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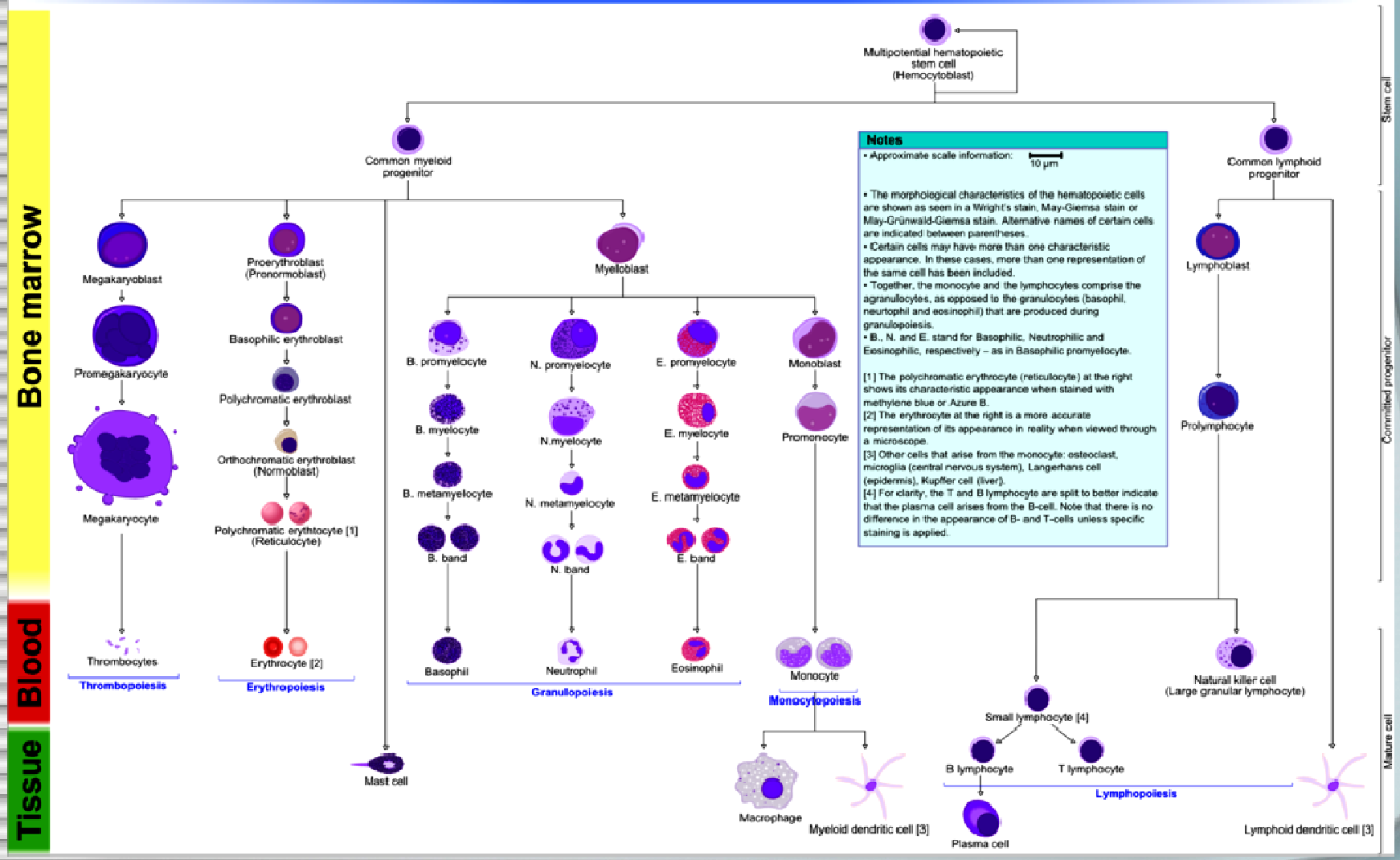
HEMATOLOGICAL MALIGNANCIES: CLASSIFICATION, ETIOLOGY, PATHOGENESIS. ACUTE LEUKEMIAS.

CHISINAU - 2020

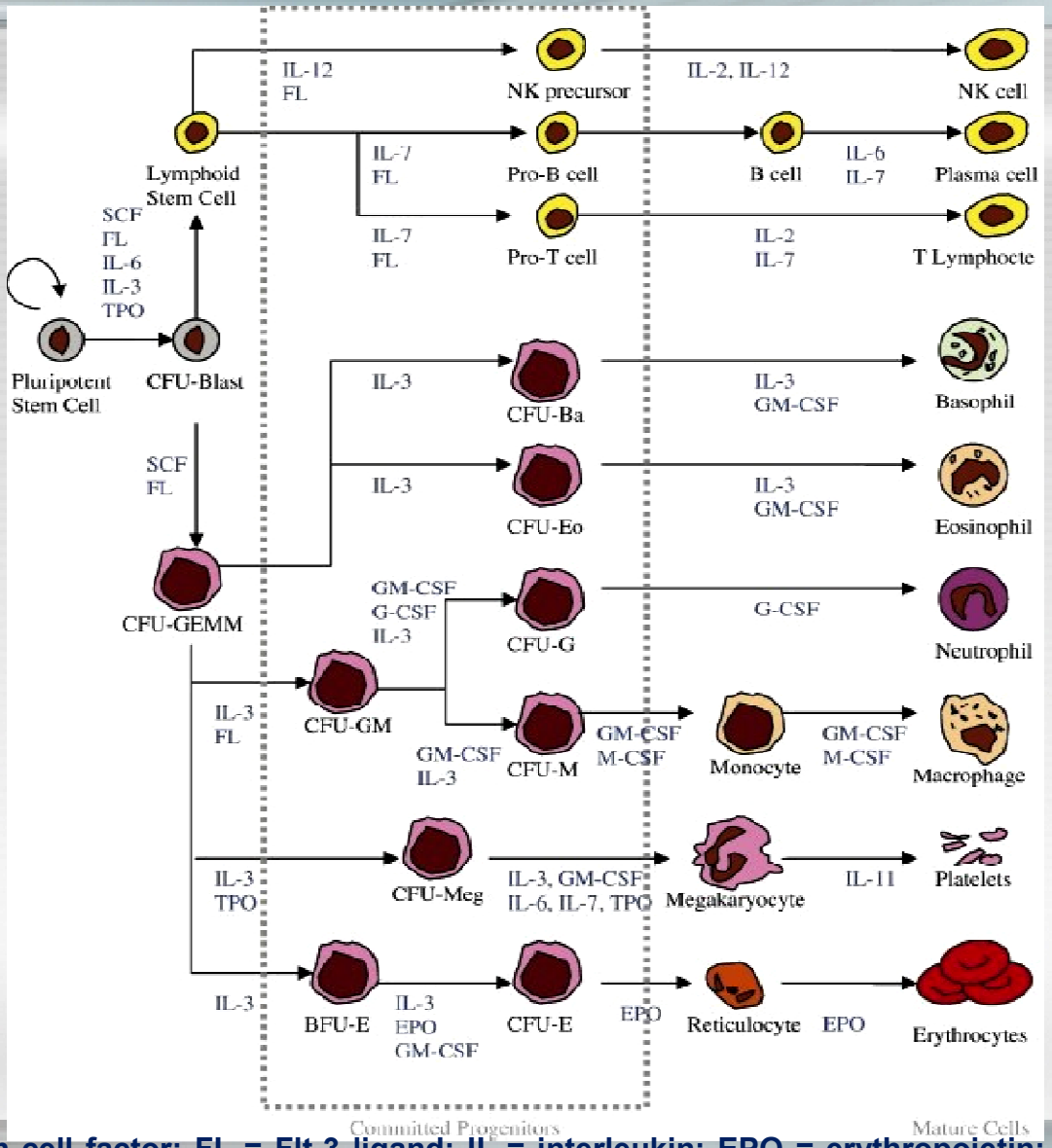
Hematopoiesis in humans



A. Rad, 2006

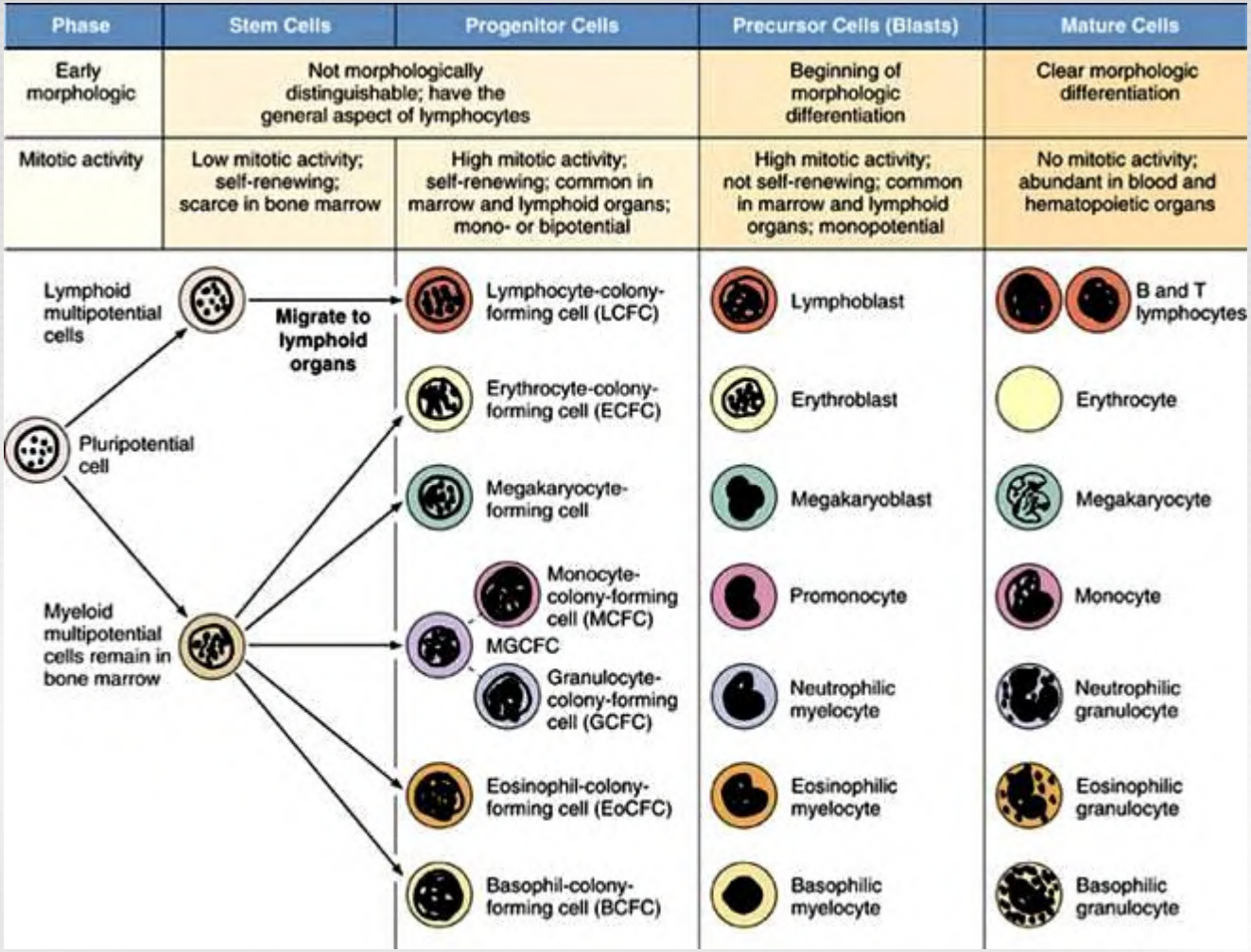
THE HAEMATOPOIESIS CELL CYCLE

(Biotechnology Advances, Volume 25, Issue 4, 2007)

