Acute myeloid leukemia

M. Kaźmierczak 2016

Acute myeloid leukemia

- **Malignant clonal disorder of immature hematopoietic cells characterized by clonal proliferation of abnormal blast cells and impaired production of normal blood cells**

- **Leukamic blasts may express capabilities for maturation to a variable degree, which lead to morphological heterogeneity**

Acute leukemias

- Adults:

- acute myeloid leukemia (AML) 80%
- acute lymphoblastic leukemia (ALL) 20%

Acute myeloid leukemia

- The incidence 4/100 000 population per year
- Median age 60 years with an incidence 10/100000 population per year in individuals 60 years and older

Acute myeloid leukemia

Clinical features

- Suddent onset of the disease and very fast progression
- If not treated $\rightarrow$ death after a few months
- Most of the common systemic manifestations, such a fatigue, weakness, fever and weight loss, are non-specific

Acute myeloid leukemia

Clinical features

1. • Infiltation of bone marrow by leukemic cells

2. • Supression of normal hematopoietic progenitor cells growth
   - Granulocytopenia
   - Thrombocytopenia
   - Anemia

3. • Consequences of cytopenias
   - infection of skin, mucous membranes, gums, respiratory, GI and GU tracts
   - bleeding in skin, mucous membranes, gums, GI and GU tracts
   - fatigue, weakness

Acute myeloid leukemia

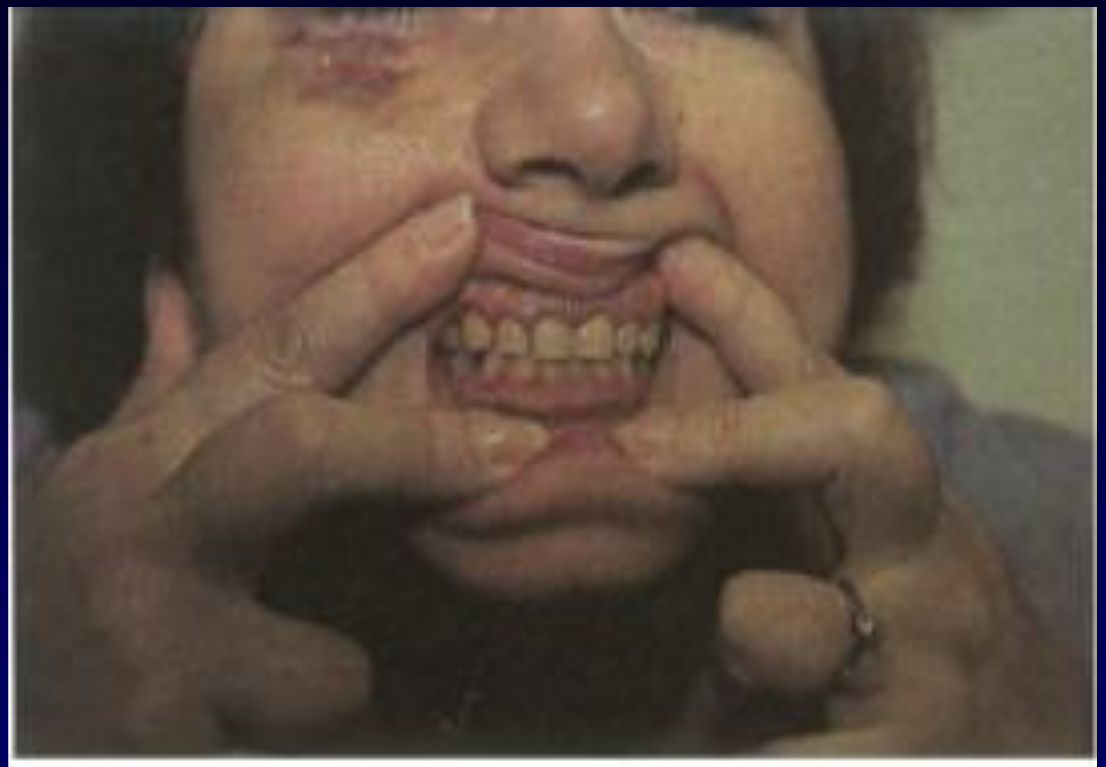
Clinical features

- The prevalence and degree of organ infiltration vary somewhat with the different types of leukemia
  - abdominal fullness (enlargement of the liver and spleen)
  - bone and join pain and tenderness
  - gum hypertrophy (myelomonocytic and monocytic leukaemia)
  - neurological symptoms: headache, nausea, vomiting, blurred vision, cranial nerve dysfunction (myelomonocytic and monocytic leukemia)
  - DIC (promyelocytic leukemia)

