Acute Myelogenous Leukemia

Paul Imbach

Acute myelogenous leukemia (AML) represents a heterogeneous group of malignant hematological precursor cells of the myeloid, monocytic, erythroid or megakaryocytic cell lineage (see Chap 1).

Epidemiology

- Incidence: 15–20% of all leukemias in children
- Seven in 1 million children develop AML each year
- Frequency of AML remains stable throughout childhood with a slight increase during adolescence
- There is no difference in incidence of AML between boys and girls
- There is a slightly higher incidence in white children than in other groups

Predisposing Factors

See Chap 1.

Differential Diagnosis

- Infectious mononucleosis
- Juvenile rheumatoid arthritis
- Aplastic anemia
- Acquired neutropenia
- Megaloblastic anemia
- Autoimmune cytopenia
- Leukemoid reaction
- Transient myeloproliferative syndrome in infants with Down syndrome
- Metastatic neuroblastoma, rhabdomyosarcoma, retinoblastoma, non-Hodgkin lymphoma
- Myelodysplastic syndrome
- Myeloproliferative syndrome
- Juvenile myelomonocytic leukemia and chronic myelogenous leukemia

In cases of difficult bone marrow aspiration ("dry" taps), bone marrow biopsy is recommended

Classification

AML is heterogeneous concerning the predisposing condition, pathogenesis, geno- and phenotype and response to therapy. Prognosis depends on age, initial presentation and subtype.

FAB classification of acute myelogenous leukemia	
M0	Immature myeloblastic leukemia
M1	Myeloblastic leukemia – Blasts with few azurophile granules or Auer rods – Positive peroxidase or Sudan black (>5% of blasts) reaction can be helpful
M2	Myeloblastic leukemia with signs of maturation – Myeloblasts and leukemic promyelocytes represent the majority of nucleus-containing bone marrow cells – Auer rods common
M3	Promyelocytic leukemia – Mostly abnormal promyelocytes with lots of granulation; some Auer rods
M4	Myelomonocytic leukemia – Mostly myeloblasts and promyelocytes, promonocytes and monocytoid cells with granulocytic and monocytic differentiation
M5	Monocytic leukemia – Moderately differentiated to well-differentiated monocytic cells – Esterase reaction may be positive
M6	Erythroleukemia – More than 50% of the nucleus-containing cells of bone marrow are erythroblasts – Erythroblasts show a bizarre morphology
M7	Megakaryocytic leukemia

Histochemical Classification and Frequency

Histochemical characteristics							Frequency (%)
M0	-	SB	-	-	-	-	<3
M1	MPO	SB	-	-	-	-	20
M2	MPO	SB	-	-	-	-	25
M3	MPO	SB	-	-	(NSE)	-	5–10
M4	MPO	-	-	NASD	NSE	-	25–36
M5	MPO	-	-	NASD	-	-	15
M6	-	-	PAS	-	-	Glycophorin A	<5
M7	a	-	-	NASD	NSE	-	5–10

Parentheses: variable; underlining: pathognomonic; *MPO* myeloperoxidase, *NASD* naphthol-ASD, *NSE* nonspecific esterase, *PAS* periodic acid-Schiff, *SB* Sudan black; a: Intraplasmatic MPO detectable by electron microscopy only

Myelo-blasts	Cluster determination (CD)												B cell	T cell			
M0	-	13	-	15	33	34	(36)	31/61	42	65	117a	HLA-DR	19	2	(4)	(7)	(56)
M1	-	13	-	15	33	34	-	-	-	65	117	HLA-DR	-	2	-	(7)	(56)
M2	-	13	-	15	33	34	-	-	-	65	117	HLA-DR	-	2	-	7	(56)
M3	11b	13	-	15	33	34	-	-	-	65	117	(HLA-DR)	-	2	-	7	(56)
M4	11b	13	14	15	33	34	36	-	-	65	117	HLA-DR	-	2	4	7	56
M5	11b	13	14	15	33	34	36	-	-	65	(117)	HLA-DR	-	2	4	7	56
M6	-	13	-	-	33	-	-	-	-	65	(117)	-	-	-	-	7	-
M7	-	13	-	-	-	34	36	41/61	42	65	117	HLA-DR	-	2	4	7	56

Parentheses: variable; underlining: pathognomonic

HLA human leukocyte antigen

a: c-kit oncoprotein

French–American–British Classification of AML

The French–American–British (FAB) classification is based on morphological and histochemical characteristics and is supplemented by immunophenotypical and cytogenetic characteristics.

