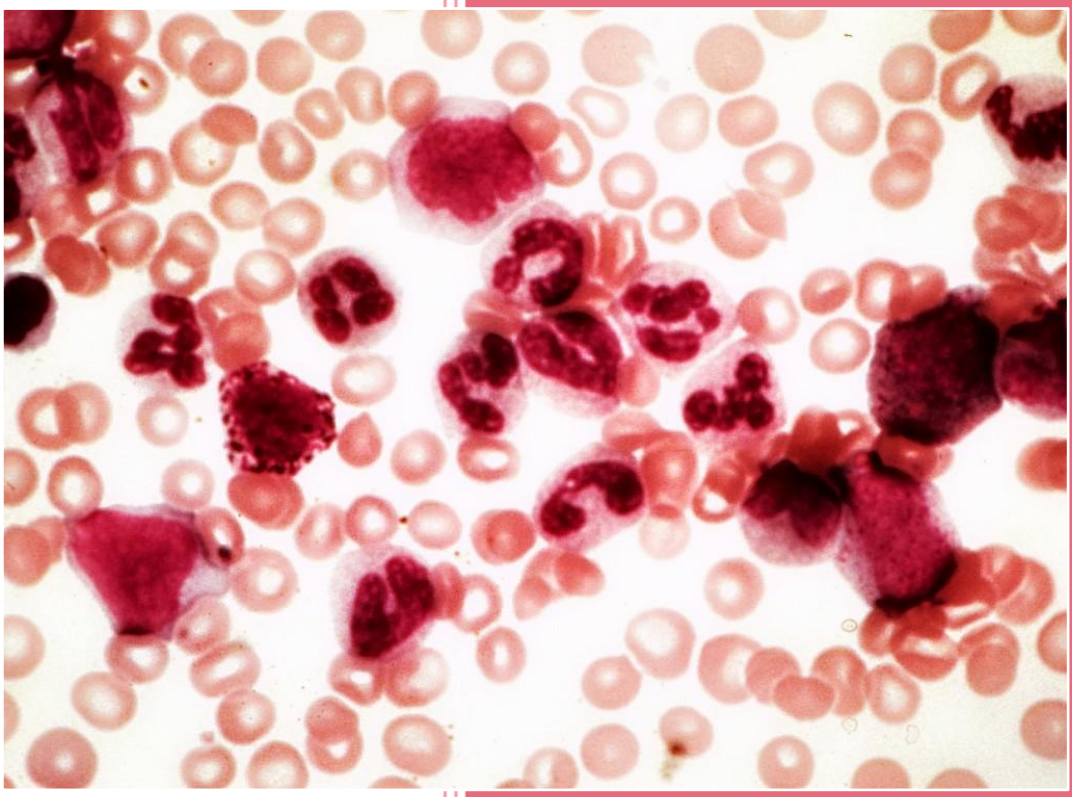
Medicine

Leukemias



Sources: Dr. Aamer Aleem's lecture, 427 Clinical Medicine Notes, Step-Up to Medicine 7E

429 Medicine Team

Questions? http://ask.fm/TeamNotes429

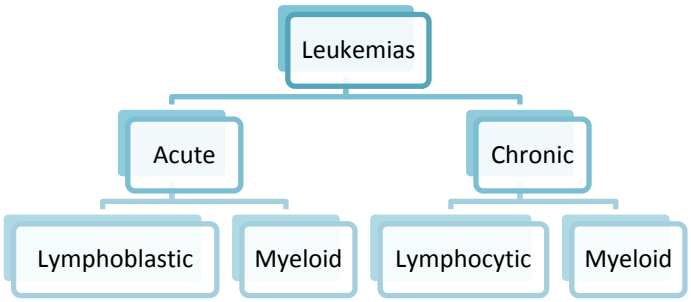
Leukemias

Introduction

Definition

- ***Leukemias are a group of cancers of the blood or bone marrow and are characterized by an abnormal proliferation (production by multiplication) of blood cells, usually white blood cells (leukocytes).***
- ***Leukemia is a broad term covering a spectrum of diseases. Any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs and which is usually accompanied by anemia and thrombocytopenia***

