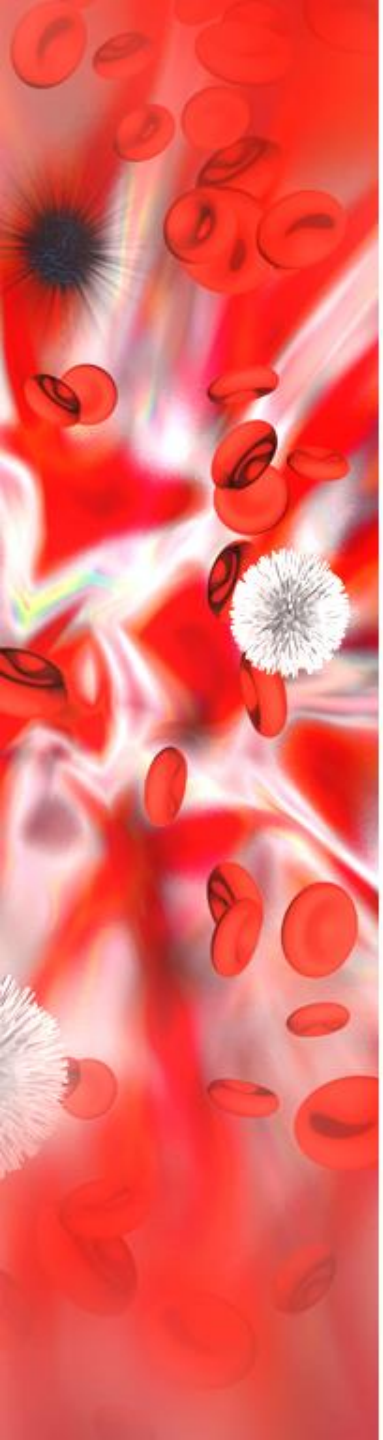
Lecture 6:
Acute Leukemia I



Acute Leukemia

- Aggressive malignant hematopoietic disorders results in accumulation of abnormal blasts. (Immature precursors of WBCs) in bone marrow and blood leading to:

1. Bone marrow failure: (anemia, neutropenia & thrombocytopenia)
2. Organ infiltration: (hepatospleenomegaly; lymphoadenopathy)

Epidemiology

- Represents 8% of neoplastic diseases and 4% of malignant-related deaths
- Acute myeloid leukemia is **more common in adults** > 15 per 100.000/year
- Acute lymphoid leukemia is **usually affecting children** 76%

Pathogenesis

Environmental
e.g radiation

Genetic factor

Infection
e.g Viral

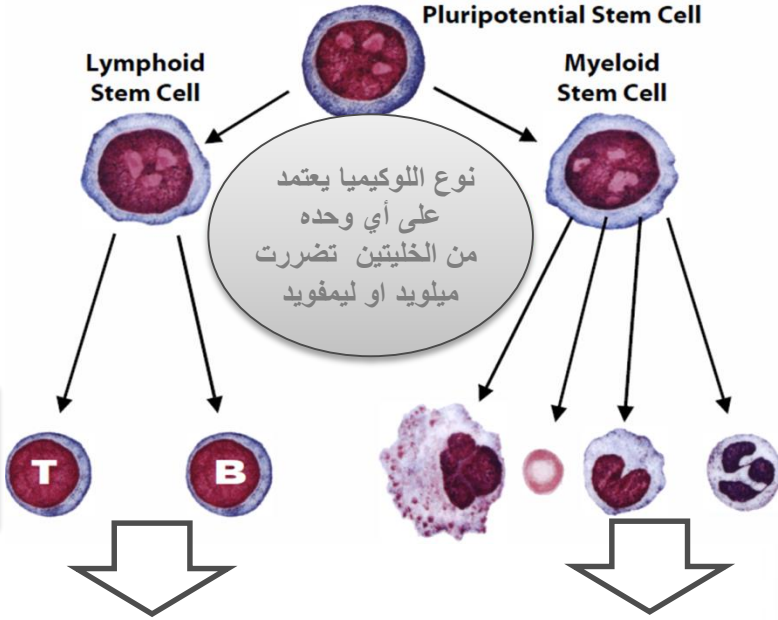
Other hematological disorders

Aggressive therapy
e.g. aggressive chemotherapy

Unknown Mechanism

Genetic alteration in immature precursor Of WBCs.