Acute myeloid leukemia

Approximate frequency of organ infiltration

Organ	Percent on initial exam	Percent at autopsy
Lymph nodes	**10**	**50**
Liver	**40**	**90**
Spleen	**35**	**90**
Bone and joint	**2**	**5**
Lungs	**5**	**50**
Heart	**2**	**35**
CUN	**1**	**27**
GI	**-**	**10**



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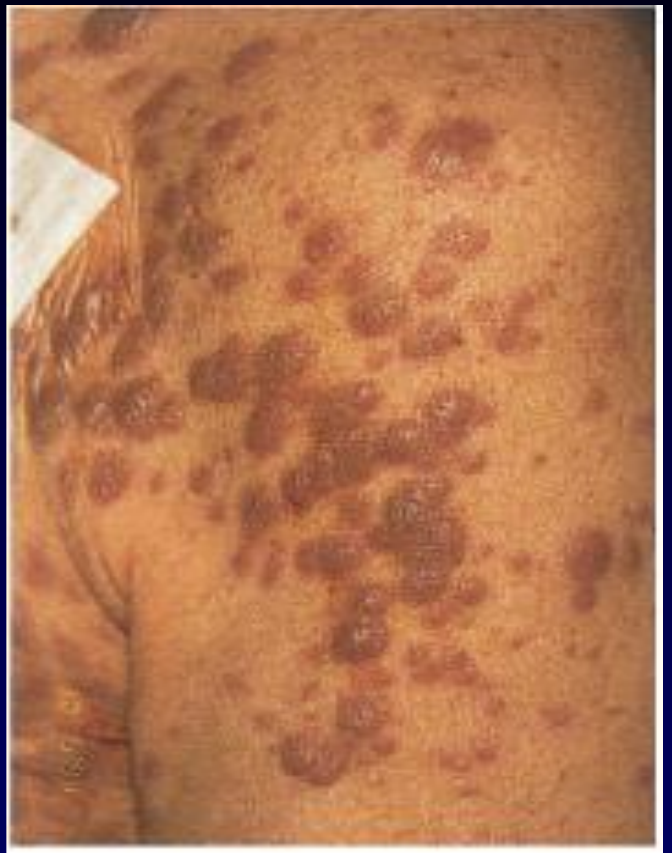

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Acute myeloid leukemia

- The diagnosis of AML primarily based on morphological and cytochemical criteria

  20% and more of blasts and suppression of other lineages

- Immunophenotyping, cytogenetic analysis and molecular examination employed to add specific information for a more precise diagnosis

World Health Organization (WHO) classification of AML

AML with certain genetic abnormalities

- AML with a translocation between chromosomes 8 and 21
- AML with a translocation or inversion in chromosome 16
- AML with a translocation between chromosomes 9 and 11
- APL (M3) with a translocation between chromosomes 15 and 17
- AML with a translocation between chromosomes 6 and 9
- AML with a translocation or inversion in chromosome 3
- AML (megakaryoblastic) with a translocation between chromosomes 1 and 22

AML with myelodysplasia-related changes

AML related to previous chemotherapy or radiation

AML not otherwise specified (This includes cases of AML that don't fall into one of the above groups, and is similar to the FAB classification.)

- AML with minimal differentiation (M0)
- AML without maturation (M1)
- AML with maturation (M2)
- Acute myelomonocytic leukemia (M4)
- Acute monocytic leukemia (M5)
- Acute erythroid leukemia (M6)
- Acute megakaryoblastic leukemia (M7)
- Acute basophilic leukemia
- Acute panmyelosis with fibrosis

Myeloid sarcoma (also known as granulocytic sarcoma or chloroma)

Myeloid proliferations related to Down syndrome

Undifferentiated and biphenotypic acute leukemias (leukemias that have both lymphocytic and myeloid features). Sometimes called ALL with myeloid markers, AML with lymphoid markers, or mixed phenotype acute leukemias.