Classification



Myeloid Vs. Lymphoid Leukemia

- *Any disease that arises from the myeloid elements (white cell, red cell, platelets) is a myeloid disease (AML & CML)*
- *Any disease that arises from the lymphoid elements is a lymphoid disease (ALL & CLL)*

Acute Vs. Chronic Leukemia

	Acute	Chronic
Cells	*Young, immature, blast cells in bone marrow*	*Mature differentiated cells in marrow & blood*
Onset	*More fulminant presentation*	*Subclinical or incidental presentation*
Course	*More aggressive course*	*More indolent course*
		Splenomegaly is frequent

The Acute Leukemias

Definition

- *Acute leukemia is the result of a malignant event or events occurring in an early hematopoietic precursor. The affected cell gives rise to progeny that fail to differentiate but continue to proliferate in an uncontrolled fashion.*
- *As a result, immature myeloid cells in acute myeloid leukemia, or lymphoid cells in acute lymphoblastic leukemia - called blasts - rapidly accumulate and replace the bone marrow, diminishing the production of normal red cells, white cells, and platelets.*
- *This loss of normal marrow function → clinical complications of leukemia: anemia, infection, and bleeding.*
- *With time, the leukemic blasts pour out into the blood stream → occupy the lymph nodes, spleen, and other vital organs.*
- *If untreated, acute leukemia is fatal; most patients die within several months after diagnosis.*

Malignancies of immature hematopoietic cells (> 20% blast cells in the bone marrow)

Epidemiology & Etiology

- *Childhood (< 15)* *> 80%* *ALL*
- *Adult (> 15)* *> 80%* *AML*
- *Elderly (> 60 years)* *median age at diagnosis of AML*

ALL is the most common cancer & the 2nd leading cause of death in children < 15 yrs

In most cases, acute leukemia develops for no known reason, but sometimes a possible cause can be identified.

- ***Radiation*** *e.g. for ankylosing spondylitis, Hiroshima survivors: ↑ risk of AML, ALL & CML. Depends on the dose of radiation, its distribution in time, and the age of the individual (Greater risk results from higher-dose radiation delivered over shorter periods to younger patients)*
- ***Oncogenic viruses***
  - *Human T-cell lymphotropic virus type I (HTLV-I): ssRNA virus (retrovirus) → causative agent of adult T-cell leukemia (ATL) → treat w/anti-retroviral drug*
  - *Epstein Bar virus (EBV): DNA virus that causes infectious mononucleosis → Burkitt's lymphoma & mature B-cell leukemia*
- ***Chemicals & drugs***
  - *Occupational exposure to benzene & benzene containing substances e.g. kerosene*
  - *Tobacco*
  - *Chemotherapy: Alkylating agent (Chlorambucil, N mustard, Melphalan), Topoisomerase inhibitors (Etoposide)*
    - *Cytotoxic effects → myelodysplastic syndrome → secondary AML - typically develop 4 to 6 years after exposure*
- *Genetic: trisomy 21 (Down), and XXY (Klinefelter) → AML*
- *Myelodysplastic syndrome* *See Summary page 10*

Classification

Acute Myeloid Leukemia

See Figure 3, page 9

M0	***Acute undifferentiated leukemia***	***Uniform, very undifferentiated***
M1	*Acute myeloid leukemia with minimal differentiation*	*Undifferentiated, few azurophilic granules*
M2	*Acute myeloid leukemia with differentiation*	*Granulated blasts; +/- Auer rods*
M3	*Acute promyelocytic leukemia*	*Hypergranular promyelocytes*
M4	*Acute myelomonocytic leukemia*	*Monoblasts and myeloblasts are present*
M5	*Acute monocytic leukemia*	*Monoblasts predominate*
M6	*Acute erythroleukemia*	*Erythroblasts & megaloblastic precursors*
M7	*Acute megakaryocytic leukemia*	*Undifferentiated blasts*