Immunophenotyping

The cluster-determination (CD) classification has a high specificity and sensitivity for distinguishing acute lymphoblastic leukemia (ALL) and AML from normal hemopoietic precursor cells.
Biphenotypic leukemia expresses myeloid and lymphoid markers. Therefore more than one marker of the other cell lineage has to be expressed. Biphenotypic leukemia has to be distinguished from mixed-lineage leukemia, which shows blasts with more than one phenotype. Furthermore there are leukemias that express M6 and M7 markers, and which are described as erythromegakaryocytic.

Cytogenetics

Fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) techniques (Chap 2) detect subtypes of AML according to specific chromosomal abnormalities that correlate to alterations in cell survival, cell differentiation, and cell cycle regulation.

Cytogenetic abnormalities in childhood AML

FAB	Chromosomal abnormalities	Affected gene	Comments
M1/M2	t(8;21)	*ETO-AML 1*	Auer rods
M3	t(15;17)	*PML-RARA*	Promyelocytic leukemia with coagulopathy; ATRA responsiveness
	t(11;17)		Coagulopathy, ATRA unresponsiveness
M4 or M5	t(9:11)	*AF9-MLL*	Infants; high initial WBC
M5	t(11q23)	*MLL*	Infants; high initial WBC
M5	t(1b;11)	*AF10-MLL*	Infants; high initial WBC
M5	t(11;17)	*AF17-MLL*	Infants; high initial WBC
M6			Glycophorin-positive
M7	t(1;22)		Infants with Down syndrome

ATRA all-*trans* retinoic acid, *WBC* white blood cell count

The combination of the characteristics described above helps determine the recommended type of treatment of AML subtypes.

Clinical Presentation

In addition to general symptoms of leukemia (compare Chap 2) patients with AML often present with the following symptoms: bleeding, leukostasis, tumor lysis syndrome and infections.

Bleeding

- Besides thrombocytopenic bleeding there is often coagulopathy with mucosal (epistaxis, oral bleeding), gastrointestinal, or central nervous system (CNS) bleeding
- The coagulopathy results in disseminated intravascular coagulation (DIC) which occurs in parallel with infection and/or release of proteins with anticoagulant activities from the leukemia cells (i.e. thromboplastin). DIC is most frequently observed in acute promyelocytic leukemia (APL, M3)
- Therapy:
  - Platelet transfusion when platelet count is less than 20×10^9/l (substitution of coagulation factors is controversial)
  - In severe anemia, erythrocytes have to be substituted

Leukostasis

- If WBC is higher than 200×10^9/l, leukemic blasts may clump intravascularly. Small vessels may be blocked resulting in hypoxia, infarction and hemorrhage, mostly in the lungs or CNS
- Because of the large size of the monocytes in M5 AML leukostasis may occur with a WBC higher than 100×10^9/l
- Therapy:
  - Rapid cytoreduction if WBC is more than $100–200 \times 10^9$/l by leukapheresis or exchange transfusion
  - Hydroxyurea for prevention of rebound phenomena after leukapheresis
  - Prevention of tumor lysis syndrome

Tumor Lysis Syndrome

See Chap 18.

Infection

- The absolute neutrophil count (ANC) is often below 1×10^9/l and the frequency of fever and bacteremia is high
- For use of antibiotics and cytokines see Chap 18
- The risk of fungal infection is high especially during long periods of neutropenia or aplasia
- Lymphocytopenia may result in opportunistic infections

Therapy

- Before 1970 nearly all children with AML died. Since then cooperative study protocols with different cytotoxic drug combinations have led to long-term remission in 35–38% of children
- The use of autologous and allogenous stem cell transplantation increases the incidence of an event-free survival of more than 50%
- In addition to specific leukemic therapy management of complications and morbidity have to be conducted
- CNS prophylaxis includes either intrathecal cytarabine (ara-C) or cytarabine in combination with methotrexate and prednisone, often in parallel with systematic high-dose cytarabine treatment. This procedure seems equally successful to prophylactic CNS irradiation. The incidence of CNS relapse is dramatically decreased (less than 5%)
- Certain subtypes of AML are still associated with a poor prognosis (for instance AML with monosomy 7 or secondary AML)