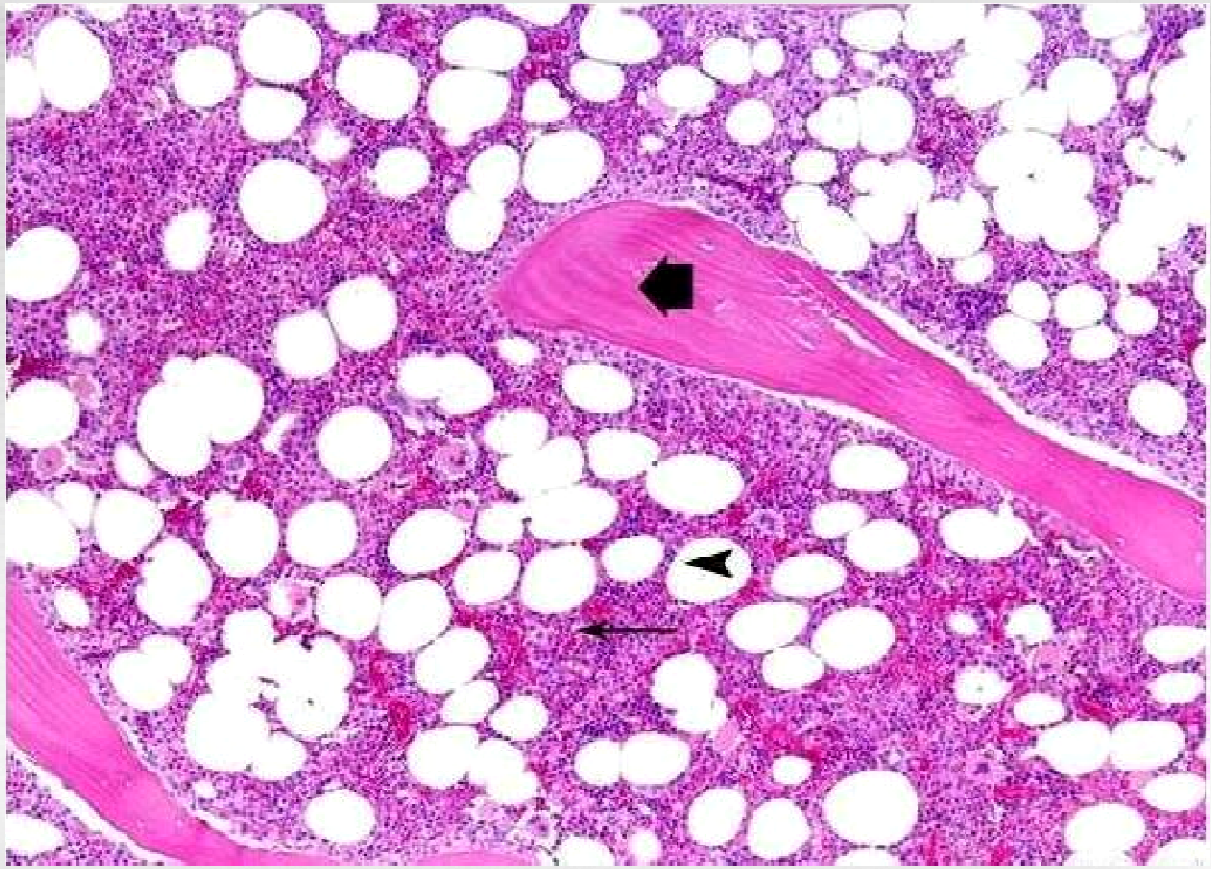


Cytokines: SCF = stem cell factor; FL = Flt-3 ligand; IL = interleukin; EPO = erythropoietin; TPO = thrombopoietin; GM-CSG = granulocyte-macrophage-colony-stimulating factor; G-CSG = granulocyte-CSF; M-CSF = macrophage-CSF lineages: CFU = colony forming unit; GEMM = granulocyte erythrocyte macrophage and monocyte; Ba = basophil; Eo = eosinophil; Meg = megakaryocyte; E = erythrocyte; NK = natural killer (adapted from Kufe et al., 2003)

DIFFERENTIATION OF PLURIPOTENTIAL STEM CELLS DURING HEMATOPOIESIS



TREPANOBIOPSIA MĂDUVEI OSOASE: TABLOUL HISTOLOGIC MEDULAR NORMAL



WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

MYELOPROLIFERATIVE NEOPLASMS (MPN)

- **Chronic myelogenous leukemia, *BCR-ABL1–positive***
- **Chronic neutrophilic leukemia**
- **Polycythemia vera**
- **Primary myelofibrosis**
- **Essential thrombocythemia**
- **Chronic eosinophilic leukemia, not otherwise specified**
- **Mastocytosis**
- **Myeloproliferative neoplasms, unclassifiable**

MYELOID AND LYMPHOID NEOPLASMS ASSOCIATED WITH EOSINOPHILIA AND ABNORMALITIES OF *PDGFRA, PDGFRB, OR FGFR1*

- **Myeloid and lymphoid neoplasms associated with *PDGFRA rearrangement***
- **Myeloid neoplasms associated with *PDGFRB rearrangement***
- **Myeloid and lymphoid neoplasms associated with *FGFR1 abnormalities***

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN)

- **Chronic myelomonocytic leukemia**
- **Atypical chronic myeloid leukemia, *BCR-ABL1–negative***
- **Juvenile myelomonocytic leukemia**
- **Myelodysplastic/myeloproliferative neoplasm, unclassifiable**
  - ***Provisional entity: refractory anemia with ring sideroblasts and thrombocytosis***

WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

MYELODYSPLASTIC SYNDROME (MDS)

Refractory cytopenia with unilineage dysplasia

- **Refractory anemia**
- **Refractory neutropenia**
- **Refractory thrombocytopenia**

Refractory anemia with ring sideroblasts

Refractory cytopenia with multilineage dysplasia

Refractory anemia with excess blasts

Myelodysplastic syndrome with isolated del(5q)

Myelodysplastic syndrome, unclassifiable

Childhood myelodysplastic syndrome

- ***Provisional entity: refractory cytopenia of childhood***

ACUTE MYELOID LEUKEMIA AND RELATED NEOPLASMS

Acute myeloid leukemia with recurrent genetic abnormalities

- **AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1***
- **AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11***
- **APL with t(15;17)(q22;q12); *PML-RARA***
- **AML with t(9;11)(p22;q23); *MLLT3-MLL***
- **AML with t(6;9)(p23;q34); *DEK-NUP214***
- **AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1***
- **AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1***
  - ***Provisional entity: AML with mutated NPM1***
  - ***Provisional entity: AML with mutated CEBPA***

WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified

- **AML with minimal differentiation**
- **AML without maturation**
- **AML with maturation**
- **Acute myelomonocytic leukemia**
- **Acute monoblastic/monocytic leukemia**
- **Acute erythroid leukemia**
  - **Pure erythroid leukemia**
  - **Erythroleukemia, erythroid/myeloid**

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

- **Transient abnormal myelopoiesis**
- **Myeloid leukemia associated with Down syndrome**

Blastic plasmacytoid dendritic cell neoplasm

WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

ACUTE LEUKEMIAS OF AMBIGUOUS LINEAGE

Acute undifferentiated leukemia

Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*

Mixed phenotype acute leukemia with t(v;11q23); *MLL rearranged*

Mixed phenotype acute leukemia, B-myeloid, NOS

Mixed phenotype acute leukemia, T-myeloid, NOS

Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma

B LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

B lymphoblastic leukemia/lymphoma, NOS

B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

- **B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL 1***
- **B lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL rearranged***
- **B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) *TEL-AML1* (*ETV6-RUNX1)***
- **B lymphoblastic leukemia/lymphoma with hyperdiploidy**
- **B lymphoblastic leukemia/lymphoma with hypodiploidy**
- **B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) *IL3-IGH***
- **B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1***

T LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

NEOPLASTIC DISEASES OF THE HEMATOPOIETIC SISTEM **are the disorders which develop as the result of a malignant transformation of cells of the hematopoietic tissue situated in or outside the bone marrow. A certain hematopoietic cell gives rise to a corresponding hematologic malignancy that reflects the correlation between the classification of the hematologic neoplastic disorders and the scheme of hematopoiesis.**

HEMATOLOGIC MALIGNANCIES **originating from the bone marrow hematopoietic cells are known as leukemias. Those which develop from the extramedullary hematopoietic cells (in the lymph nodes, spleen, etc.) are named malignant lymphomas. There are acute and chronic leukemias.**

ACUTE LEUKEMIAS **are the neoplastic disorders originating from blast cells. Chronic leukemias represent the hematologic malignancies, which develop from the precursor hematopoietic cells maintaining the ability for maturation up to mature cells. Acute leukemias can't be transformed in chronic leukemias.**

In the majority of countries, in particular in Republic of Moldova leukemias and lymphomas are approximately equally frequent – by 50%. Malignant lymphomas comprise Hodgkin lymphoma, non-Hodgkin lymphomas, and histiocytoses. Acute leukemias are common in U.S.A., Canada, Israel, Scandinavian countries. In these states the incidence of acute leukemias ranges from 7.0 to 11.3 cases per 100000 population in males and from 5.0 to 7.0 per 100 000 in females.

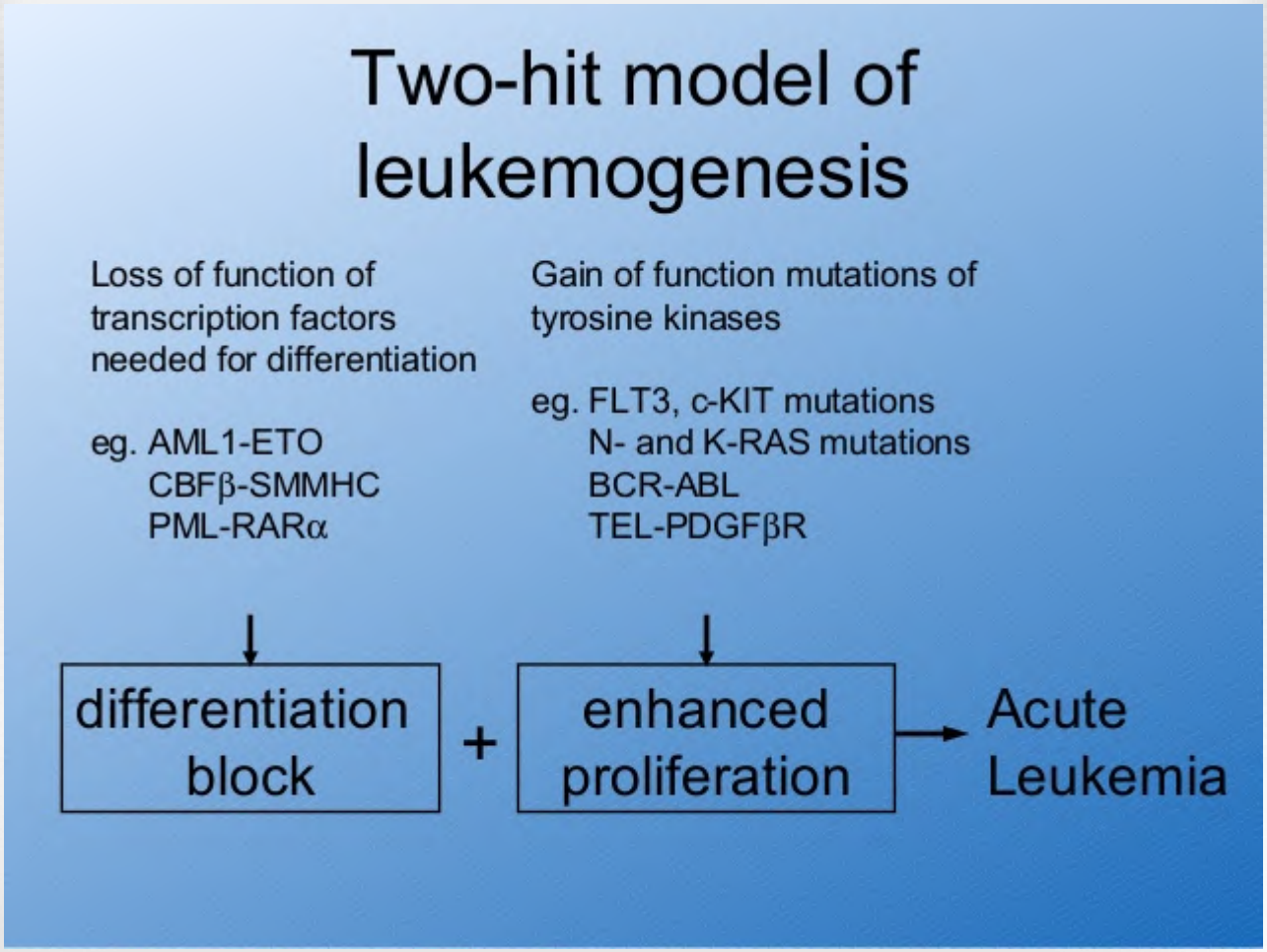
ACUTE LEUKEMIAS **– are the malignant disorders resulting from a clonal proliferation and accumulation of blast cells. Acute leukemias affects persons of all ages and occurs more frequently in males. The morbidity by acute leukemias correlates with age. The incidence in Republic of Moldova constitutes 2.4 per 100 000 population. Acute lymphoblastic leukemia is common (85%) in children. Acute myeloid leukemias predominate in adults (85% of all cases).**

PATHOGENESIS. **Acute leukemias evolve from a single transformed blast cell. Neoplastic cell clone suppresses and replaces the normal cell clone. The failure of production of normal blood cells is caused by lack of normal hematopoiesis in the bone marrow. It is proved, that clinical manifestations of acute leukemias appear when the number of leukemic cells in organism constitutes approximately one billion.**

CLINICAL PICTURE **reflects the abnormalities in the bone marrow and in the blood.**
Anemic syndrome **includes such symptoms as fatigue, dizziness, dispnea, palpitation, and pallor, weakness.**
Hemorrhagic syndrome **is caused by thrombocytopenia and comprises petechiae, ecchymoses, epistaxis, mucous membrane bleeding (gastrointestinal, etc.), cerebral bleeding, etc.**
Neutropenia may lead to a predisposition to infections **which may be focal (such as otitis, pharyngitis, or pneumonia) or systemic, with the signs and symptoms of sepsis.**
Proliferation syndrom: **The enlargement of lymph nodes is present in about 50% of cases, splenomegaly – in 30 %, and hepatomegaly is observed 49% of patients. Mediastinal lymphadenopathy is observed in 8% of patients. Blast cells may infiltrate the skin.**