Acute Lymphocytic Leukemia

L1	*Acute lymphoid leukemia, childhood variant*	*Small, monomorphic, nucleoli indistinct*
L2	*Acute lymphoid leukemia, adult variant*	*Larger, heterogeneous, nucleoli present*
L3	*Burkitt-like acute lymphoid leukemia*	*Large w/ strongly basophilic cytoplasm & vacuoles*

Clinical Features

Symptoms

- *Usual 1-3 Month History: MDS – 1yr*
- *Features of BM failure & infiltration*
  - *Fatigue, malaise, dyspnea (anemia)*
  - *Bleeding e.g. after dental procedure, bruisability, epistaxis*
  - *Testicular infiltration; orchidomegaly*
  - *CNS; seizures, meningism etc*
  - *Fever (infections)*
  - *Bone Pain*

Infections: pneumonia, UTI, esophagitis, pharyngitis, cellulitis; usually life-threatening (Due to neutropenia)

*CNS & testicle involvement: especially in **ALL***

Bone pain: Due to bone marrow expansion by leukemic cells/peri-osteal infiltration

Signs

- *Pallor*
- *Hemorrhage (gums, skin, fundus, GI tract, urinary tract; epistaxis, petechiae/echymosis)*
- *Hepato-splenomegaly*
- *Enlarged lymph nodes*
- *Gum (hypertrophy) or skin infiltration (M5)*
- *Fever (sepsis, pneumonia)*

Organ infiltration occurs more with ALL = lymphadenopathy, hepatosplenomegaly, CNS

Diagnosis

Differential Diagnosis

- *Aplastic anemia*
- *Myelodysplastic syndromes*
- *Multiple myeloma*
- *Lymphomas*
- *Severe megaloblastic anemia*
- *Leukemoid reaction*

Aplastic anemia is an autoimmune disease causing bone marrow failure & pancytopenia, treated with immunosuupressives

Multiple myeloma: bone marrow is replaced by malignant plasma cells. Presents with profound anemia while other cell lines are intact. Eventually pancytopenia develops. Very difficult to cure.

*Leukemoid reaction: A benign condition; leucocytosis that is a physiological response to stress/infection. Commonly confused w/CML. Work up: **Philadelphia chromosome assay**.*

Lab Tests

1. *CBC*
   a. *Anemia*
   b. *Thrombocytopenia*
   c. *WBC: high (usually), normal, low*
2. *Coagulation studies (M3-DIC)*
3. *Biochemical studies (U/E, LFT)*
4. ***Peripheral Blood smear** – blasts in almost all cases*
5. ***Bone Marrow Examination (>20% blasts)***
6. *Flow cytometry (surface immunophenotype of blast cells)*
7. *Cytogenetics (chromosomal analysis)*
8. *CSF analysis (all ALL patients, some AML)*
9. *HLA typing (for younger high risk patients)*

Electrolyte disturbances (hyperuricemia, hyperkalemia, hyperphosphatemia)

Disseminated intravascular coagulation (DIC) can be present in APL (M3); it is caused by tissue thromboplastins that are present in the leukemic cells and released as these cells die.

Acute monocytic or myelomonocytic leukemias (M4 & M5) are the forms most likely to have extramedullary involvement

Bone marrow required for diagnosis: replacement by blasts

Important Diagnostic Methods

- ***Bone marrow aspirate & Romanowsky stain (morphology)***
  Enumeration of blasts, maturing cells, recognition of dysplasia
- ***Cytochemistry***
  Myeloperoxidase, Sudan Black B, esterases to determine involved lineages
- ***Immunophenotyping***
  Defines blast cell lineage commitment as myeloid, lymphoid or biphenotypic
- ***Cytogenetics & molecular studies (FISH, PCR)***
  Detects clonal chromosomal abnormalities, including those of prognostic importance