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

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Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS

Cytological criteria for the diagnosis of acute myeloid leukaemia: French-American-British (FAB) classification

- Eight morphologic subtypes (M0-M7) are distinguished according to FAB classification system based on the morphologic features of the blasts and histochemical staining

The French-American-British (FAB) classification of AML

M0 - Undifferentiated acute myeloblastic leukemia
M1- Acute myeloblastic leukemia with minimal maturation
M2- Acute myeloblastic leukemia with maturation
M3- Acute promyelocytic leukemia (APL)
M4- Acute myelomonocytic leukemia
M4 eos - Acute myelomonocytic leukemia with eosinophilia
M5- Acute monocytic leukemia
M6 Acute erythroid leukemia
M7- Acute megakaryoblastic leukemia

AML – cytochemistry

Reaction	M0	M1	M2	M3	M4	M5	M6	M7
Peroxidase (POX)	-	+	+	+	+/-	-	+/-	-
Sudan Black B	-	+	+	+	+/-	-	+/-	-
Unspecific esterases	-	-	-	-	+	+	-	-
PAS	-	-	-	-	-	-	+	-

Immunophenotype of AML subtypes

Antigen	M0	M1	M2	M3	M4	M5	M6	M7	ALL
HLA -DR	++	++	+	-	++	++	+	-	+
CD11b	+	+	+	-	+++	+++	-	-	-
CD13	+++	+++	+++	+++	+++	++	++	+	+/-
CD14	-	+	+	-	+++	+++	-	-	-
CD15	-	-	+++	+	+	+	-	-	-
CD33	+++	+++	+++	+++	+++	+++	++	+	+/-
CD41, CD61	-	-	-	-	-	-	-	+++	-
Glycophorin A	-	-	-	-	-	-	+++	-	-
TdT	++	+	+	-	-	-	-	-	+++
CD117	+++	+++	++	+		++	++	+	-
CD2	+	+	-	++	++	-	-	-	+++
CD7	+	+	-	-	-	-	-	++	++
CD19	+		++	-	-	-	-	-	++++
CD34	+++	++	++	-	+	-	-	+	++

Prognostic factors for acute myeloid leukemia

Chromosome abnormalities and gene mutations

Acute myeloid leukemia

cytogenetic risk groups

- Favorable risk disease
  - t(8;21), t(15;17) inv 16
- Intermadiate risk disease
- Unfavorable risk disease
  - abnormalities of chromosome 5, complex changes, monosomy 7 and 3q-

Chromosome Aberrations, Gene Mutations and Expression Changes, and Prognosis in Adult Acute Myeloid Leukemia

Krzysztof Mrózek and Clara D. Bloomfield

Table 1. Risk group assignments of younger adults with acute myeloid leukemia (AML) with the more frequent cytogenetic findings.

Favorable-Risk Group	
Balanced structural rearrangements:	**t(15;17)(q22;q12-21)**
	t(8;21)(q22;q22)
	inv(16)(p13q22)/t(16;16)(p13;q22)
Intermediate-Risk Group	
	Normal karyotype*
Balanced structural rearrangement:	t(9;11)(p22;q23)†
Unbalanced structural rearrangements:	del(7q)‡
	del(9q)‡
	del(11q)†
	del(20q)§
Numerical aberrations:	**–Y**
	+8‖
	+11
	+13
	+21
Unfavorable-Risk Group	
	Complex karyotype¶
Balanced structural rearrangements:	**inv(3)(q21q26)/t(3;3)(q21;q26)**
	t(6;9)(p23;q34) #
	t(6;11)(q27;q23)**
	t(11;19)(q23;p13.1)**
Unbalanced structural rearrangement:	del(5q)††
Numerical aberrations:	–5
	–7

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Chromosome Aberrations, Gene Mutations and Expression Changes, and Prognosis in Adult Acute Myeloid Leukemia

Krzysztof Mrózek and Clara D. Bloomfield

Table 3. Genetic alterations affecting clinical outcome of cytogenetically normal acute myeloid leukemia (AML) patients.