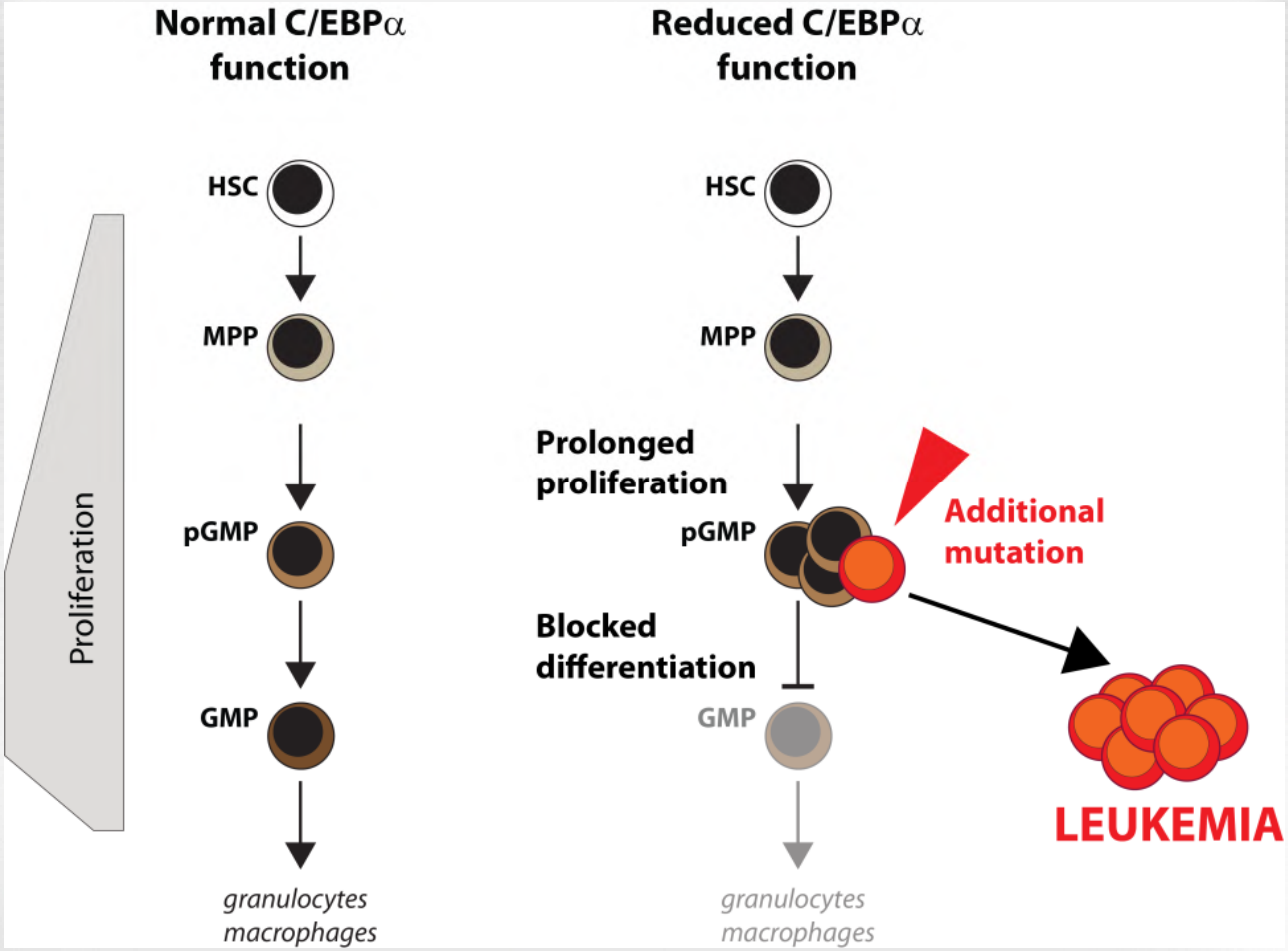
PATHOGENESIS OF ACUTE LEUKEMIAS

(source: Pradip Katwal, 2013)



PATHOGENESIS OF ACUTE LEUKEMIAS

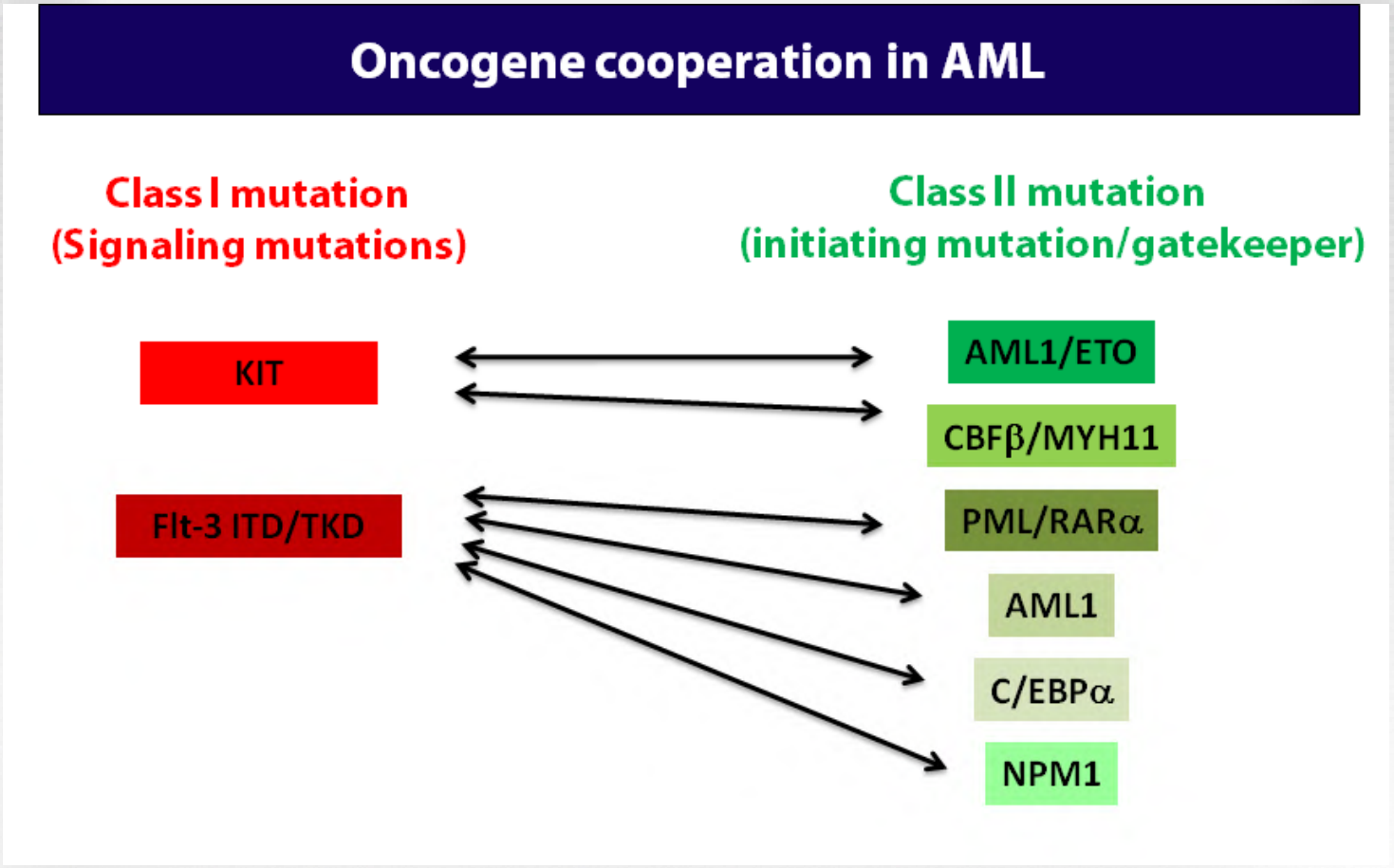
(source: Reckzeh K., Lund University, 2012: Deciphering the Pathogenesis of Acute Myeloid Leukemia)



Transcription factors (TF) such as C/EBPα control differentiation by activating myeloid gene programs and inducing cell cycle arrest. Due to reduced TF function highly proliferating progenitors do not enter the differentiation program and acquire additional mutations, preferentially those mutations that confer a growth or survival advantage such as FLT3-ITD (Rosenbauer and Tenen, 2007).

PATHOGENESIS OF ACUTE LEUKEMIAS

(source: Reckzeh K., Lund University, 2012: Deciphering the Pathogenesis of Acute Myeloid Leukemia)

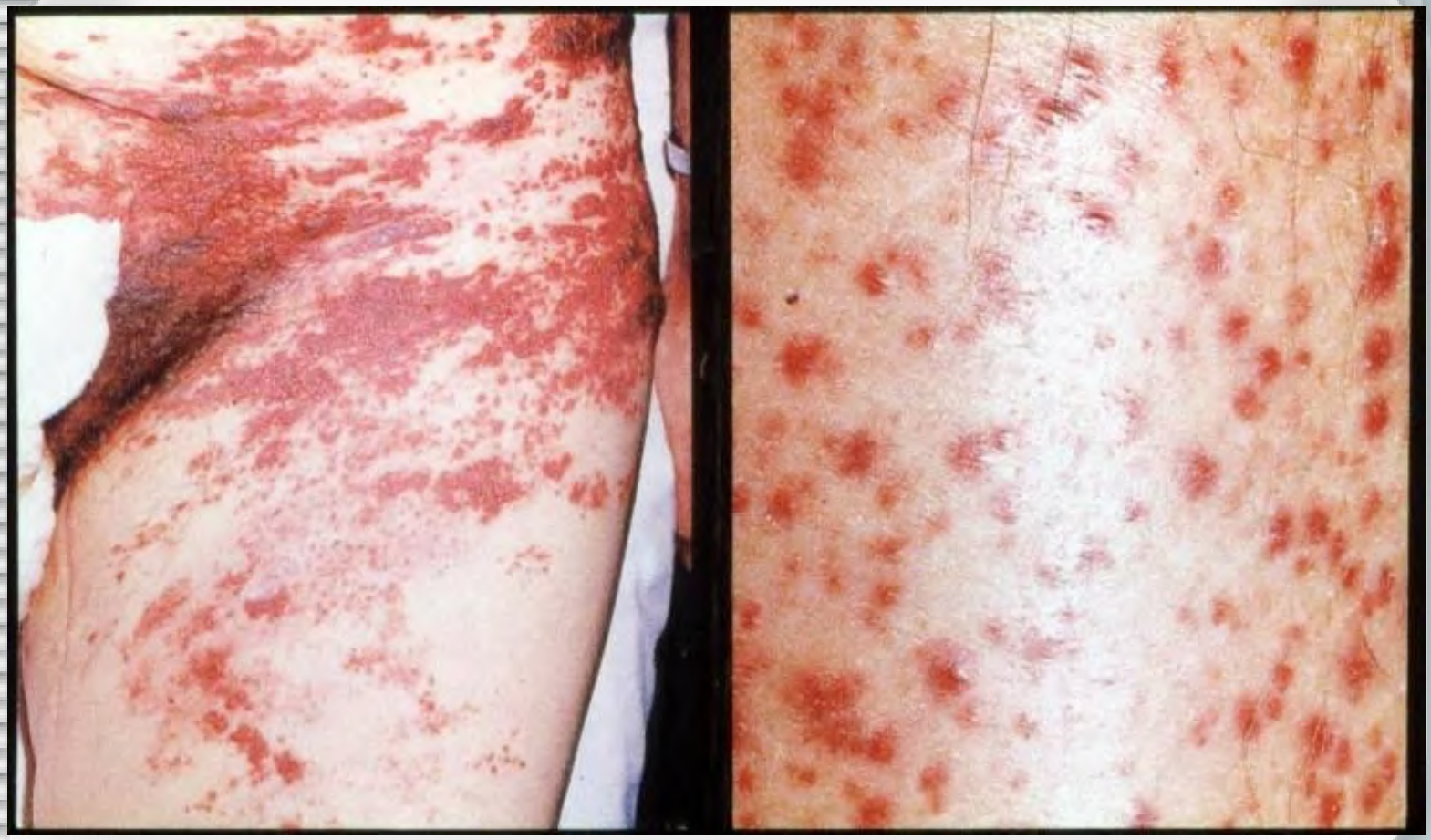


Growing body of evidence suggests that signaling mutations cooperate with specific partners in leukemogenesis. Alterations of the same class are absent/rarely observed in AML. In addition, translocations inculding t(8;21) and inv(16) cluster together with KIT alterations whereas t(15;17), point mutations in *AML1 and CEBPA coincide* with FLT3 activating mutations (Haferlach, 2008).