Block differentiation , enhanced proliferation & *decreased apoptosis.



1.ALL

2.AML

*Decreased apoptosis: decrease normal programmed cell death of abnormal blasts.
*ALL: acute lymphoid leukemia AML: acute myeloid leukemia

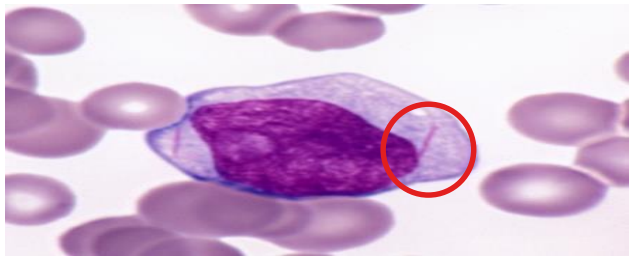
Classification

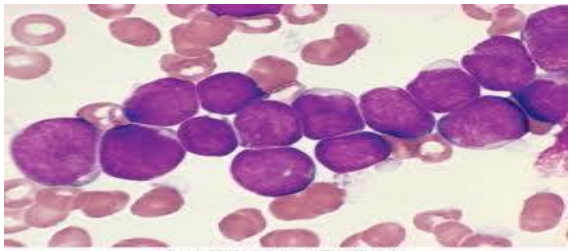
- Acute myeloid leukemia
- *Acute leukemia of ambiguous lineage
- Acute lymphoid leukemia

* very rare condition, in which the cells are Undistinguished , you can not determine is it a myeloid or a lymphoid blast .

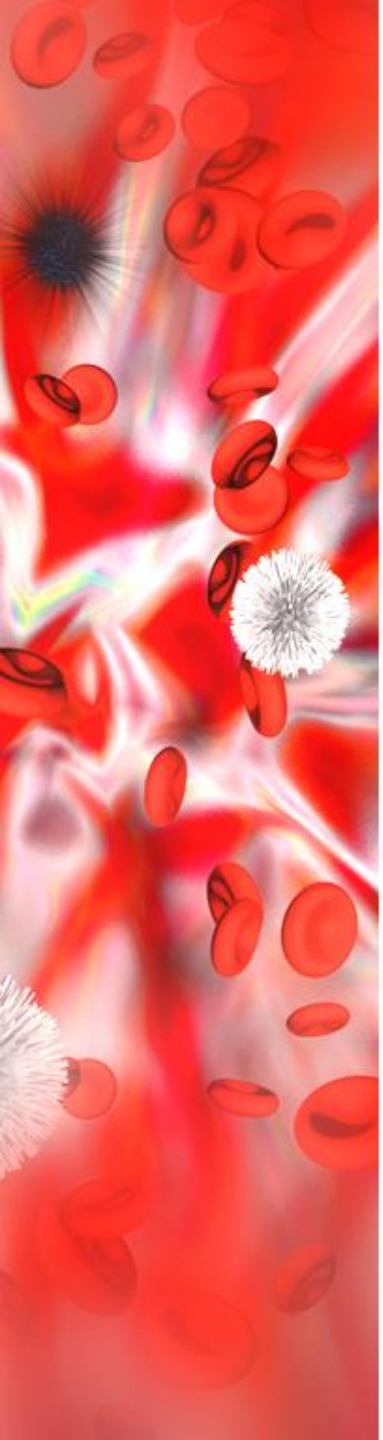
Basis of classification:

1. Clinical history
2. Light microscopy: blood smear, bone marrow aspirate or biopsy
   -the blast count should be >20-30% in bone marrow to diagnose as leukemia.
3. Morphology:





Myeloblast > AML	Lymphoblast > ALL
Size: medium-large Nucleus: oval, round or irregular Nucleolus: prominent Cytoplasm: abundant & granular Presence of **Auer rods**	Size: small-medium Nucleus: round Nucleolus: not prominant Cytoplasm: scanty & agranular May be vaculated



4- Flow cytometry:

Laser based technology allows for cells counting & detection of their surface &cytoplasmic markers by suspending them in a stream of fluid followed by analysis through electronic system.

