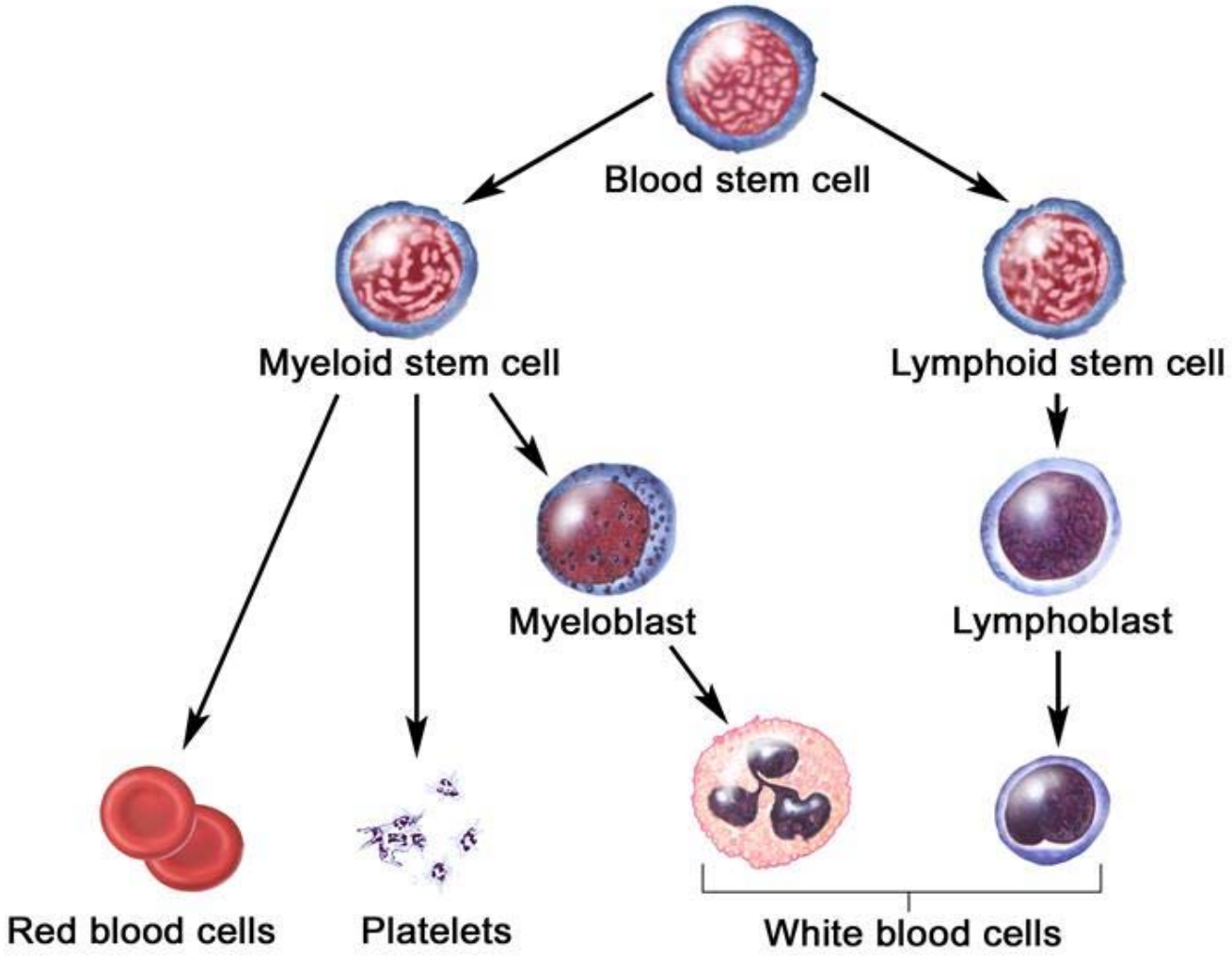
Leukemia

- Leukemia vs lymphoma
- The major types of leukemia are based on whether the disease is:
- Acute or chronic
- Lymphocytic or myeloid

Acute vs chronic leukemia

- rapid increase in immature blood cells.
- rapid progression and accumulation of the malignant cells over weeks or months.
- Immediate treatment is required in acute leukemia
- most common forms of leukemia in children.
- excessive build up of relatively mature, but still abnormal, white blood cells.
- Typically taking months or years to progress,
- chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy.
- Chronic leukemia mostly occurs in older people.