PATHOGENESIS OF ACUTE LEUKEMIAS

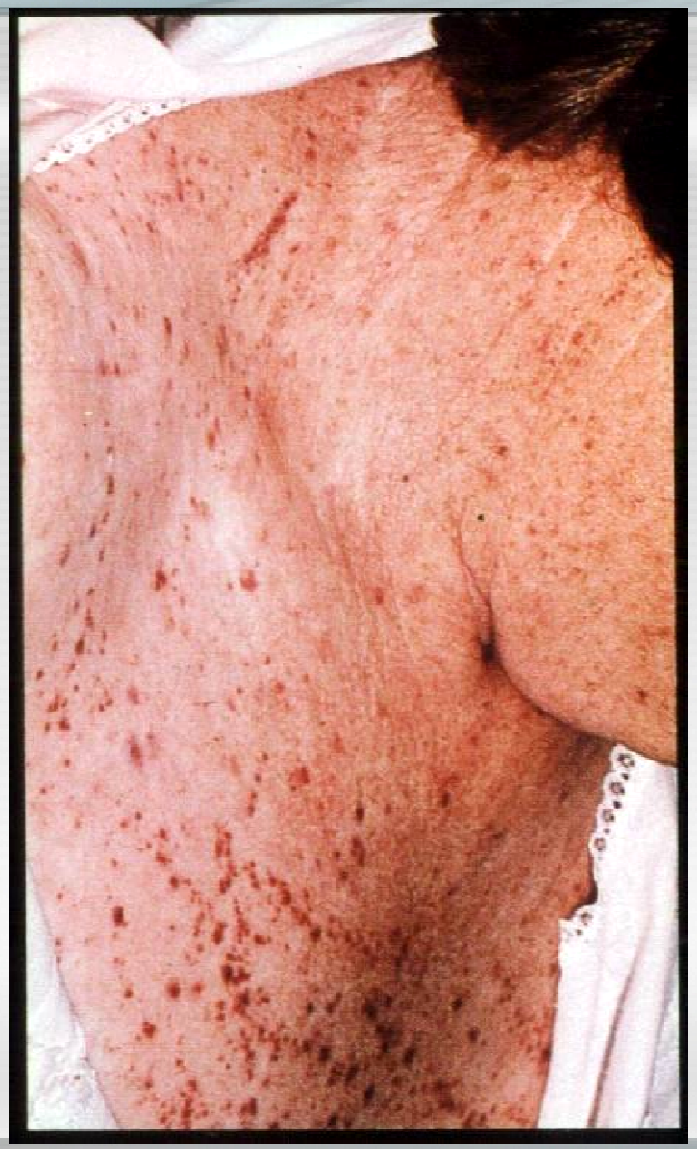
Acute Myeloid Leukemia.mp4

HEMORRHAGIC SYNDROME IN ACUTE LEUKEMIA

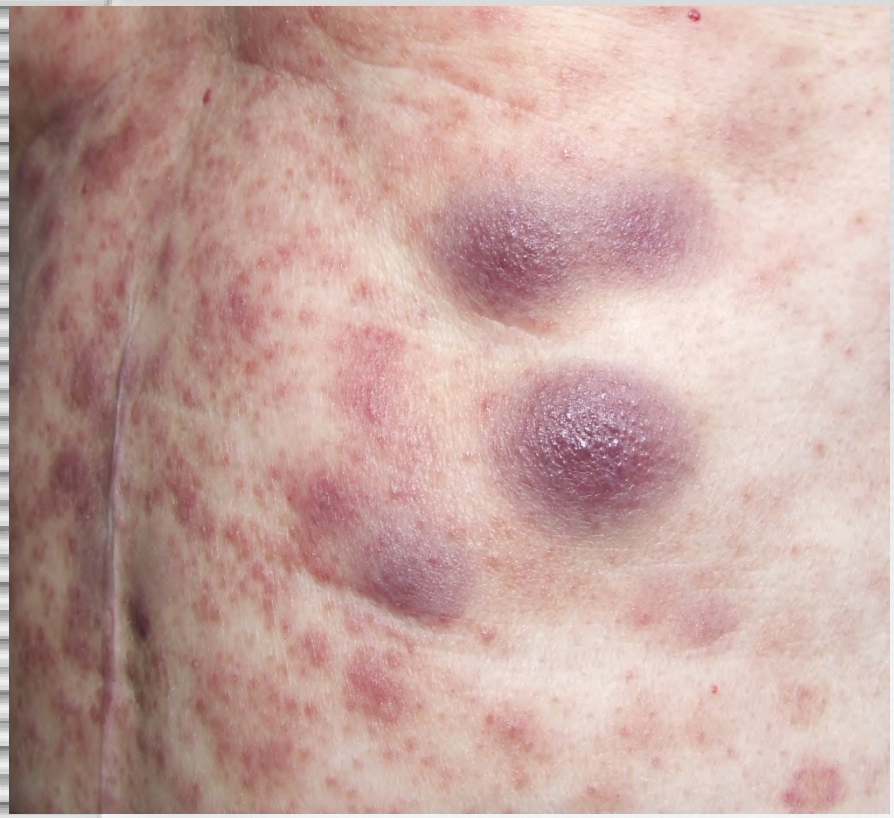


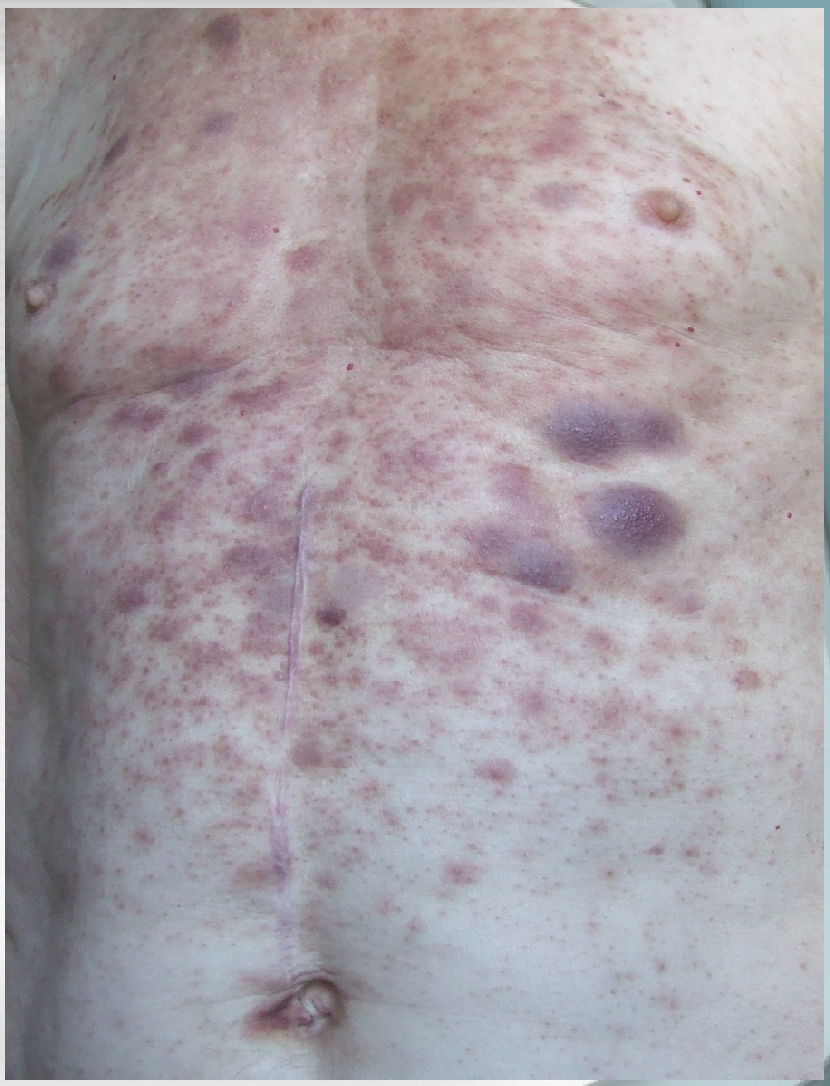
Hemorrhagic syndrome is caused by thrombocytopenia and comprises petechiae, ecchymoses, epistaxis, mucous membrane bleeding (gastrointestinal, etc.), cerebral bleeding, etc.