5- Chromosomal Karyotype :

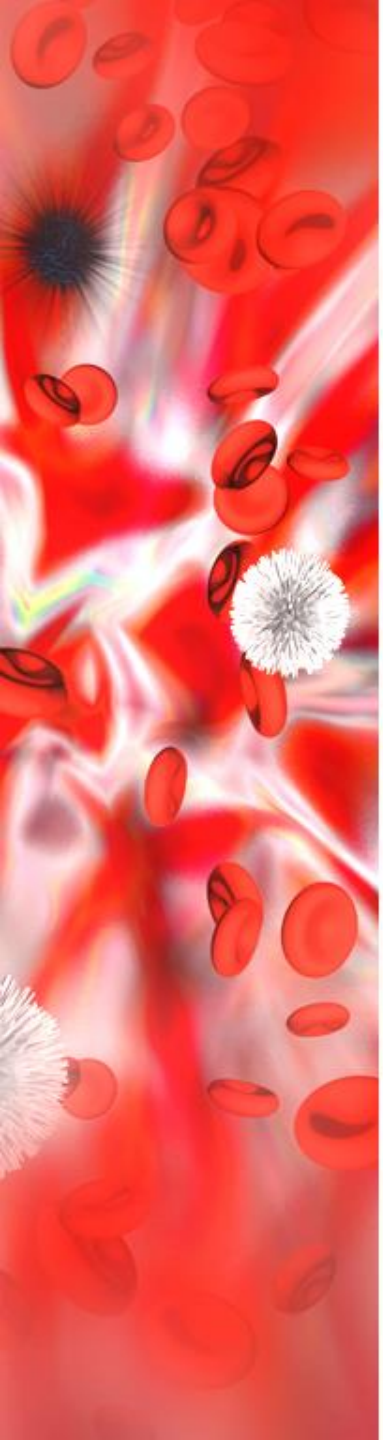
Set of the chromosomes from one cell during metaphase to study the numerical(deletion &trisomy) and structural (translation &inversion) abnormality.

4- Molecular studies:

Several techniques used to detect and localize the presence or absence of specific DNA sequences on chromosomes :

Fluorescent In-Situ Hybridization (FISH)

Polymerase Chain Reaction (PCR)



Cont' basis of classification

*Stem cells markers also called:
Blast markers or Immature markers or precursor markers

*"Stem cells markers": **blast count >20-30%** + **positive CD34 & TDT** • indication of leukaemia:

Myeloid	B-Lymphoid	T-Lymphoid
"Mainly" MPO: Myeloid peroxidase. CD13, CD33	CD10 **CD19** CD22 CD79a	**CD3 > the strongest** CD4 CD5 CD7 CD8
CD14, CD64 > Monocytic		
CD41 > Megakaryocytic		
CD235a> Erythrocytic		

Recurrent genetic abnormalities

AML

Karyotypes	Molecular
T(8;21)	AML1-ETO
t (16;16) or inv(16)	CBFB-MYH11
t (15;17)	PML-RARA
t (9;11)	MLLT1-MLL