Induction Therapy

- Cytarabine (e.g. ara-C) and anthracyclines (e.g. daunorubicin) lead to approximately 70% remission (less than 5% blasts in bone marrow) within 4–6 weeks and no other evidence of leukemias
- Other combinations such as 6-thioguanine, etoposide or the use of other anthracyclines (idarubicin, rubidomycin) and mitoxantrone result in remissions up to 85%
- Supportive therapy and prophylaxis (antibacterial, antiviral, antifungal) and the use of hematopoietic growth factors reduce morbidity and lethality. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) shorten the periods of neutropenia and diminish the frequency of infections and days of hospitalization, but do not influence the rate of remission or overall outcome

Remission and Postremission Therapy

- Consolidation and intensification therapy over the course of approximately 6–12 months results in an overall survival of between 45% and 55%. Some treatment programs use maintenance therapy

Allogeneic Hematopoietic Stem Cell Transplantation

- The possibility of an antileukemic effect of the donor immune system ("graft vs leukemia," GVL) together with supportive therapy and therapy against graft-versus-host disease (GVHD) results in an improved outcome for certain subtypes of AML
- The GVL effect is less effective in transplantation between identical twins or after extensive T-cell depletion of the donor stem cells

- Problems after transplantation include chronic GVHD, growth retardation, sterility and the risk of secondary malignancy
- The frequency of leukemia-free survival after transplantation is 50–70%. Prognostic factors of AML have to be taken into consideration in prognostic estimations

Autologous Hematopoietic Stem Cell Transplantation

- The advantages of this therapy are the absence of GVHD and the availability of donor cells for most patients. The disadvantages in comparison with allogeneic stem cell transplantation are the lack of GVL effect and the potential for leukemic cells in the returned stem cells

Prognostic factors in AML

	Favorable	Unfavorable
WBC	<100,000	>100,000
FAB class	M1 with Auer rods	Infants with 11q23
	M3 (APL)	Secondary AML
	M4 with eosinophils	CNS involvement
Chromosomal abnormalities	t(8;21) and t(15;17)	Mutation of *FLT3* receptor
	inv(16), t(9;11)	(Type-III tyrosine kinase receptor)
	Wild-type *FLT3*	
	Whites	t(9;22)
		del(7) and del(11)
		Expression of MDR P-glycoprotein genes with CD34 antigen (particularly in adults)
		Mutant *FLT3* (particularly internal tandem duplication)
Ethnicity	Whites	Blacks
	MRD-negative	MRD-positive
	Rapid response to therapy in bone marrow within 7–14 days	
Time of remission	>1 year	<1 year

MRD minimal residual disease

- Advantages and disadvantages of the autologous hematopoietic stem cell transplantation and morbidity equalize the prognosis in comparison with intensive postremission chemotherapy

Characteristics of and Therapy for AML Subtypes

- The therapeutic index for AML, the necessary dose of cytotoxic drugs against leukemic cells and the limitation of toxicity for normal precursor cells in the bone marrow are similar

Acute Promyelocytic Leukemia (APL, M3)

- Characterized by malignant cells at the stage of promyelocytes
- Mostly in young adults
- Symptoms: purpura, epistaxis, gingival bleeding
- Hemorrhagic complications are frequent
- Signs of intracranial high pressure as a manifestation of CNS bleeding
- Hepatosplenomegaly and/or lymphadenopathy usually not prominent
- Laboratory findings:
  - Marked thrombocytopenia, WBC variable
  - Bone marrow: mainly promyelocytes with azurophile granules, Auer rods are common; peroxidase-positive, Sudan black-positive, esterase-positive, PAS-negative
  - Prolonged prothrombin time and thrombin time: serum fibrinogen, factor V and factor VII decreased
  - D-Dimers increase in DIC caused by procoagulants from leukemic promyelocytes
  - The t(15;17) chromosomal abnormality is pathognomonic
- Therapy:
  - Standard-risk AML induction treatment plus ATRA (induction of differentiation of promyeloblasts)
  - ATRA maintenance with 6-mercaptopurine and methotrexate in high-risk patients
- Prognosis:
  - In cases of complete, continuous remission there is a high rate of long-term survival