HEMORRHAGIC SYNDROME IN ACUTE LEUKEMIA

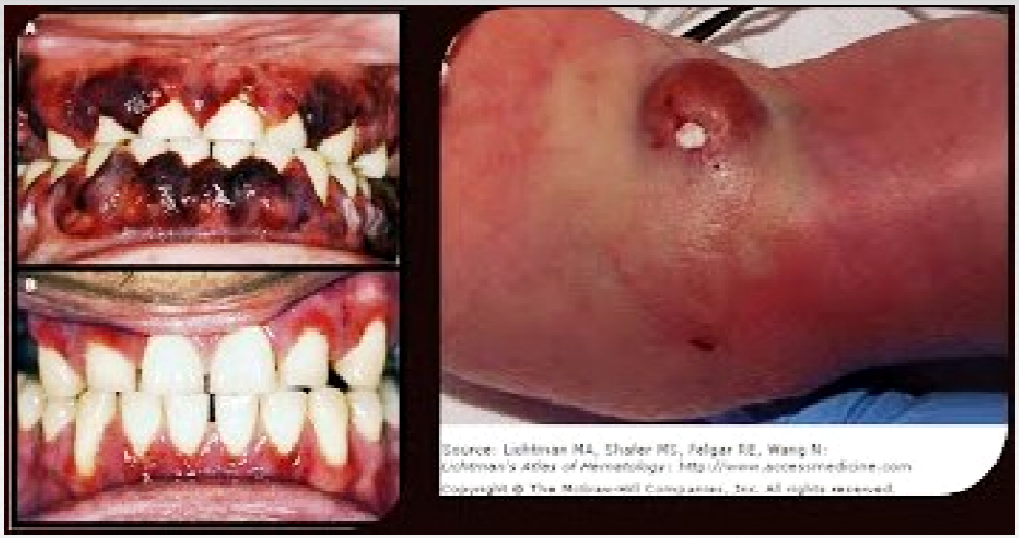


SKIN INFILTRATION BY BLAST CELLS IN ACUTE LEUKEMIA

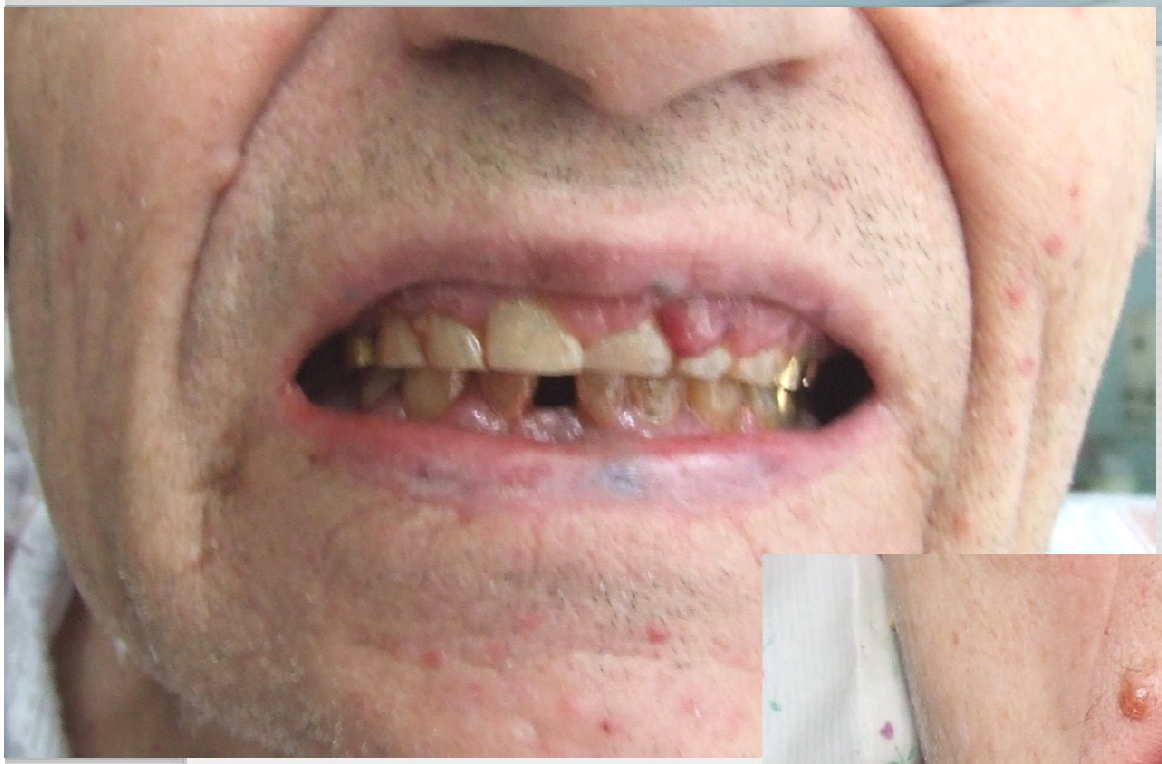


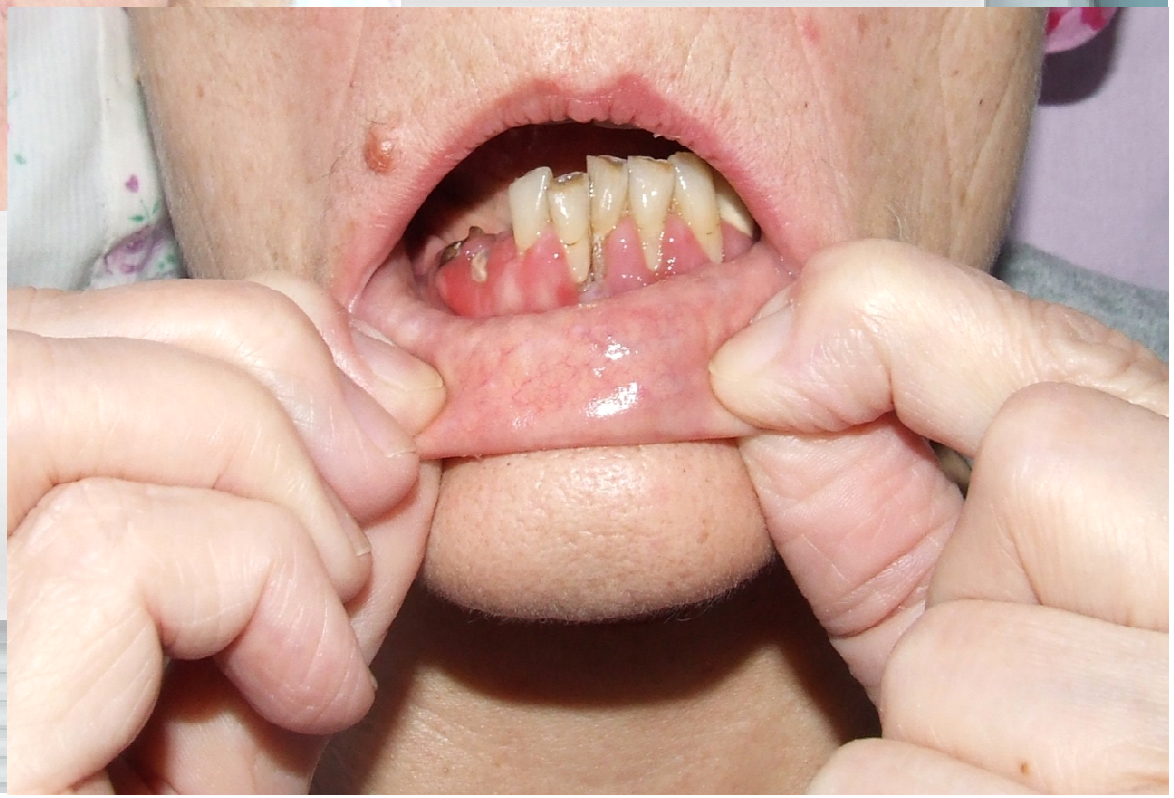


CLINICAL SIGNS OF ACUTE MYELOBLASTIC LEUKEMIA



GINGIVAL INFILTRATION BY BLAST CELLS IN ACUTE LEUKEMIA

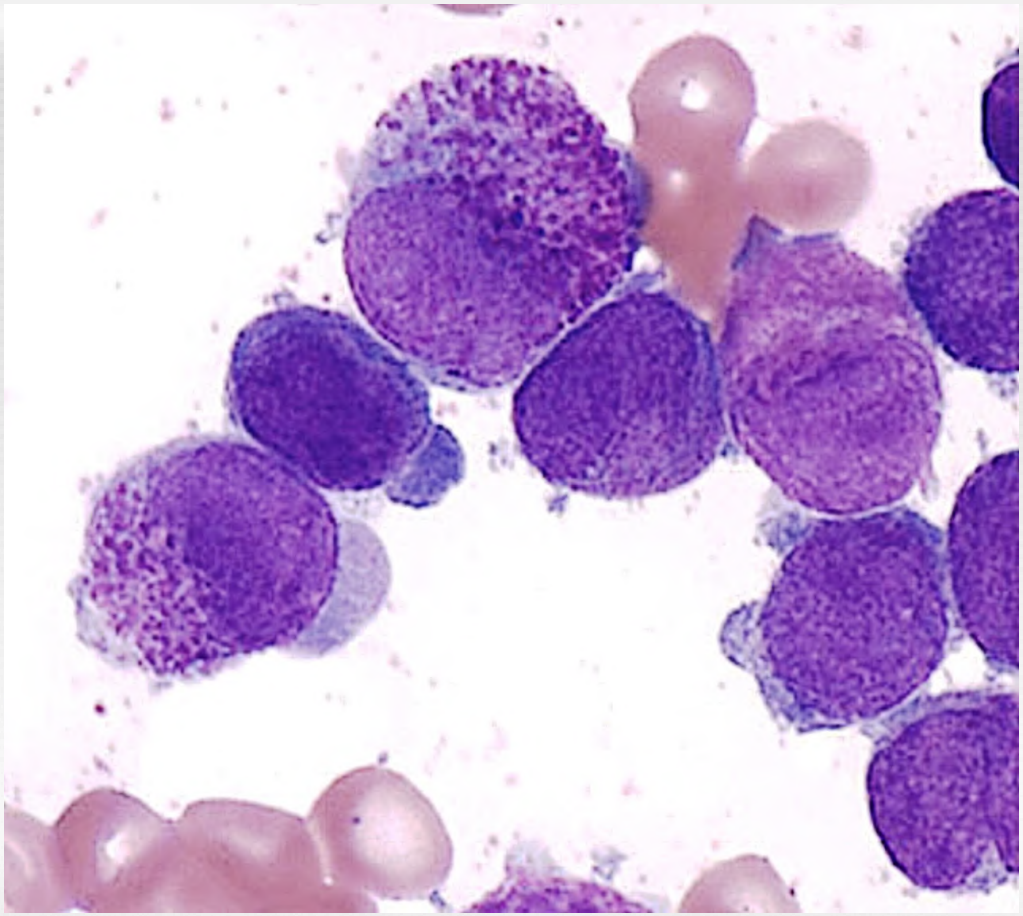




Leucemie acută

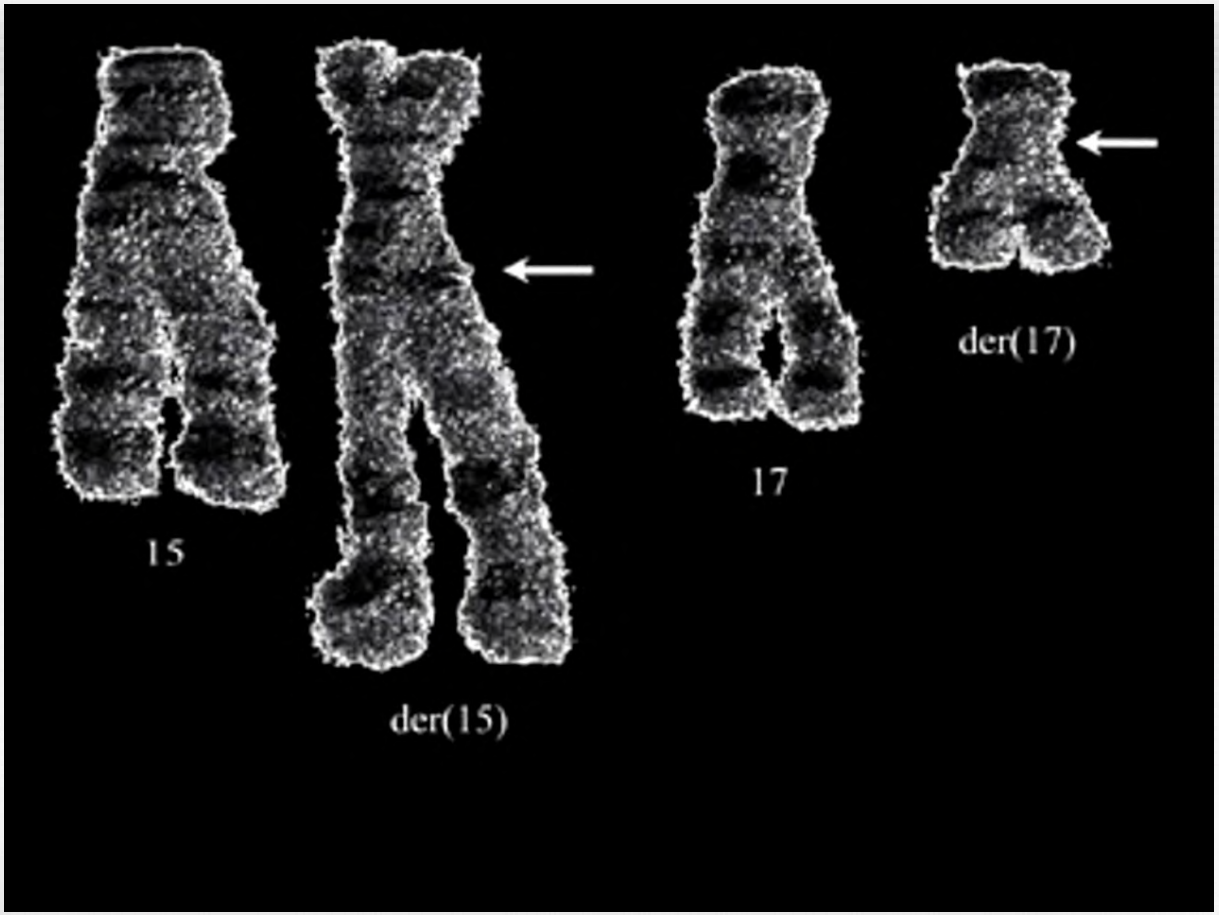
Hemoglobina (g/l)	**53**	**80**	**112**
Eritrocite (10^{12}/l)	**1,68**	**2,44**	**3,3**
Leucocite (10^{9}/l)	**5,25**	**97,5**	**1,0**
Celule blastice (%)	**46**	**74**	**8**
Promielocite (%)	**—**	**3**	**—**
Mielocite (%)	**1**	**1**	**—**
Metamielocite (%)	**—**	**—**	**—**
Nesegmentate (%)	**5**	**5**	**2**
Segmentate (%)	**8**	**5**	**18**
Eozinofile (%)	**—**	**—**	**—**
Bazofile (%)	**—**	**—**	**—**
Limfocite (%)	**39**	**5**	**70**
Monocite (%)	**1**	**7**	**2**
Trombocite (10^{9}/l)	**solitare**	**24,4**	**170,0**
VSH (mm/oră)	**70**	**10**	**11**

BLOOD SMEAR IN ACUTE PROMYELOCYTIC LEUKEMIA



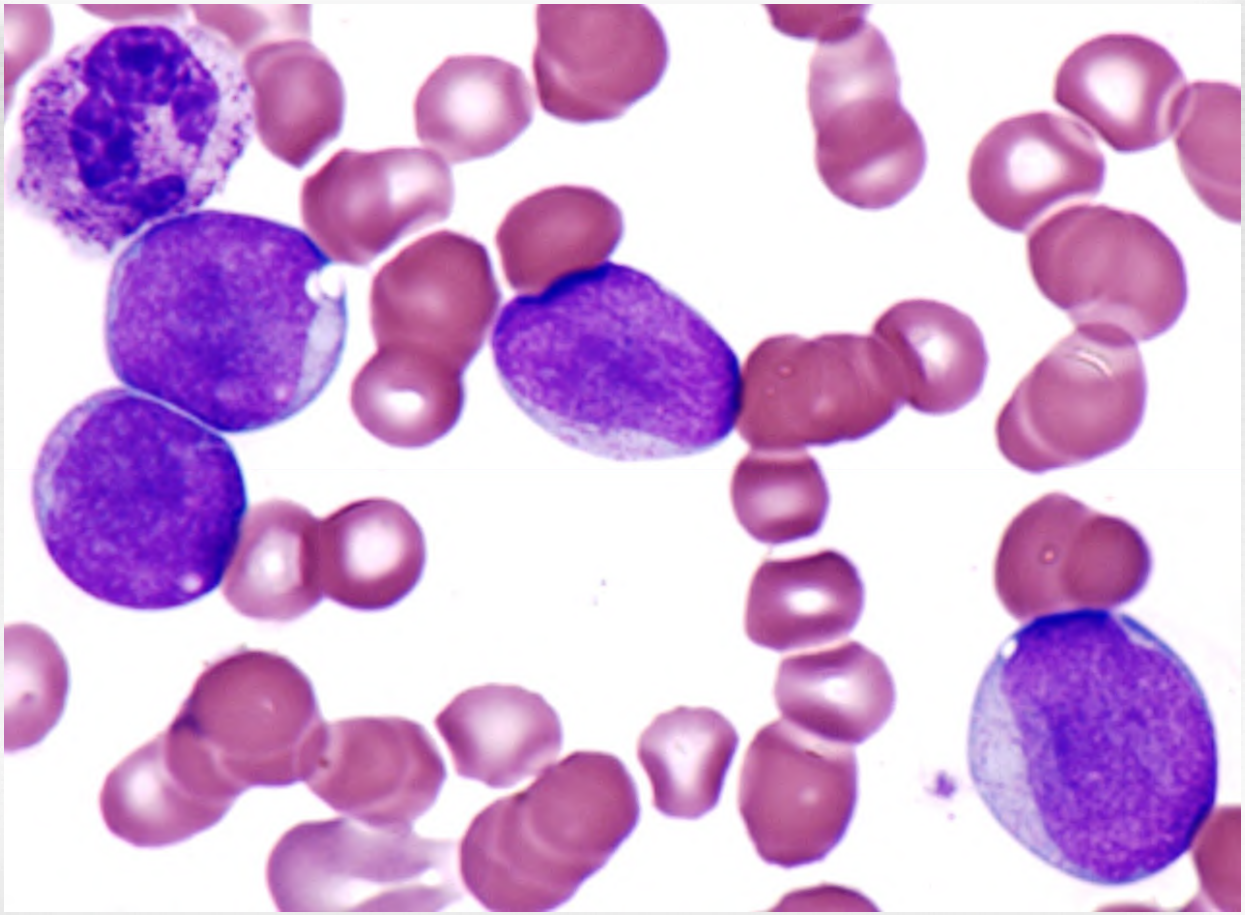
Promyelocytes are heavily granulated

CYTOGENETIC MARKER OF ACUTE PROMYELOCYTIC LEUKEMIA



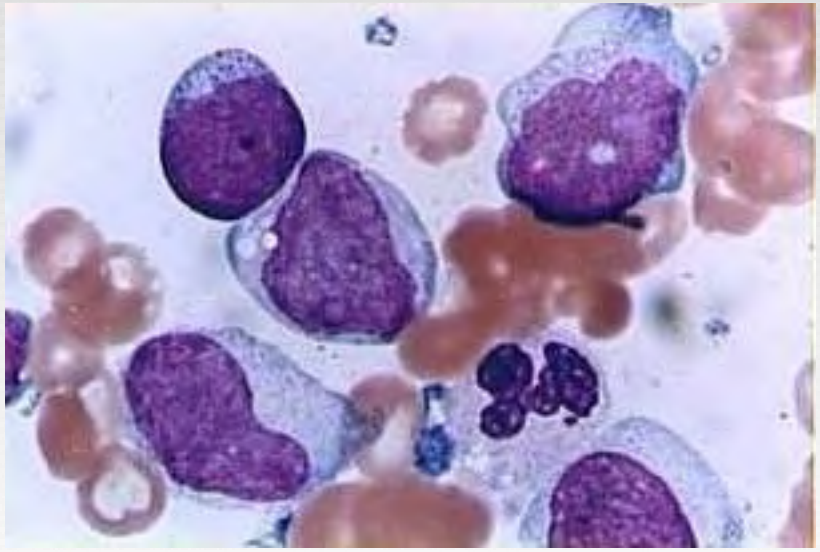
t(15;17)(q22;q12)