Prognosis

Acute Myeloid Leukemias

APL (M3) has the best prognosis

- ***Age** : Above the age of 50 years the complete **remission rate falls** progressively*
- ***Cytogenetics**: Three risk groups defined*
  - ✓ *Good risk (better prognosis): patients with t(8;21), t(15;17) and inv/t(16)*
  - *Intermediate risk: Normal, +8, +21, +22, 7q-, 9q-, abnormal 11q23, all other*
  - *Poor risk (worse prognosis): patients with -7, -5, 5q-, abnormal 3q and complex karyotypes*
- *Importance of cytogenetics for prognosis in children and adults < 55 years old:*
  - ***Good risk cytogenetic group: 91% remissions, 65% five year survival***
- ✗ ***Treatment response** : Patients with **>20% blasts in the marrow after first course** of treatment have short remissions (if achieved) and **poor overall survival***
- ✗ ***Secondary AML**: Patients with AML following chemotherapy or myelodysplasia **respond poorly** to treatment*
- ✗ ***Trilineage myelodysplasia**: Patients with trilineage myelodysplasia have a **lower remission rate***
- ***Intensive chemotherapy***
  - ✓ *Patients **< 55 years old**: 80% remissions*
  - ✗ *Patients **> 55 years old**: progressive reduction in remission rate*
- ✓ ***Bone marrow (stem cell) transplantation***
  - *Autologous and allogeneic transplants **reduce the relapse rate***

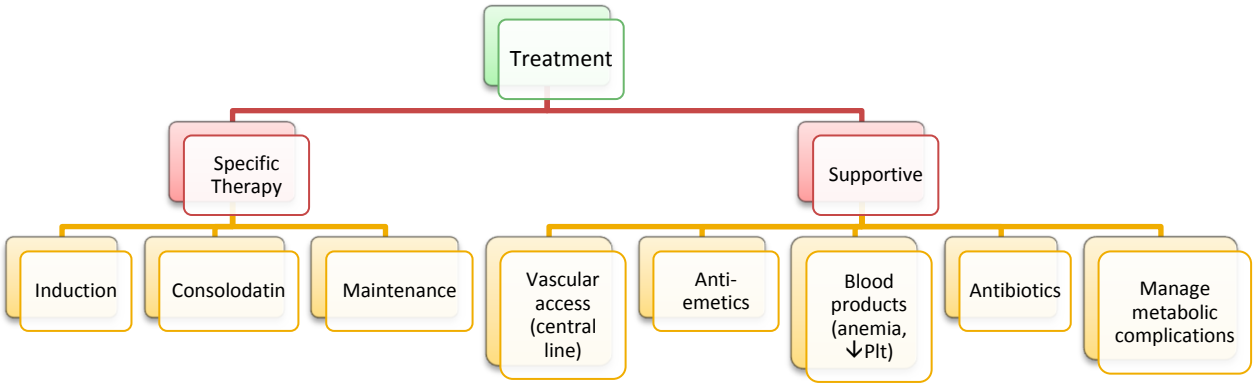
Acute Lymphoid Leukemia

Poor Prognostic Factors

ALL is the leukemia most responsive to therapy

- ***Age** < 2 yrs and >10 yrs*
- ***Male sex***
- *High WBC count (> 50 x10^9/L)*
- *Presence of **CNS disease***
- ***Cytogenetics***
  - *Good risk (better prognosis): Hyperdiploid (>50 chromosomes)*
  - *Poor risk (worse prognosis): Hypodiploid; t(9:22), t(4:11)*
- ***Bone Marrow:** Blasts present on day 14*
- *Day 28: No complete response*

Treatment



Specific Therapy

1. Induction

Obtained by using high doses of chemotherapy

- *Severe bone marrow hypoplasia*
- *Allowing re-growth of normal residual stem cells to re-grow faster than leukemic cells.*

Remission: defined as < 5% blast in the bone marrow

- *Normal neutrophil count*
- *Normal platelet count*
- *Normal hemoglobin level*

2. Consolidation

- *Different or same drugs to those used during induction*
- *High doses of chemotherapy*
- *Advantage: Delays relapse and improved survival*

3. Maintenance

- *Smaller doses for longer period*
- *Produce low neutrophil counts & platelet counts*
- *Objective is to eradicate progressively any remaining leukemic cells.*

Acute Myeloid Leukemia	**Acute Lymphoid Leukemia**
☑ Induction	☑ Induction
☑ Consolidation	☑ Consolidation
☒ No maintenance	☑ Maintenance
CNS prophylaxis for selected groups only	CNS prophylaxis **<u>for all patients</u>**