Genetic Alteration	Prognostic Significance
Favorable	
NPM1 mutations	Patients with *NPM1* mutations who do not harbor *FLT3*-ITD have significantly better CR rates, EFS, RFS, DFS, and OS than patients without *NPM1* mutations and *FLT3*-ITD. *NPM1* mutations do not have a significant effect on prognosis of patients with *FLT3*-ITD.
CEBPA mutations	Patients with *CEBPA* mutations have CRD and OS significantly longer than patients with the wild-type *CEBPA* gene.
Unfavorable	
FLT3-ITD	Patients with *FLT3*-ITD have significantly shorter CRD, DFS and OS than patients who do not harbor *FLT3*-ITD. Particularly poor prognosis is conferred by *FLT3*-ITD coupled with no expression of a *FLT3* wild-type allele or a high *FLT3* mutant to *FLT3* wild-type allele ratio.
MLL-PTD	Patients with *MLL*-PTD have remission duration significantly shorter than patients without *MLL*-PTD.
BAALC overexpression	Patients with high expression of the *BAALC* gene in blood have significantly worse CR rates and shorter DFS, EFS and OS than patients with low expression of the *BAALC* gene.
ERG overexpression	Patients with high expression of the *ERG* gene in blood have significantly shorter OS and higher CIR than patients with low expression of the *ERG* gene.

Genetic alterations affecting clinical outcome of cytogenetically normal AML pts

- **Unfavorable**
  - FLT3-ITD (internal tandem duplication)
    - Significantly shorter DFS (Disease Free Survival) and OS (overall survival)

    FLT3- fms-related tyrosine kinase 3; an important role in the proliferation of hematopietic progenitor cells
- **Favorable**
  - NPM1 mutations
    - Pts with NPM1 mutations who do not harbor FLT3-ITD. have significantly better CR rate, DFS, OS
  - CEBP mutations
    - Better OS
- NPM1- nucleophosmin
- CEBPA- CCAAT/enhancer binding protin alfa

Other prognostic factors for AML

Markers on the leukemia cells

If the leukemia cells have the CD34 protein and/or the P-glycoprotein (MDR1 gene product) on their surface, it is linked to a worse outcome.

Age

White blood cell count

A high white blood cell count (>100,000) at the time of diagnosis is linked to a worse outlook.

Prior blood disorder leading to AML

Myelodysplastic syndrome is linked to a worse outcome.

Treatment-related AML

AML that develops after treatment for another cancer tends is linked to a worse outcome.

Infection

Having an active systemic (blood) infection at the time of diagnosis makes a poor outcome more likely.

Leukemia cells in the central nervous system

Treatment of AML-strategy

- Induction chemotherapy
  - The aim: obtaining complete remission
    - reduction of the blast cells in the marrow < 5% (inapparent) and normalization of the picture of the peripheral blood
- Postremission therapy
  - The aim: elimination of residual disease

Induction chemotherapy

- Gold standard „3+7” (?)
  - The anthracyclin drug for 3 days
  - Cytarabine for 7 days
- Complete remission- 60-70%

- Modification of standard chemotherapy
  - Purine analoges (fludarabina, 2-CDA)
  - High doses of Ara-C
  - 6-TG
  - etoposide

Postremission therapy

- Intensification of remission
  - High-dose cytarabine based regimens with anthracycline drug
- Allogeneic HSCT
- Autologous HSCT
- Maintance chemotherapy
  - Low-dose Ara-C, 6-TG, anthracycline drug

Acute myeloid leukemia

- CNS prophylaxis/treatment
  - if clinical symptoms suggest meningeal leukemia
  - myelomonocytic and monocytic leukaemia
  - patients < 18 years old

→ combination of drugs administered intrathecally

(Ara-C plus Fenicort, MTX plus Fenicort)

or

CNS radiotherapy

The results of treatment

Complete remission is usually defined as having no evidence of disease after treatment. This means the bone marrow contains fewer than 5% blast cells, the blood cell counts are within normal limits, and there are no signs or symptoms of the disease.

Minimal residual disease is a term used after treatment when leukemia cells can't be found in the bone marrow using standard tests (cytologic evaluation of the peripheral blood/bone marrow smear), but more sensitive tests (such as flow cytometry or PCR) find evidence that there are still leukemia cells in the bone marrow.