Myeloid vs lymphoid



Acute myeloid leukemia

Incidence ~ 3.5/100000 people/year
M/F = 4.3 : 2.9
Incidence increases with age 1.7<65yrs
15.9>65yrs

Etiology

- Hereditary down syndrome (trisomy 21chromosome), fanconi anemia, bloom syndrome, ataxia telangiectasia & kostmann syndrome
- Radiation survivors of atomic bomb explosion
- Chemicals benzene exposure used as a solvent in chemical, plastic, rubber & pharmaceutical industries. exposure to petroleum products, paints, embalming fluids, ethylene oxide, herbicides & pesticides
- Drugs alkylating agents, topoisomerase II inhibitors, chloramphenicol, phenylbutazone

Classification(morphology,cytochemistry)

French-American-British (FAB) Classification	**Incidence**
M0: Minimally differentiated leukemia	5%
M1: Myeloblastic leukemia without maturation	20%
M2: Myeloblastic leukemia with maturation	30%
M3: Hypergranular promyelocytic leukemia	10%
M4: Myelomonocytic leukemia	20%
M4Eo: Variant: Increase in abnormal marrow eosinophils	
M5: Monocytic leukemia	10%
M6: Erythroleukemia (DiGuglielmo's disease)	4%
M7: Megakaryoblastic leukemia	1%

WHO Classification
(clinical,cytogenetics,molecular)

I. **AML with recurrent genetic abnormalities** AML with t(8;21)(q22;q22) Acute promyelocytic leukemia [AML with t(15;17)(q22;q12) AML with 11q23 (*MLL*) abnormalities

II. **AML with myelodysplasia related changes** Following a myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative disorder Without antecedent myelodysplastic syndrome

III. **Therapy related myeloid neoplasms**, therapy-related Alkylating agent–related Topoisomerase type II inhibitor–related

IV. **AML not otherwise categorized**

V.Myeloid sarcoma

VI.Myeloid proliferations related to Down syndrome

VII.Blastic plasmacytoid dendritic cell neoplasm

VIII.Acute leukemia of ambiguous lineage

Clinical feature

- Anemia fatigue, weakness, anorexia,
- Leucopenia/leucocytosis/leucocyte dysfn fever, recurrent infection
- Thrombocytopenia bleeding episodes
- Nearly half have symptoms >3 months before leukemia was diagnosed.
- Mass lesion –located in soft tissue (granulocytic sarcoma, chloroma)
- Sign –fever, splenomegaly, hepatomegaly, lymphadenopathy,sternal tenderness, evidence of infection, hemorrhage, bleeding tendency(M3),infiltration of gingiva, skin,soft tissue,meninges(M4&M5)

Investigation

- Anemia NN,RC low
- Leucocyte ↓ / ↑ 25-40% <5000/ul
  20% >1lakh/ul
- Platelet 75% <1lakh/ul
  25%<25,000/ul
- Biochemistry : electrolyte, creatinine, calcium,phosphate, LFT,LDH
- Coagulation profile
- Marrow aspirate & biopsy
- HLA typing

Diagnosis ≥ 20%myeloblasts –blood/marrow, cytoplasmic granules, auer rods, A+ MPO reaction >3%blast

Prognostic factors

- Advance age –poor prognosis
- Performance status
- A/c medical problems at diagnosis –decrease survival rate
- Chromosomal finding

  good prognosis t(8;21),Inv(16),t(15;17)

  poor prognosis Inv(3)
- A prolonged symptomatic interval -decrease survival rate
- Anemia ,leucopenia, thrombocytopenia >1 month before diagnosis of AML – poor prognosis
- Secondary AML –extremely difficult to treat

Pretreatment Evaluation- **History**

- Increasing fatigue or decreased exercise tolerance (anemia)
- Excess bleeding or bleeding from unusual sites (DIC, thrombocytopenia)
- Fevers or recurrent infections (granulocytopenia)
- Headache, vision changes, nonfocal neurologic abnormalities (CNS leukemia or bleed)
- Early satiety (splenomegaly)
- Family history of AML (Fanconi, Bloom, or Kostmann syndromes or ataxia telangiectasia)
- History of cancer (exposure to alkylating agents, radiation, topoisomerase II inhibitors)
- Occupational exposures (radiation, benzene, petroleum products, paint, smoking, pesticides)