BLOOD SMEAR IN ACUTE MYELOMONOBLASTIC LEUKEMIA



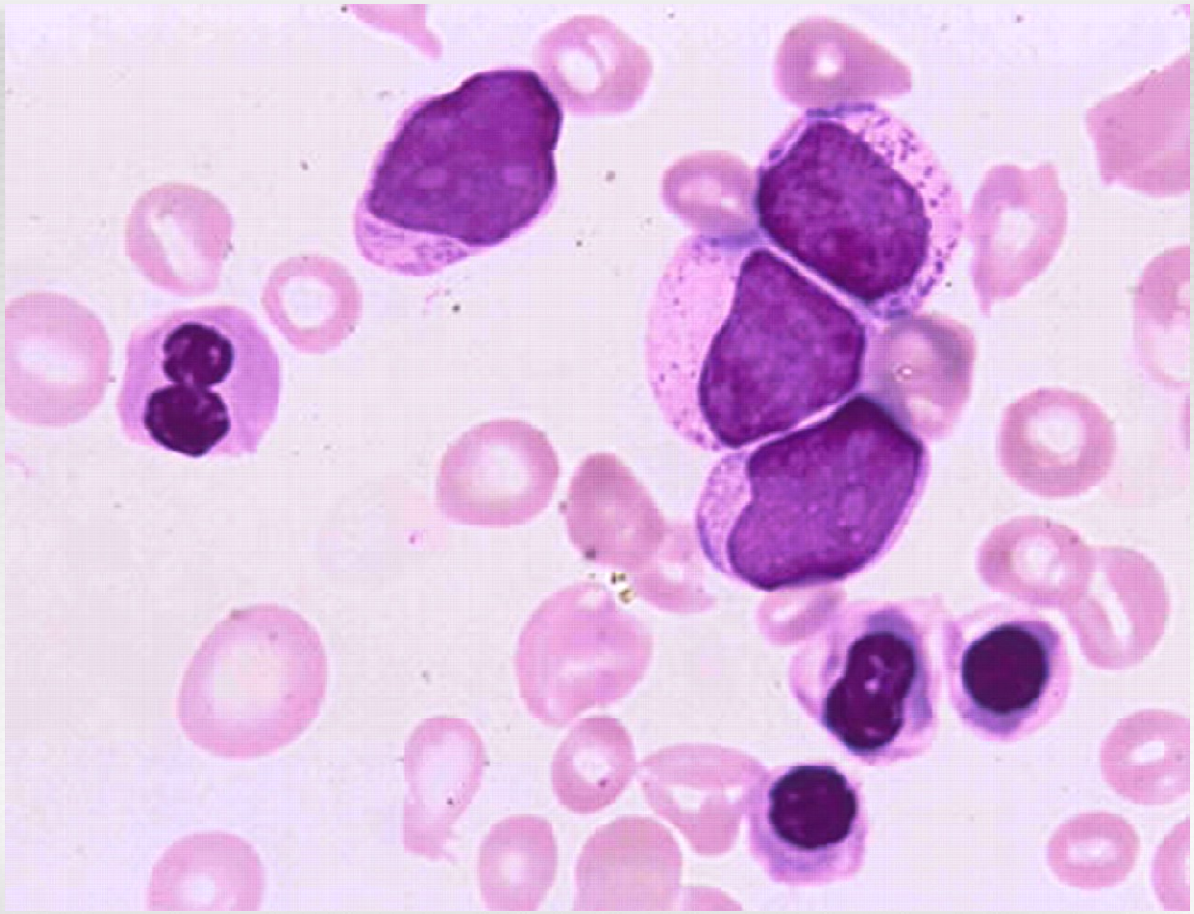
Faint granulation is, however, present in the cytoplasm of some of the blasts, suggesting myeloid lineage

BLOOD SMEAR IN ACUTE MYELOMONOBLASTIC LEUKEMIA



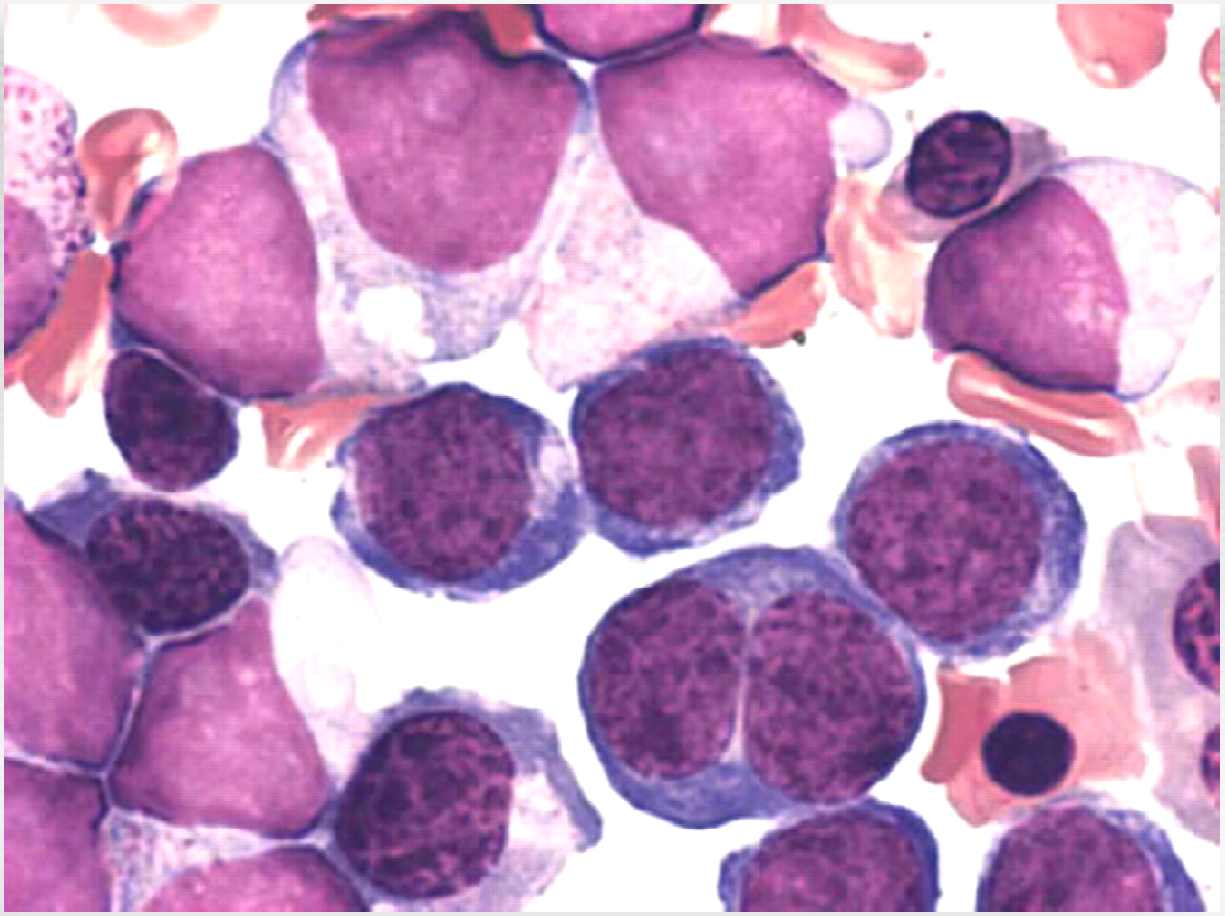
May-Giemsa, x1000

BLOOD SMEAR IN ACUTE ERYTHROLEUKEMIA



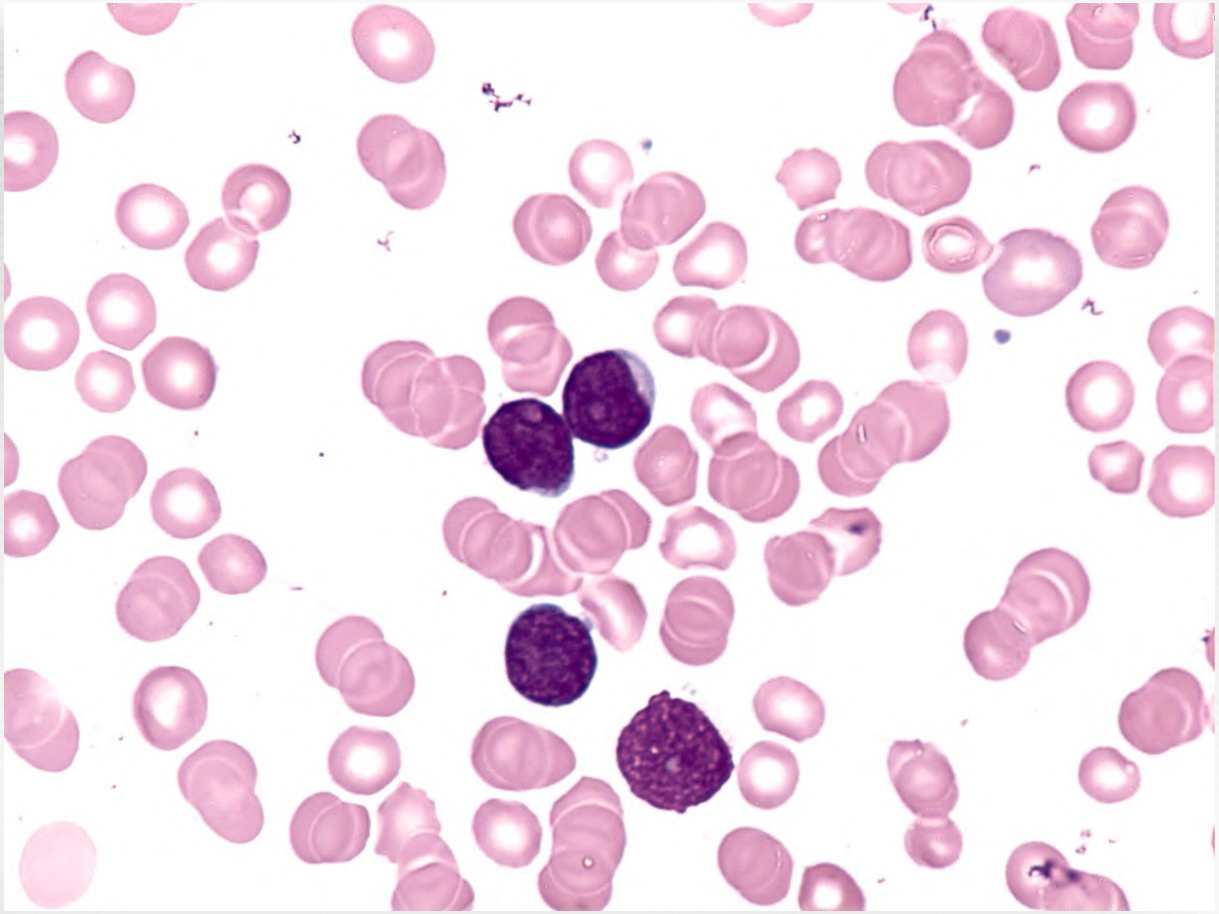
Faint granulation is, however, present in the cytoplasm of some of the blasts, suggesting myeloid lineage

BONE MARROW SMEAR IN ACUTE ERYTHROLEUKEMIA



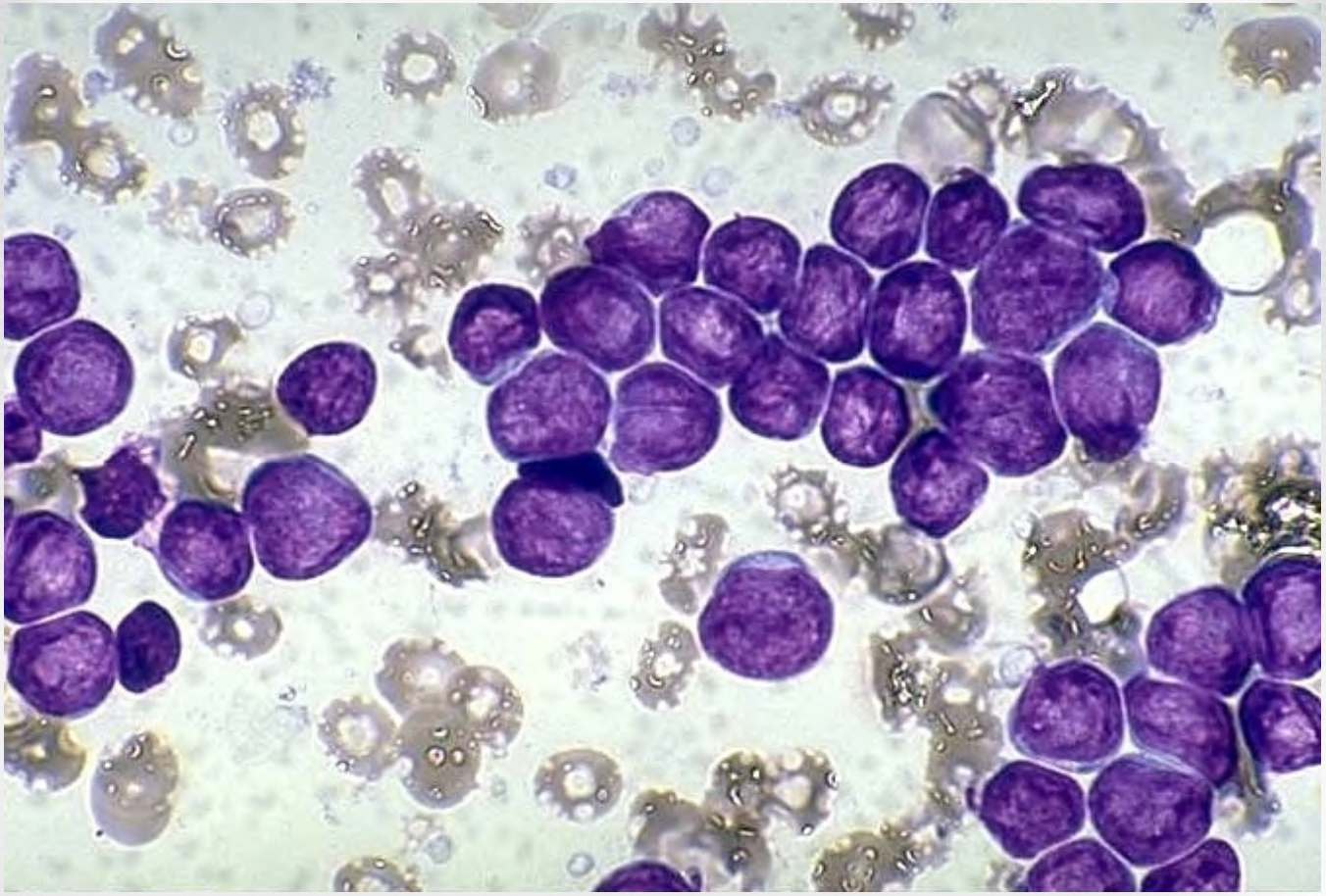
Bone marrow smear showing erythroblasts with diffusely red-stained cytoplasm *(PAS stain)*