The results of postremission therapy in patients in CR1

- 3-5 years Disease Free Survival

Chemotherapy	autoHSCT	alloHSCT
30%-40%	40%-50%	40%-55%

ACUTE LEUKAEMIA REGISTRY : 1ST & 2N TRANSPLANT
JANUARY 1994 - JANUARY 2008 *(n=51023)*

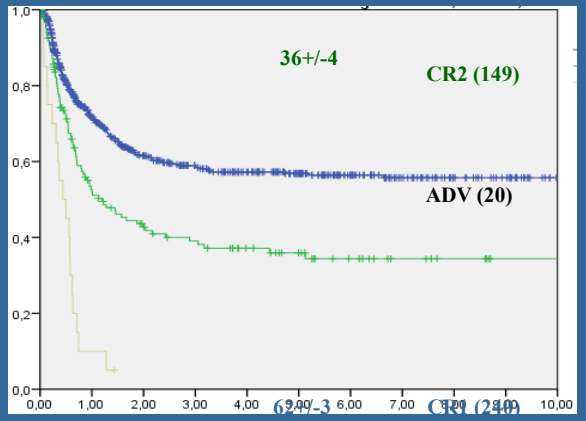
AUTOLOGOUS TRANSPLANT

CR1

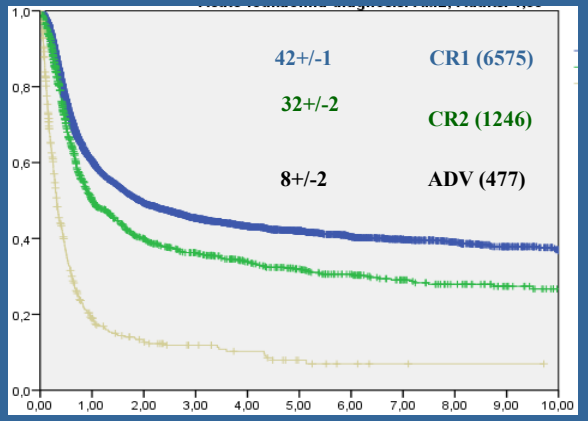
CR2

ADVANCED

CHILDREN : AML *(n=839)*



ADULTS : AML *(n=8298)*



ACUTE LEUKAEMIA REGISTRY : 1ST & 2N TRANSPLANT
JANUARY 1994 - JANUARY 2008 *(n=51023)*

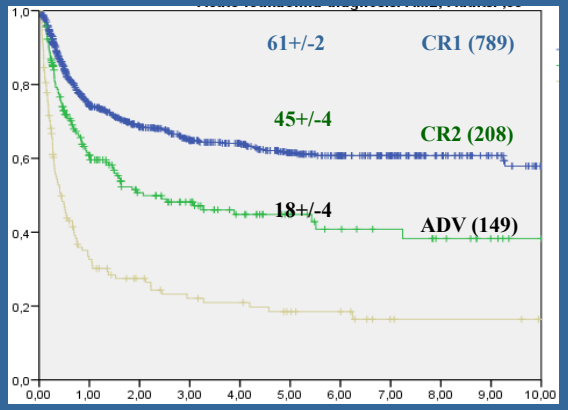
HLA IDENTICAL TRANSPLANT

CR1

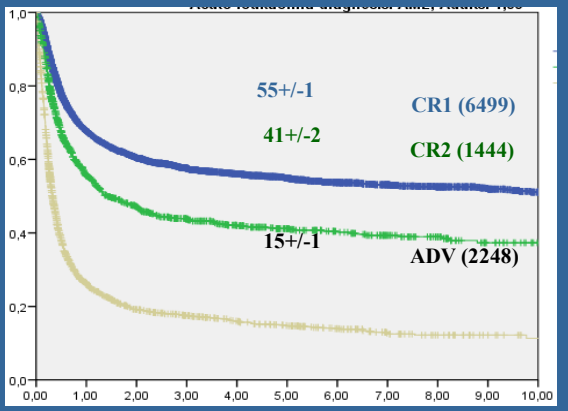
CR2

ADVANCED

CHILDREN : AML *(n=1146)*



ADULTS : AML *(n=10191)*



Treatment of acute promyelocytic leukaemia
t(15:17)/ PML/RAR-alfa gene

- All-trans retinoic acid (ATRA) based induction and intensification regimen in combination with anthracycline-based chemotherapy or arsenic trioxide (ATO)
- ATRA targets RAR-alfa moiety of the fusion transcript and induces differentiation of leukemic clone
- CR 85%, approximately 70% of pts can be cured