Physical Examination

- Performance status (prognostic factor)
- Ecchymosis and oozing from IV sites (DIC, possible acute promyelocytic leukemia)
- Fever and tachycardia (signs of infection)
- Papilledema, retinal infiltrates, cranial nerve abnormalities (CNS leukemia)
- Poor dentition, dental abscesses
- Gum hypertrophy (leukemic infiltration, most common in monocytic leukemia)
- Skin infiltration or nodules (leukemia infiltration, most common in monocytic leukemia)
- Lymphadenopathy, splenomegaly, hepatomegaly
- Back pain, lower extremity weakness [spinal granulocytic sarcoma, most likely in t(8;21) patients]

Laboratory and Radiologic Studies

- CBC with manual differential cell count
- Chemistry tests (electrolytes, creatinine, BUN, calcium, phosphorus, uric acid, hepatic enzymes, bilirubin, LDH, amylase, lipase)
- Clotting studies (prothrombin time, partial thromboplastin time, fibrinogen, D-dimer)
- Viral serologies (CMV, HSV-1, varicella zoster)
- HLA typing of patient, siblings, and parents for potential allogeneic SCT
- Bone marrow aspirate and biopsy (morphology, cytogenetics, flow cytometry, molecular studies)
- Cryopreservation of viable leukemia cells
- Echocardiogram or heart scan
- PA and lateral chest radiograph
- Placement of central venous access device

Treatment

Symptomatic therapy

- Cytopenia – G-CSF, GM-CSF
- Multilumen R atrial catheter insertion
- Thromboctopenia –thrombopoietin, platelet transfusion
- Anemia –erythropoietin, packed cell transfusion
- Oral nystatin or clotrimazole is recommended to prevent localized candidiasis
- Infection –prompt & early initiation of empirical broad spectrum antibiotics & antifungal

Allogenic SCT – treatment of choice

Chemothreapy - Induction therapy (aim – complete remission)

- Post remission therapy
- Relapse

Treatment cont.