The Chronic Leukemias

Neoplastic proliferations of mature hemopoeitic cells

Chronic Lymphocytic Leukemia

Definition

- *Neoplastic proliferation of mature lymphocytes* — *B-cell proliferation*
- *Distinguished from ALL by*
  - *Morphology of cells*
  - *Degree of **maturation** of cells*
    - *Immunologically immature blasts in ALL*
    - *Mature cells in CLL*
  - *CLL affects mainly **elderly***

Clinical Features

Symptoms

Symptoms may be entirely absent in 40%

- *Weakness, easy fatigue, vague sense of being ill*
- *Night sweats*
- *Feeling of lumps*
- *Infections especially pneumonia*

Signs

- *Pallor*
- *Lymphoadenopathy (**generalized**)*
  - *Cervical, supraclavicular nodes more commonly involved than axillary or inguino-femoral*
  - ***Non-tender**, not painful, discrete, firm, easily movable on palpation*
- *SPLENOMEGELY (mild to moderate)*
- *HEPATOMEGALY*

Staging

Stage 0-1	*Lymphocytosis +/- LNs (lymph nodes)*
Stage 2	***+ Hepatosplenomegaly***
Stage 3-4	***Anemia (Hb <10 g/L)*** ***Thrombocytopenia (platelet count <100 x 10^9/L)***

Diagnosis

- *Lymphocyte count > 5 x 10^9/L (5 -500 x 10^9/L).*
- *Platelets may be decreased (thrombocytopenia)*
- *Hb may be low (anemia)*
- *Blood film (peripheral blood smear): Absolute lymphocytosis & presence of smudge cells*
- *PB immunophenotyping*
- *Bone marrow biopsy (needed before starting treatment): infiltrating leukemic cells*
- *Imaging*

Smudge cells: leukemic cells that are "beaten up"/damaged during slide preparation

Treatment

- *Observation*
- *Chemotherapy: Oral chlorambucil Fludarabine, cyclo*
- *Immunotherapy*
  - *Anti-CD 20 (**rituximab**)*
  - *Anti-CD 52 (**Alemtuzumab**)*
- ***FC-R is the current standard***

CLL is the least aggressive type of leukemia

Indications for starting chemotherapy

- *Progressive Symptoms*
- *Progressive Anemia or Thrombocytopenia*
- *Bulky LN, large spleen*
- *Recurrent Infections*

Chronic Myeloid Leukemia

Definition

- *CML is a clonal stem cell disorder characterised by increased proliferation of myeloid elements at all stages of differentiation.*
- ***Epidemiology**:*
  - *Incidence increases with age*
  - *Males > Females*

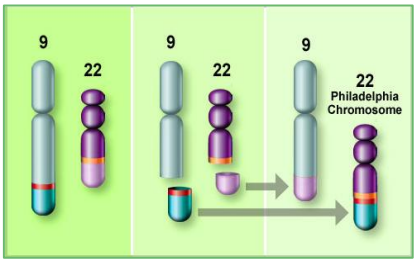


Figure 1

CML is characterised by 3 distinct phases:

- ***Chronic Phase:** Proliferation of myeloid cells, which show a full range of maturation*
- ***Accelerated Phase**: Decrease in myeloid differentiation*
- ***Blast crisis (acute leukemia)***

Cytogenetics

See Figure 1, page 7

Philadelphia (Ph) chromosome is an acquired cytogenetic abnormality in all leukaemia cells in CML

Reciprocal translocation of chromosomal material between chromosome 22 and 9 t(9;22)

Clinical Features

Symptoms

- *Asymptomatic (50% of patients)*
- *Fatigue, weight loss & anorexia*
- *Abdominal fullness, abdominal pain, esp. splenic area*
- *Increased sweating*
- *Easy bruising or bleeding*

Signs

- *Splenomegaly (95%): 50% of patients have a palpable spleen ≥ 10 cm below the costal margin (usually firm and non-tender)*
- *Hepatomegaly (50%)*

Diagnosis

Chronic phase: Peripheral blood:

- *WBCs 20,000 - 500, 000/μL (neutrophilia)*
- *Basophilia* (Not used anymore)
- *↓Leukocyte Alkaline Phosphatase (LAP) score* (Not used anymore)
- *Blasts < 5%*
- *Nucleated RBCs*
- *Thrombocytosis*
- *Anaemia*

CML Vs. Leukemoid Reaction

1. *LAP Score*
2. *Philadelphia Chromosome*
3. *Basophilia*
4. *Splenomegaly*

Peripheral smear: *leukemic cells in the peripheral blood (myelocytes, metamyelocytes, bands & segmented forms)*

Treatment

Response criteria

- *Hematological response: Normalization of blood count*
- *Cytogenetic response*
  - *Major cytogenetic response: 1-35% Ph +ve cells in metaphase*
  - *Minor cytogenetic response: 36-65% Ph +ve cells in metaphase*
- *Molecular response: Absence of BCR/ABL gene*

Principles

- *Control & prolong chronic phase (non-curative)*
  - *Tyrosine kinase inhibitors-Imatinib (Glivec)*
  - *Alpha-Interferon*
  - *Oral chemotherapy (Hydroxyurea, ARA-C)*
- *Eradicate malignant Clone (curative)*
  - *Allogeneic bone marrow/stem cell transplantation*
  - *Alpha Interferon?*
  - *Imatinib? 2nd line TKIs*

- ***TYROSINE KINASE INHIBITOR*** *(TKI)* ***Imatinib (Glivec)*** *is the* ***1ST LINE*** *treatment*
- *In resistent cases* ***2ND LINE*** *TKIs* ***Nilotinib, Dasatinib, Bosutinib*** *(very useful)*
- *Allogenic bone marrow trasnsplantation can be curative in pts resisrant to TKIs but has significant complications & mortality*

Accelerated and blast phase

- *Glivec & 2nd line TKIs (Treat like AML or ALL followed by bone marrow transplant)*

Bone Marrow and Peripheral Blood Stem Cell Transplantation

Types of transplant

1. *Autologous transplant*
2. *Allogeneic Transplant*

Purpose of transplant

- ***Autologous:*** *To deliver a high dose of chemo to kill any residual cancer (lymphoma, multiple myeloma)*
- ***Allogeneic:*** *To eradicate residual leukemia cells [Graft vs. leukemia effect]*

Technique of transplantation

- *MHC + HLA matching*
- *Chemotherapy*
- *Total body irradiation*
- *GVHD prophylaxis*

Complications of transplantation

- ***Prolonged BM suppression (graft failure)***
- ***Serious infections***
- ***Mucositis***
- ***Graft versus host disease (GVHD)***

Acute GVHD describes a distinctive syndrome of dermatitis, hepatitis, and enteritis developing within 100 days of allogeneic hematopoietic-cell transplantation.
Chronic GVHD is an extension of acute GVHD that mimics autoimmune disease. Develops after day 100.
Manifestations include: obstructive lung disease, neuromuscular symptoms, dysphagia, ocular irritation etc.

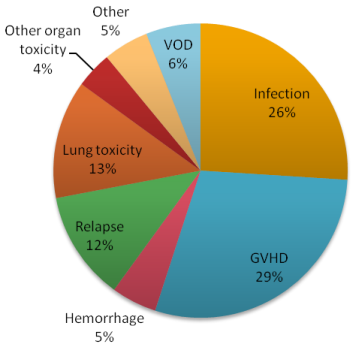
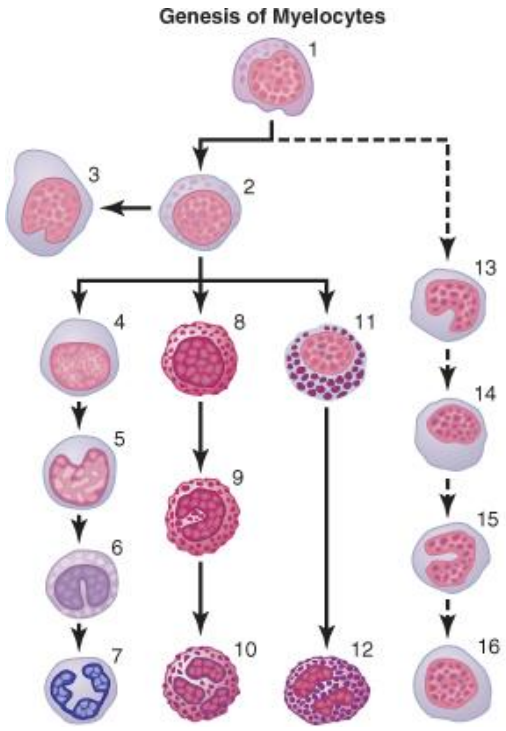