ALL

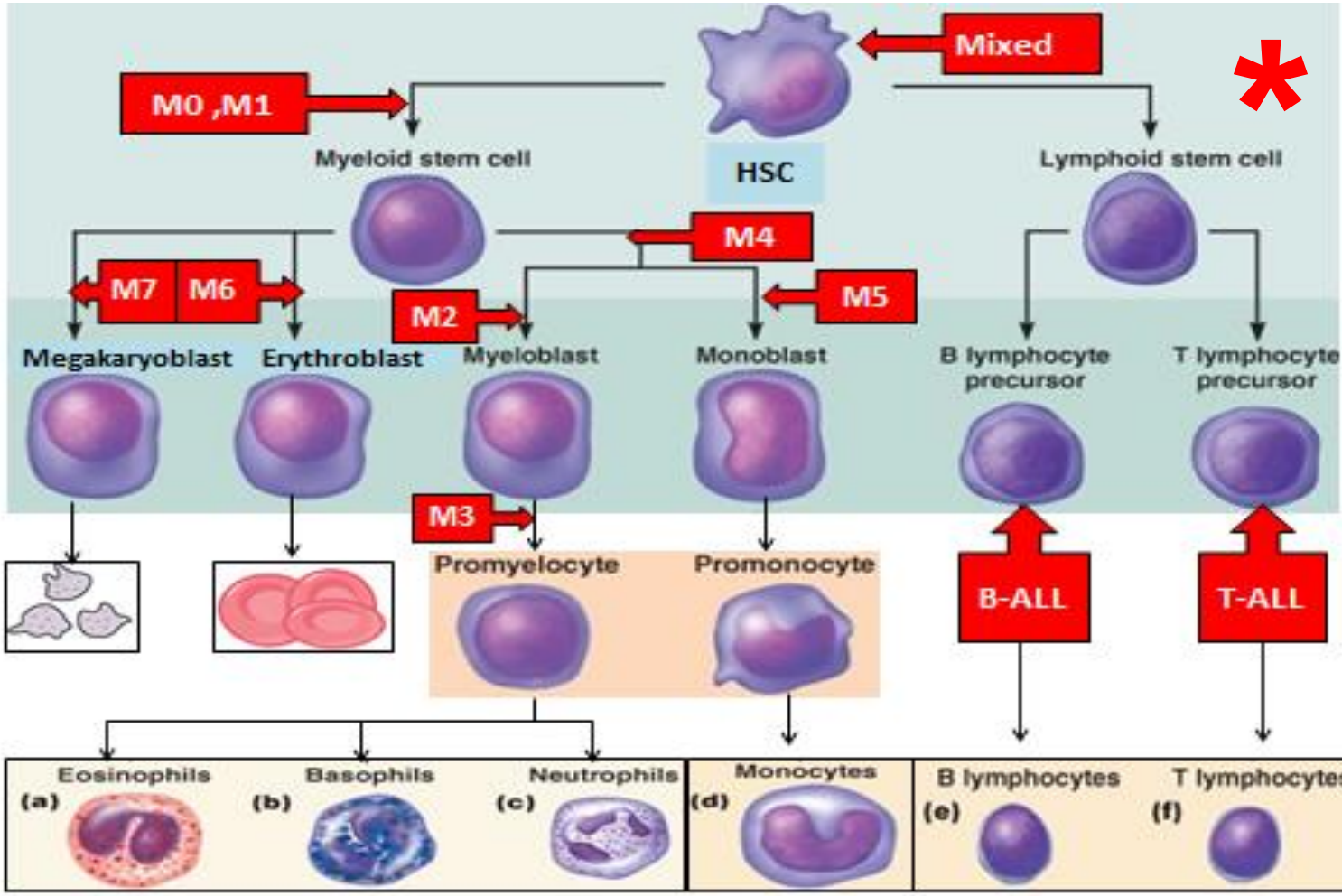
Karyotypes	Molecular
T(9;22)	BCR-ABL1
T(4;11)	AF4-MLL
T(12;21)	ETV6-RUNX1
T(5;14)	IL3-IGH