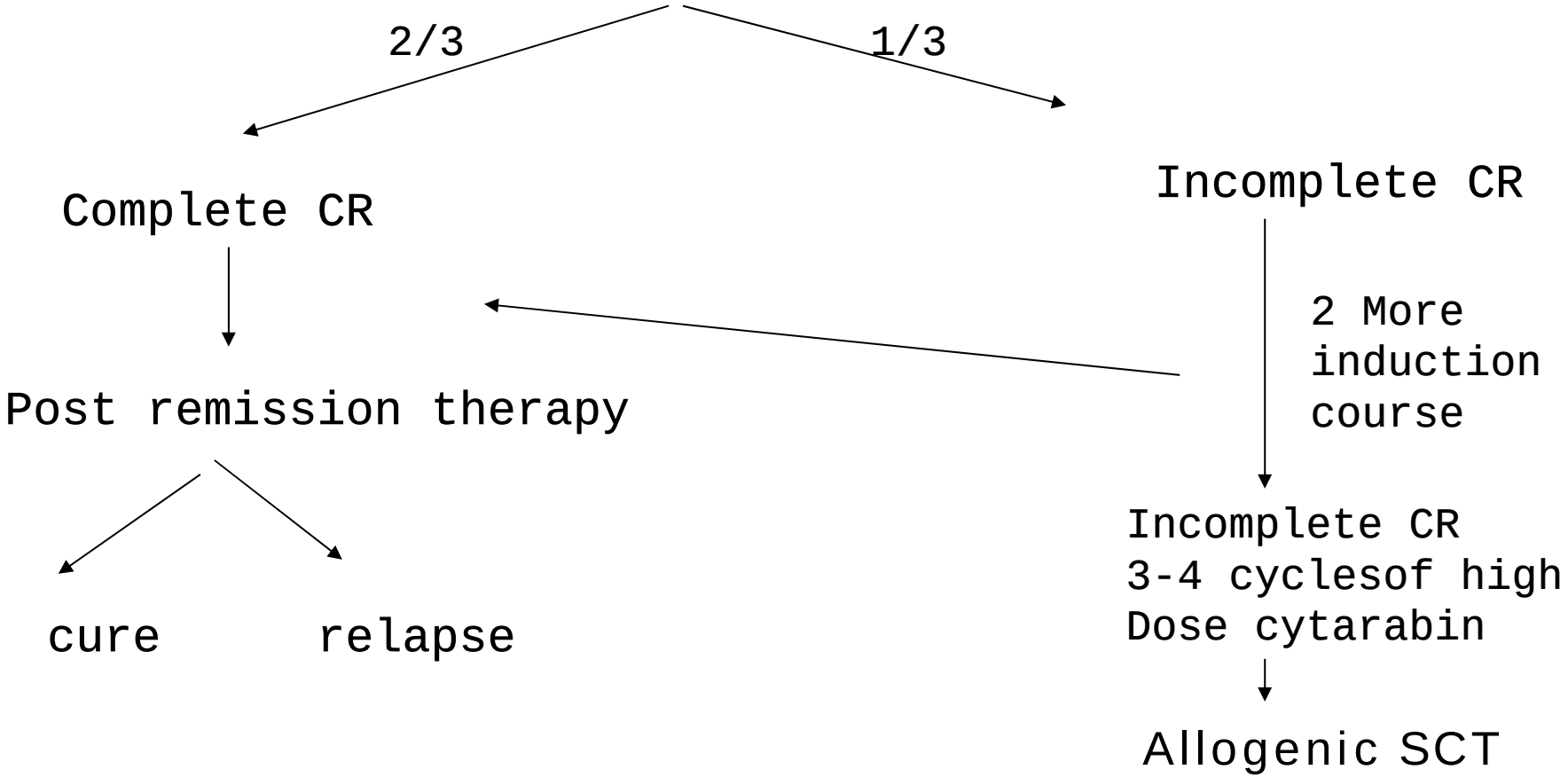
Complete remission

Blood	neutrophil ≥1000/ul
	platelet ≥1lakh/ul
	no circulating blast
Marrow	cellularity >20% trilineage maturation
	<5% blasts & auer rod absent

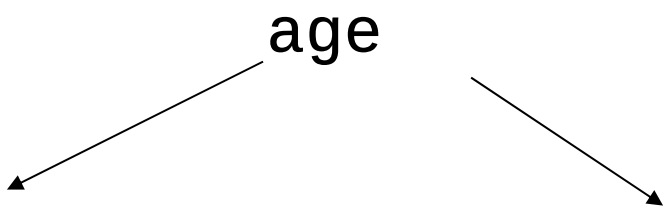
- Initiation of chemotherapy may aggravate hyperuricemia so patient are usually started immediately on allopurinol/rasburicase

Induction therapy

Cytarabin i/v infusion 100-200mg/m2 x7d
+anthracycline daunonorubicin i/v 45-60mg/m2 x1,2,3d
idarubicin i/v 12-13mg/m2 x1,2,3 d
±etoposide



Post remission therapy
Designed to eradicate any
Residual leukemic cells



<55yrs

Intensive chemotherapy
High dose cytarabin
& allogenic/autologus
SCT

>55yrs

Attenuated intensive
therapy
Chemotherapy/non
myeloablative
Allogenic SCT

Relapse

- Once relapse occurs, patients are rarely cured with further standard-dose chemotherapy. Patients eligible for allogeneic SCT should receive transplants at the first sign of relapse.
- Treatment with novel approaches should be considered if SCT is not possible. One promising therapy is **decitabine**, a nucleoside analog that inhibits DNA methyltransferase and subsequently reverses aberrant methylation in AML cells.
- For elderly patients (age >60) for whom clinical trials are not available, **gemtuzumab** ozogamicin (Mylotarg) is another alternative

Treatment of Promyelocytic Leukemia

- **Tretinoin** is an oral drug that induces the differentiation of leukemic cells bearing the t(15;17).
- Tretinoin (45 mg/m^2 per day orally until remission is documented) plus concurrent anthracycline chemotherapy appears to be among the safest and most effective treatments for APL.
- **Arsenic trioxide** produces meaningful responses in up to 85% of patients refractory to tretinoin.
- The detection of minimal residual disease by RT-PCR amplification of the t(15;17) chimeric gene product appears to predict relapse.
- Disappearance of the signal is associated with long-term disease-free survival;

Chronic myeloid leukemia

- chronic granulocytic leukemia (CGL)

- clonal bone marrow stem cell disorder in which proliferation of mature granulocyte (neutrophils, eosinophils, and basophils) and their precursors