BLOOD SMEAR IN ACUTE LYMPHOBLASTIIC LEUKEMIA L1



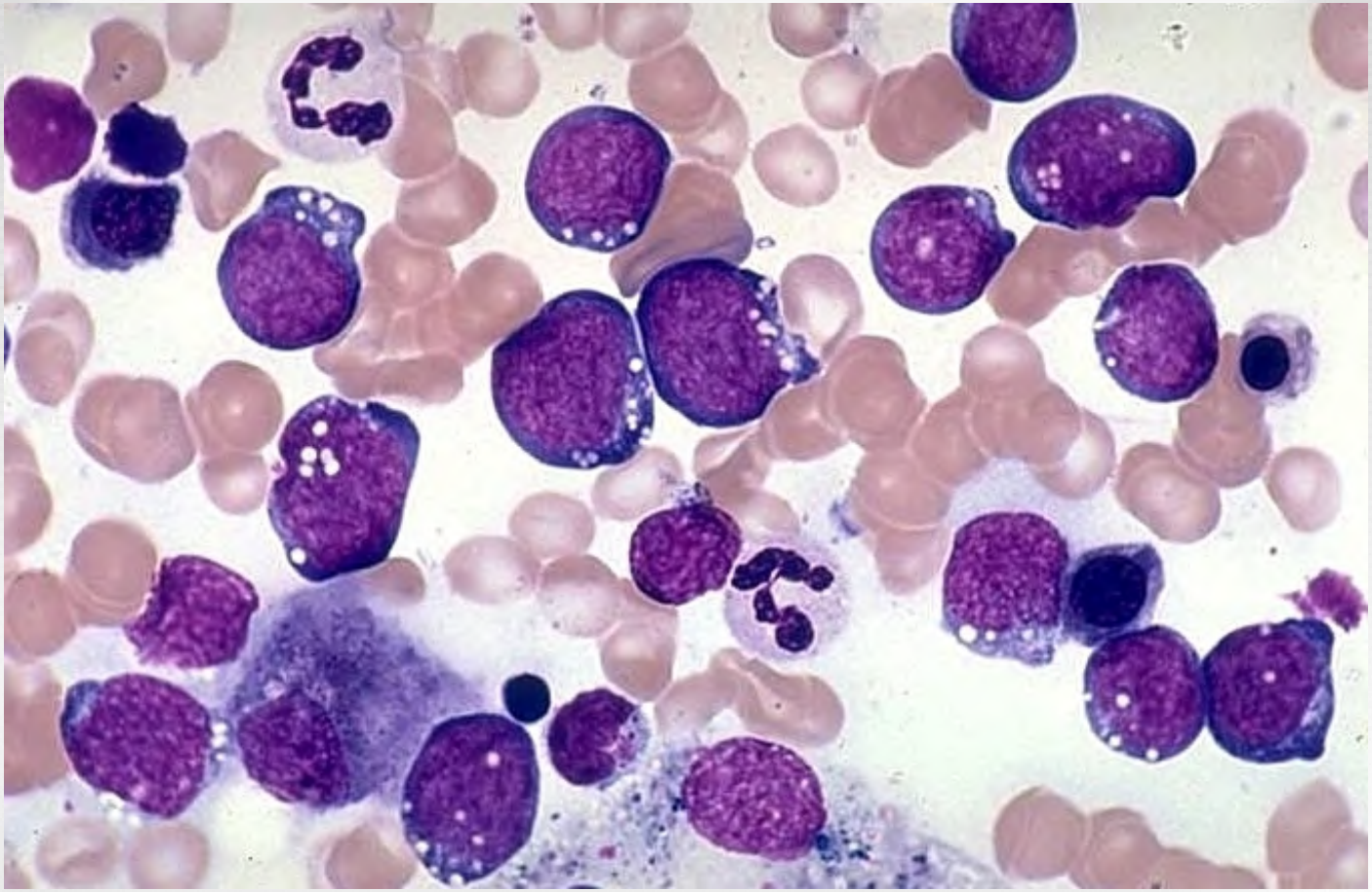
Lymphoid blasts with scant cytoplasm but prominent nucleoli

BONE MARROW SMEAR IN ACUTE LYMPHOBLASTIIC LEUKEMIA L1



May-Giemsa stain, x1000

BONE MARROW SMEAR IN ACUTE LYMPHOBLASTIIC LEUKEMIA L3



May-Giemsa stain, x1000

CYTOCHEMICAL REACTIONS IN ACUTE LEUKEMIAS

Reaction	M1	M2	M3	M4	M5	M6	L 1, 2, 3[b]
Peroxidase	+	+++	+++	+++	+	+ to ++[c]	Neg[d]
Sudan black B	+	+++	+++	+++	+	+ to ++[c]	Neg
NASDA[e]	+	+++	+++	+++	+++	+ to ++[c]	Neg
Fluoride inhibition	No	No	No	Variable	Yes	No	
PAS[f]	+	+	+	++	++	+	++ to +++
Lysozyme[d]	Neg	Low	Low	Inter-mediate	High	Low	Neg

+ = positive in a few cells; ++ = more than 25 % of cells are positive; +++ = 50 % or more of cells are positive.

[b]T - cell acute lymphocytic leukemias often show acid phosphatase positive in the Golgi region (Stein et al., 1976). Diffuse acid phosphatase reactivity is a characteristic of myeloblasts.

[c]Depending on the number of granulocytes.

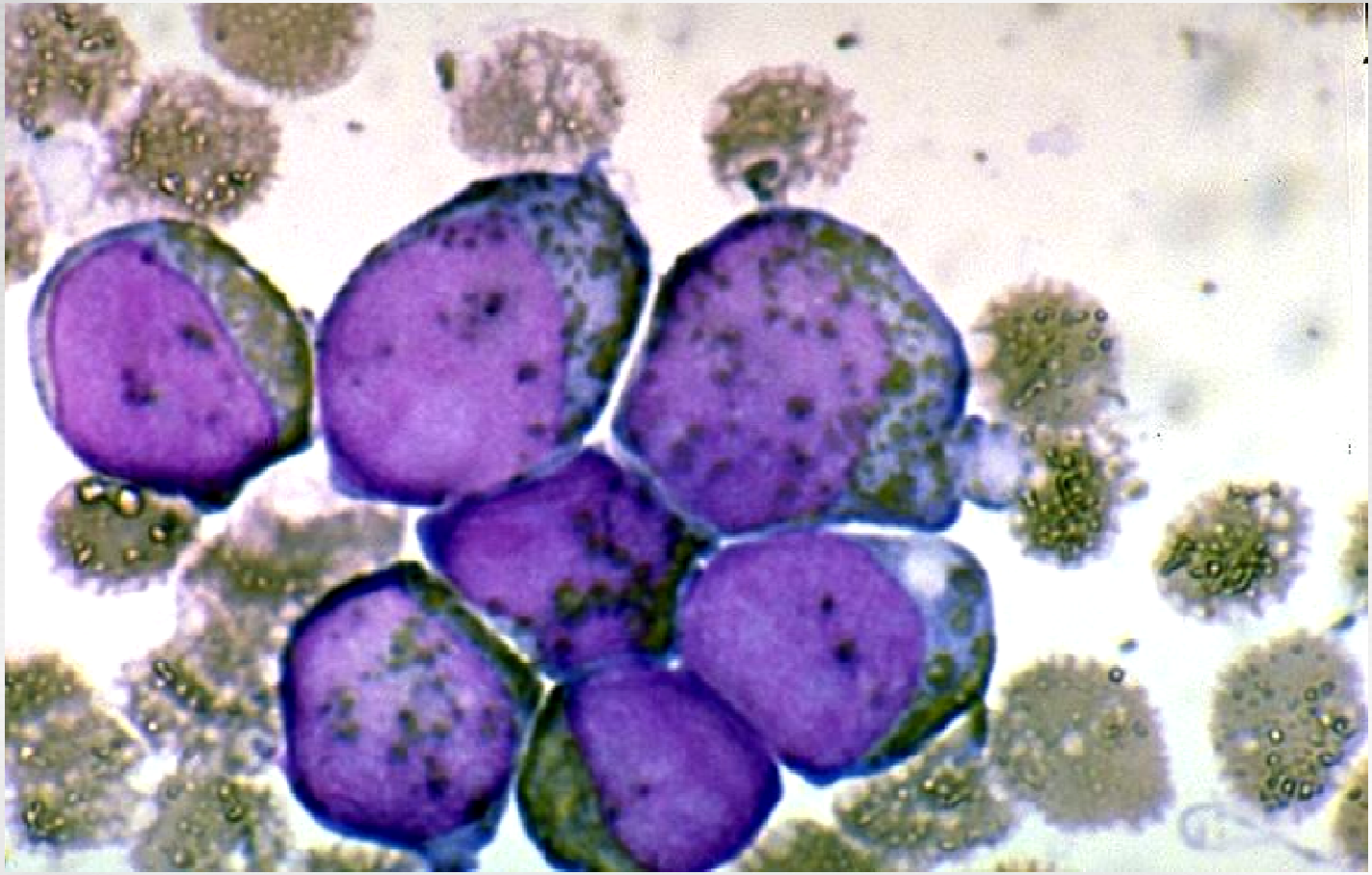
[d]Arbitrarily, when more than 3 % of the blasts are peroxidase positive, the disease is classified as other than acute lymphocytic leukemia.

[e]Naphthol ASD chloroacetate.

[f]Periodic acid - Schiff reaction.

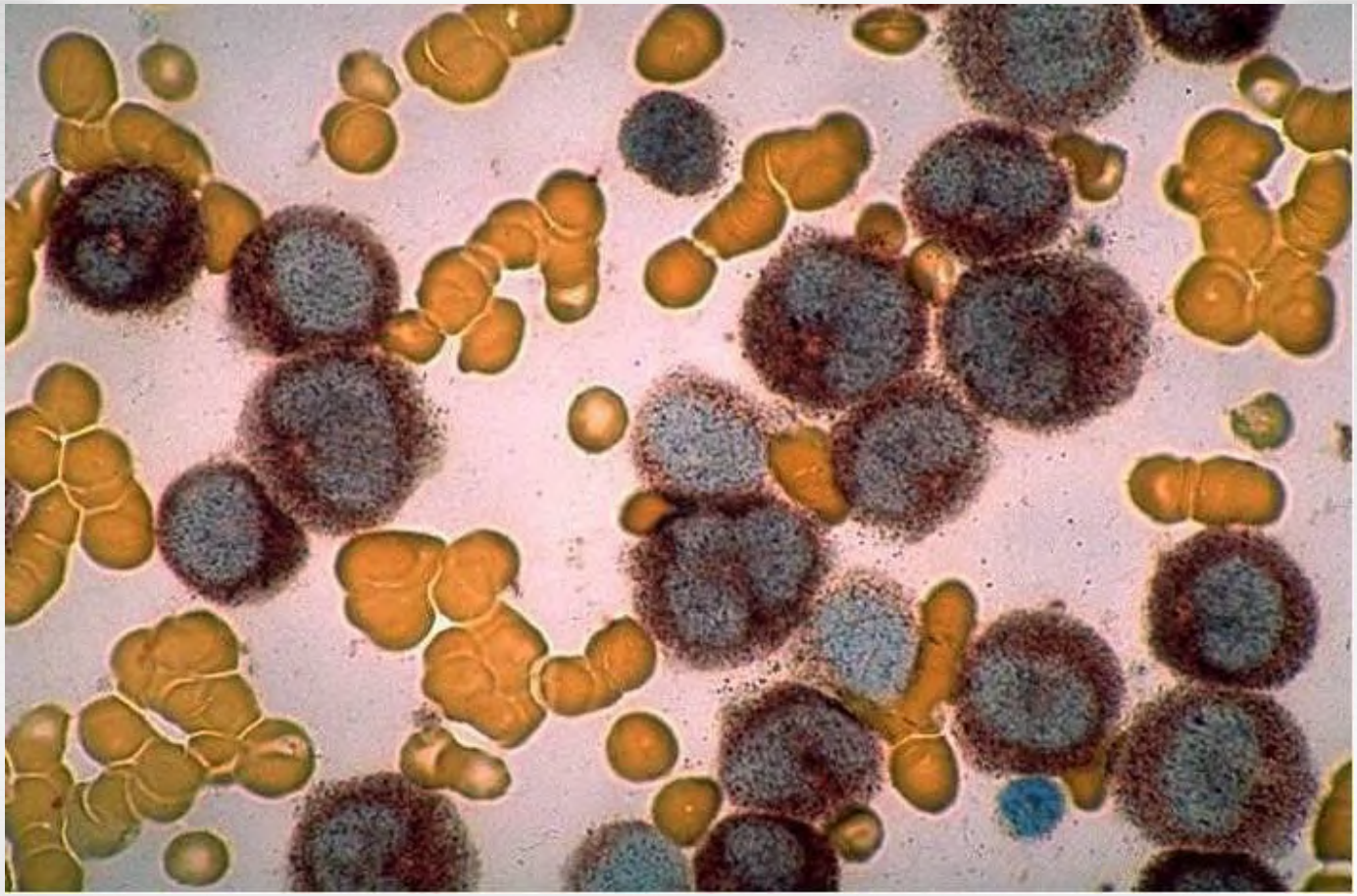
[d]In serum or urine.