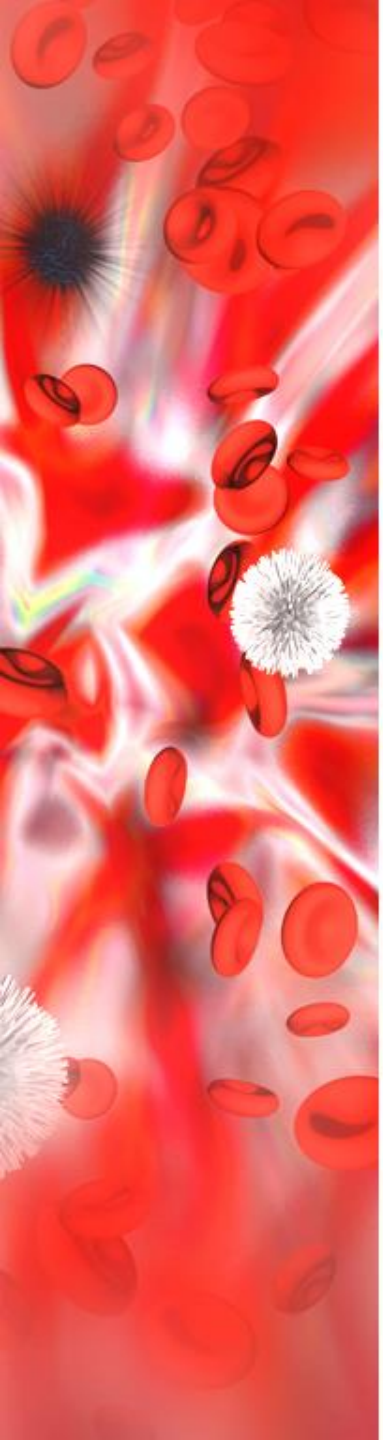
Acute Myeloid leukemia

Group of hematopoietic neoplasms caused by proliferation of malignant myeloid blasts in bone marrow and blood.

The blast ≥ 20% or t(8;21) t (16;16) or t(15;17). *the genetic abnormality in the previous slide*

More in Adults (do occur in infants!) and has Poor prognosis compared to ALL.



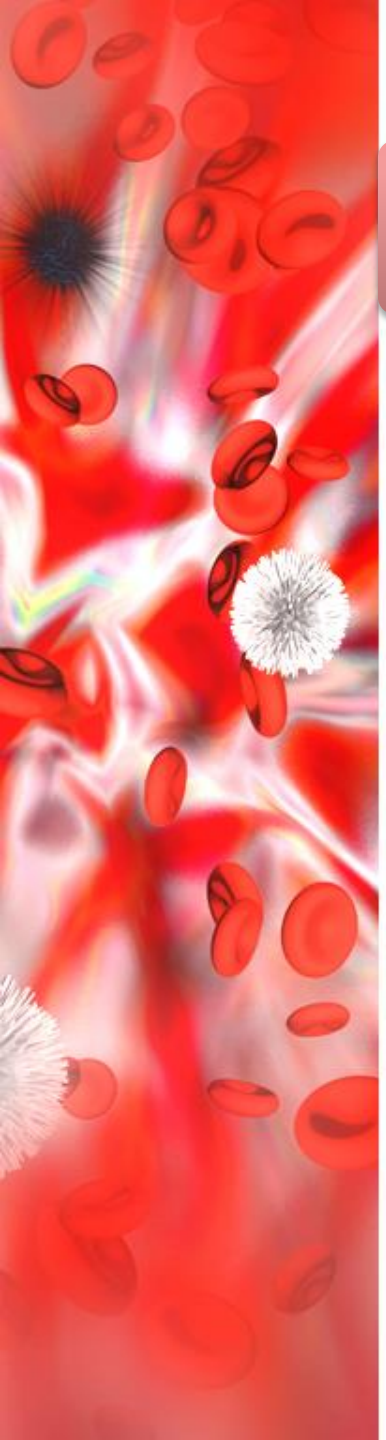


FAB Classification:

based on morphology "microscopic finding", flow cytometry and the abnormal cell:

Subtype	Feature	Genetics in WHO	NOTES
M0	Minimal differentiation of myeloid stem cell		**Only MPO is detected**
M1	Without differentiation		
M2	**With maturation**	T(8;21)	
M3	Promyelocytic	T(15;17)	**DIC*+ Auer rods + heavy granulation**
M4	Granulocytic & Monocytic	T or Inv(16;16)	**Gum hypertrophy**
M5	Monocytic M5b+Monoblastic M5a	T(9;11)	
M6	Erythrocytic(dark erythroid precursor)	**+ve CD235a**	**No mature RBcs**
M7	Megakaryoblast "platelets"	**+ve CD41**	**Thrombocytopenia**
M8	Basophilic		

*Disseminated intravascular coagulation (DIC): widespread activation of coagulation system