Chronic myeloid leukemia

Incidence 1.5/100000 people/year
M/F=1.9:1.1
increase with age

Pathophysiology

- Clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosome 9 &22 t(9;22).
- untreated disease is characterized by inevitable transition from a chronic phase to an accelerated phase and on to blast crisis.
- The product of fusion gene result from the t(9;22) plays a central role in development of CML

Clinical feature

- Insidious onset
- Anemia
- Recurrent infection
- Bleeding tendency & thrombosis (vasoocclusive disease)
- Hyper metabolic state (wt. loss, night sweats)
- Splenomegaly (early satiety, LUQ pain)
- Pruritis ,diarrhea, flushing (histamine production secondary to basophilia)

Investigation

- Anemia
- Leucocytosis with varying degree of immaturity
- Platelet
- Marrow ~~↑~~ N /low M/E ratio
- Cytogenetics - Philadelphia chromosome t(9;22)
  - 90-95% cases
- Cytochemistry neutrophil alkaline phosphatase (NAP)
  - low

Others

- serum B12 elevated & B12 binding capacity
- hyperuricimia

Classification(clinical/laboratory)

- *chronic* phase(Approximately 85%/usually asymptomatic
- *accelerated* phase
- *blast crisis(*terminal phase of CML/acute leukemia)

Disease acceleration(WHO)

- 10–19% myeloblasts (blood/bone marrow)
- >20% basophils (blood/bone marrow)
- Platelet count <100,000, unrelated to therapy
- Platelet count >1,000,000, unresponsive to therapy
- Cytogenetic evolution with new abnormalities in addition to the Philadelphia chromosome
- Increasing splenomegaly or white blood cell count, unresponsive to therapy

The patient is considered to be in the accelerated phase if any of the above are present. The accelerated phase is significant because it signals that the disease is progressing and transformation to blast crisis is imminent. Drug treatment often becomes less effective in the advanced stages

Blast crisis(WHO)

Blast crisis is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival.

Blast crisis is diagnosed if any of the following are present in a patient with CML.

- >20% myeloblasts/lymphoblasts in the blood or bone marrow
- Large clusters of blasts in the bone marrow on biopsy
- Development of a chloroma (solid focus of leukemia outside the bone marrow)

Response criteria in CML

Hematologic
Complete response ; WBC <10,000/ul N. morphology
N Hb & platelet count
Incomplete response ; WBC ≥10,000/ul

Cytogenetic - % of bone marrow metaphasis with t(9;22)

Complete response	0
Partial	≤35
Minor	36-85
No response	85-100

Molecular- presence of BCR/ABL transcript by RT-PCR
Complete response -none
Incomplete response -any

Treatment

Allogenic SCT – currently only curative therapy &when feasible is treatment of choice. outcome of SCT depends on multiple factors

- Patient (age, phase of disease)
  <65yrs,should have acceptable end organ function.
- Donor – transplant from a family donor who is either fully matched or mismatched at only one HLA locus should be considered.
  7yrs disease free survival 55%
  relapse rate 30%
- Preparative regimen - cyclophosphamide + total body irradiation
  cyclophosphamide + busulphan
- Development & type of GVHD
  Higher degree of GVHD – higher risk of relapse
  Depletion of T lymphocytes from donor marrow can prevent GVHD but results in an increase risk of relapse
- Post transplant treatment - (imatinib, interferon α)

Imatinib mesylate (STI571)

- Competitive inhibition at adenosine triphosphate (ATP) binding site of Abl kinase which leads to inhibition of tyrosine phosphorylation of proteins involved in Bcr/Abl signal transduction.
- Administered orally dose -400mg/d
- Common side effects- fluid retention, nausea, muscle cramps, diarrhoea & skin rashes. rarer –myleosuppression
- First line therapy for newly diagnosed CML patient.
- Patients in accelerated/blast phase of disease are less sensitive to imatinib.
- Most patients with CML in chronic phase have a rapid hematological response
- Dasatinib, Nilotinib,bosutinib

Treatment

- Interferon ; when allogenic SCT not feasible. interferon α is second choice to imatinib
- Side effects ; flu like symptoms, fatigue, lethargy, depression, wt.loss, myalgia, arthralgia,
- Chemothrapy hydroxyurea
  busulphan
  homoharringtonin (HHT) plant alkaloid derived from a tree
  arsenic trioxide
- **Autologous SCT**
- Leukapharesis and splenectomy (for leukostasis related complication)