Figure 2

Figure 3



1, myeloblast;

2, promyelocyte;

3, megakaryocyte;

4, neutrophil myelocyte;

5, young neutrophil metamyelocyte;
6, "band" neutrophil metamyelocyte;
7, polymorphonuclear neutrophil;

8, eosinophil myelocyte;

9, eosinophil metamyelocyte;

10, polymorphonuclear eosinophil;
11, basophil myelocyte;

12, polymorphonuclear basophil;

13-16, stages of monocyte formation

Summary

- ***What is the definition of leukemia?***
  - *Presence of more than 5% blast cells in the blood*
- ***Symptoms of leukemia depend on the type of blood disorders that accompany it:***
  - *RBC are affected or low production > symptoms of anemia: Pallor, palpitations, heart failure, fatigue, dyspnea.*
  - *Platelets: Bleeding, epistaxis, mucosal bleeding*
  - *WBC: Infection; fever, rigors, chills , sepsis, weight loss, etc*
- ***Which type of leukemia is a disease of pediatrics and is very responsive to therapy (curable)?***
  - *Acute lymphoblastic leukemia*
- ***Why is chemotherapy more effective with ALL?***
  - *MOA of chemotherapy: Damages the DNA*
  - *In ALL cells replicate rapidly and have an abundance of abnormal DNA*
- ***Hypergranular promyelocytic leukemia (M3) subtype of AML:***
  - *Most curable*
  - *Cells contain Auer rods (initiates DIC). Causes DIC*
  - *Chromosomal translocation at t(15,17)*
- ***M4 and M5 are the most common subtypes of AML***
- *L3 subtype of ALL is called: Burkitt's-cell type and is* ***highly curable***
- ***Which type of leukemia is commonly associated with down syndrome?***
  - *AML*
  - *Although AML affects adults more, it is common among children w/Down syndrome*
  - *Very sensitive to chemotherapy*
- ***Which type of leukemia needs CNS prophylaxis?***
  - *ALL (crosses BBB)*
- ***What are induction, consolidation and maintenance? And what is the most common complication of treatment of acute leukemia?***
  - *Induction: Heavy doses of chemotherapy to kill all blast cells and cause bone marrow hypoplasia + massive blood transfusion*
  - *Consolidation: high doses of different drugs*
  - *Maintenance: smaller doses for longer period*
  - *The most common complication is infection and it is usually what kills the patient – that's why you must give antibiotics*
- ***Which type of leukemia can cause symptoms of hemolysis?***
  - *CLL*
  - *Jaundice, decreased Hb and splenomegaly*
- ***What is the most common indication for bone marrow transplantation?***
  - *CML*
- ***Philadelphia chromosome:***
  - *Better prognosis*
  - *T(9,22)*
  - *Associated with CML*
  - *Treated by tyrosine kinase inhibitors*
- ***What are the most common complications of bone marrow transplantation?***
  - *GVHD (graft versus host disease)*
  - *Second most common is infection*
- ***What is myelodysplasia (Myelodysplastic syndrome)?***
  - *A group of acquired bone marrow disorders that are due to a defect in stem cells: bone marrow failure with abnormalities of myeloid cell lines (RBCs, granulocyte/monocytes & platelets)*
  - *Mainly in the elderly, and presents with symptoms of anemia, infection or bleeding due to pancytopenia.* ***High mortality & morbidity.***
  - ***Has the potential to transform into AML****. [Blast cells 5-20% ≠ AML]*

In AML blasts >20%