Acute Myelomonocytic and Acute Monocytic Leukemia (M4, M5)

- Five to ten percent of all AML in children
- Symptoms comparable with other acute leukemias
- Hypertrophy of gingiva and ulceration of mucosa in about 50% of children
- Often infiltration of skin and lymphadenopathy
- Laboratory findings:
  - Anemia and thrombocytopenia are common; WBC variable
  - DIC: Release of tissue factors/proteases during lysis of monocytes

Erythroleukemia (Di Guglielmo Syndrome, M6)

- The clinical presentation consists of fatigue, fever, petechiae and often splenomegaly
- Laboratory findings:
  - Initial phase: macrocytic anemia, erythroblasts with two or three nuclei and showing a maturation disturbance, anisocytosis and poikilocytosis, elliptocytes
  - Variable numbers of reticulocytes; oxyphilic normoblasts and often elliptocytes and macrocytes in the peripheral blood; thrombocytopenia variable; megaloblastic hyperplasia of erythropoiesis in the bone marrow; result of glycophorin analysis: low to highly positive
  - Intermediate phase: mixed erythromyeloblastic proliferation
  - Late phase: similar to AML

Acute Megakaryocytic Leukemia (AMKL)

Clinical presentation and laboratory findings are comparable with other AML subtypes, although this type of AML can be associated with low percentages of bone marrow blasts and hepatic and skeletal involvement. This leukemia is most common in children with Down syndrome. In immune phenotyping CD41/61- and CD42 are present.

Myelodysplastic Syndrome (MDS)

In about 3% of children with acute leukemia the disease begins as pre-leukemia characterized by:

- Anemia, cytopenia, blasts in peripheral blood and morphological nuclear abnormalities of blood cells
- Bone marrow: mostly hypercellular, megaloblastic, dyserythropoietic; less than 5% blasts with nuclear anomalies, large or small megakaryocytes; chromosomal abnormalities in hematopoietic cells (monosomy 7); growth irregular in cultures in vitro
- Clinical course: often develops into AML within 6–24 months
- Prognosis: often therapy-resistant subtypes of AML; bone marrow transplantation is curative

Eosinophilic Leukemia

- Rare subtype of AML
- Symptoms: nausea, fever, sweating, cough, dyspnea, thoracic pain, weight loss and pruritus
- Clinical findings: cardiac arrhythmia, cardiomegaly and hepatomegaly are common; in 50% of cases lymphadenopathy; neurological disturbances (without leukemic CNS disease) are common
- Laboratory findings: often anemia and thrombocytopenia; WBC often high, occasionally more than 100×10^9/l with predominantly eosinophilic cells with large granules; chromosomal abnormalities sometimes present
- Clinical course: during progression of disease no difference to AML

- Differential diagnosis: Hypereosinophilia parasitosis (larva migrans, *Toxocara canis*), tropical eosinophilia
- Therapy: transient response to corticosteroids and hydroxyurea; AML therapy may induce remission

Relapse of AML

- Response to reinduction is less successful; resistance against drugs is high
- Continuous, long-term remission without transplantation less than 20% (exception: after first remission of more than 1 year 5-year survival rate is 30–40%)
- Patients who have a relapse affecting the CNS frequently have a simultaneous systemic relapse
- Induction therapy with high-dose ara-C in combination with mitoxantrone, etoposide, fludarabine or 2-chlorodeoxyadenosine and G-CSF
- Prognosis is unfavorable without stem cell transplantation (allogeneic, matched or partially matched), cord blood stem cell transplantation, haploidentical transplantation
- Infusion of donor lymphocytes for increase of GVL-effect may be considered after transplantation if relapse occurs
- After allogeneic or haploidentical transplantation the risk of primary rejection and GVHD is significant – despite T-cell depletion and immunosuppressive treatment (i.e. cyclosporin A)
- In APL (M3) the rate of second remission is greater than 80%