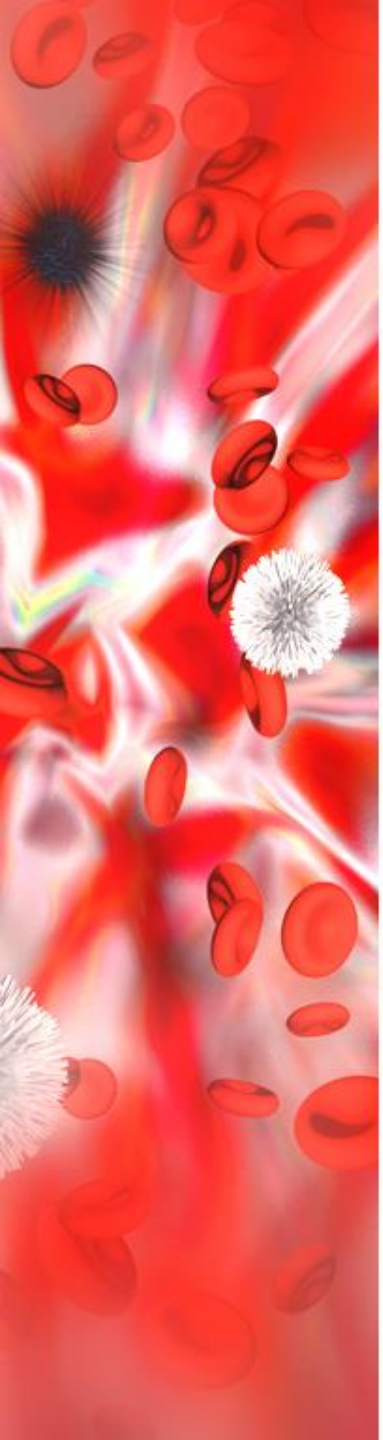


AML classification according to WHO

- **AML with recurrent genetic abnormalities**
  - **T(8;21) M2**
    T915;17) M3
    T916;16) M4
    Prognosis: **GOOD**
- **Myelodysplasia related to AML**
  - Blasts count **>20%** w/ significant dysplasia
    Prognosis: **POOR**
- **Therapy related to AML**
  - Blast count **>20%** w/ previous chemotherapy
    Prognosis: **POOR**
- **AML, not other wise specified FAB**
  - Blasts **>20%**
    Normal genetic
    No dysplasia
    Prognosis: **standard**

Clinical features

Pancytopenia **Acute onset**	Organ infiltration	Leucostasis	DIC (more with M3)
↑ Non-functional WBCs > infections (fever, septic shock) Low HB >anemia (fatigue, headache, pale) Low platelets > bleeding (bruises, epistaxis, menorrhagia)	Hepatospleenomegaly (mainly) Lymphoadenopathy Myeloid sarcoma* Gum hypertrophy* CNS diseases* *More with Acute Monoblastic Leukemia	Increased blood viscosity due to high number of WBCs	Manifestation of either Bleeding 85% Or Thrombosis 15%



Summary from essential hematology for acute myeloid leukemia

- The leukaemias are a group of disorders characterized by the accumulation of malignant white cells in the bone marrow and blood. They can be classified into four subtypes on the basis of being either *acute* or *chronic*, and *myeloid* or *lymphoid*.
- Acute leukaemias are aggressive diseases in which transformation of a haemopoietic stem cell leads to accumulation of >20% blast cells in the bone marrow.
- The clinical features of acute leukaemia result from bone marrow failure and include anaemia, infection and bleeding. Tissue infiltration can also occur.
- AML is rare in childhood but becomes increasingly common with age with a median onset of 65 years.
- The diagnosis is made by analysis of blood and bone marrow using microscopic examination (morphology) as well as immunophenotypic, cytogenetic and molecular studies.
- Cytogenetic and molecular abnormalities are used to classify and indicate prognosis in the majority of cases of AML.
- In younger patients treatment is primarily with the use of intensive chemotherapy. This is usually given in four blocks each of approximately 1 week using drugs such as cytosine arabinoside and daunorubicin.
- Acute promyelocytic leukaemia is a variant of AML that carries a t(15; 17) chromosomal translocation. It commonly presents with bleeding and is treated with retinoic acid and chemotherapy.
- The prognosis for patients with AML has been improving steadily, particularly for those under 60 years of age, and approximately one-third of this group can expect to achieve long-term cure. The outcome for elderly people remains disappointing.
- Allogeneic stem cell transplantation is useful in treating some subsets of patients and may also be curative for patients with relapsed disease.

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