BONE MARROW SMEAR IN ACUTE MYELOBLASTIC LEUKEMIA M1



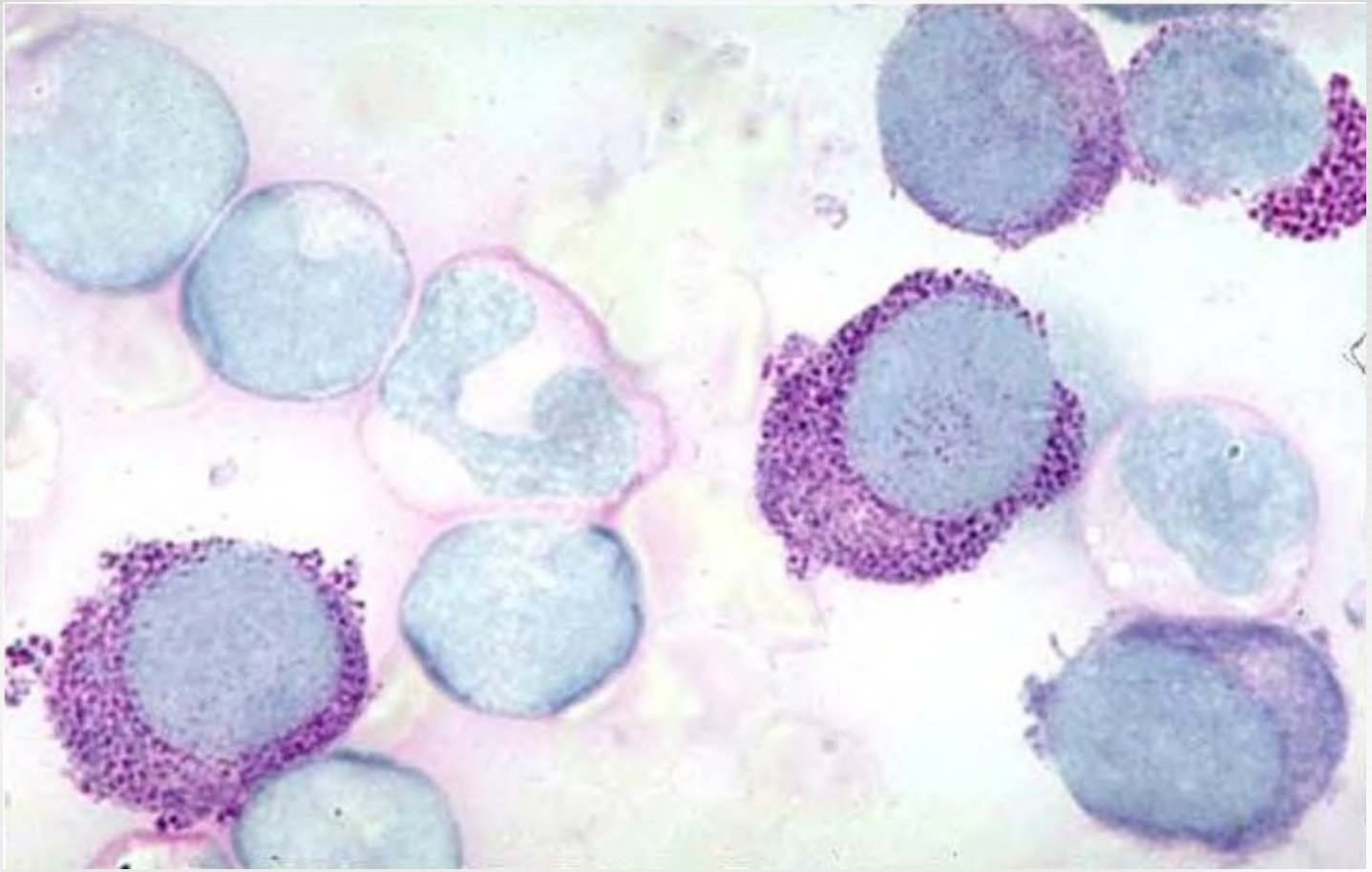
Peroxidase stain, x1000

BONE MARROW SMEAR IN ACUTE MONOBLASTIC LEUKEMIA M5b



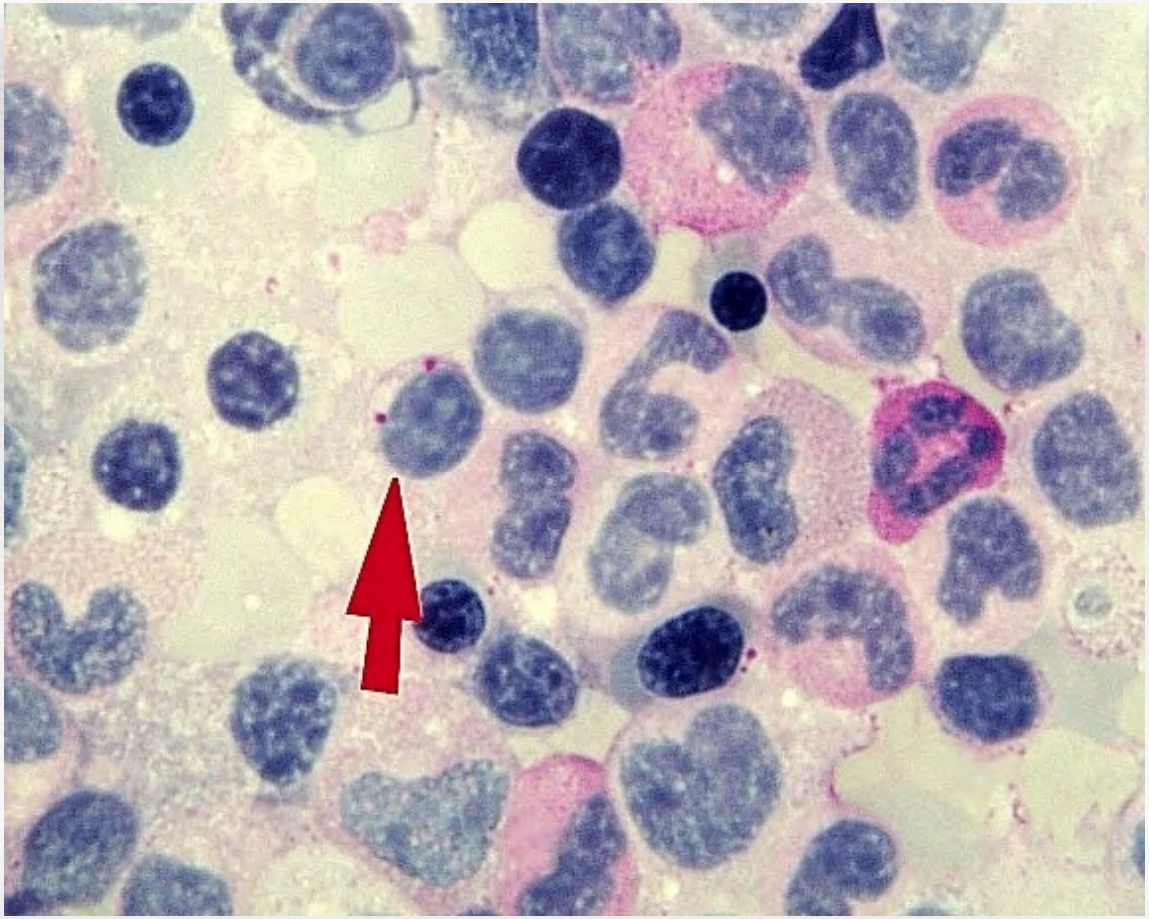
alpha-naphthyl butyrate esterase and chloroacetate esterase stain, x1000

BONE MARROW SMEAR IN ACUTE ERYTHROBLASTIC LEUKEMIA M6



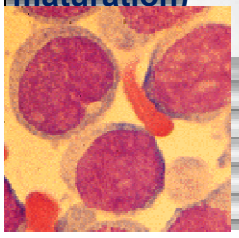
PAS stain, x1000

BONE MARROW SMEAR: PERIODIC-ACID SCHIFF (PAS) REACTION

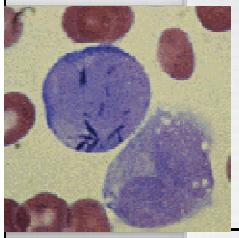
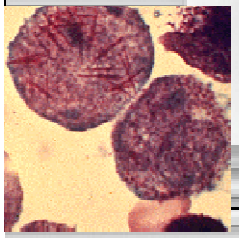


PAS stain, x1000

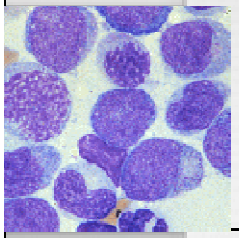
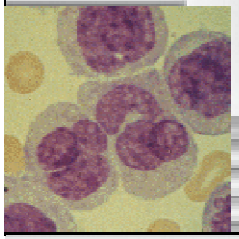
LEUKEMIA CLASSIFICATION

Classification	Morphology	Cytochemistry			General Markers		Myeloid Markers		B Cell Markers			T-Cell Markers			Platelet Marker	Other Markers
		MPO	NSE	PAS	HLA-DR	CD 34	CD 13	CD 33	CD 10	CD 19	kappa/ lambda	CD2	CD5	CD7	CD61	
AML M0 (undifferentiated)	Blasts lack definitive cytologic and cytochemical markers of myeloblasts (MPO -), but express myeloid lineage antigens & resemble myeloblasts ultrastructurally	-	-	-	+	+/-	+	+/-	-	-	-	-	-	-/+	-	
AML M1 (myeloblastic without maturation) 	Look like myeloblasts without any maturation. High N:C ratio, small nucleolus, grayish-pink cytoplasm	+	-	-	+	-/+	+	+/-	-	-	-	-	-	-/+	-	

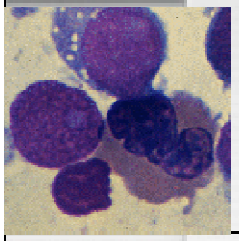
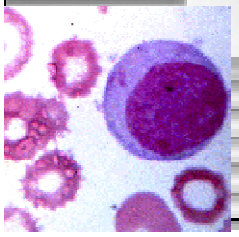
LEUKEMIA CLASSIFICATION

Classification	Morphology	Cytochemistry			General Markers		Myeloid Markers		B Cell Markers			T-Cell Markers			Platelet Marker	Other Markers
		MPO	NSE	PAS	HLA-DR	CD 34	CD 13	CD 33	CD 10	CD 19	kappa/ lambda	CD2	CD5	CD7	CD61	
AML M2 (myeloblastic with maturation) 	Full range of myeloid maturation through granulocytes. Auer rods present in most cases.	+	-	-	+	- /+	+	+ /-	-	-	-	-	-	-/+	-	
AML M3 (promyelocytic) 	Hypergranular promyelocytes , often with many Auer rods / cell.	++	-	-	-	-	+	+	-	-	-	-	-	-	-	t(15;17)

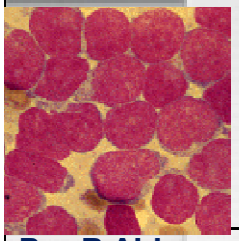
LEUKEMIA CLASSIFICATION

Classification	Morphology	Cytochemistry			General Markers		Myeloid Markers		B Cell Markers			T-Cell Markers			Platelet Marker	Other Markers
		MPO	NSE	PAS	HLA-DR	CD 34	CD 13	CD 33	CD 10	CD 19	kappa/ lambda	CD2	CD5	CD7	CD61	
AML M4 (myelomonocytic) 	Myelocytic and monocytic differentiation. Myeloid elements resemble M2 AML	+	+	+/-	+	-	+	+	-	-	-	-	-	-	-	inv(16) in M4-Eo
AML M5 (monoblastic/ monocytic) 	Monoblastic without (M5a) or with (M5b) maturation. Tissue infiltration, organomegaly, lymphadenopathy, common.	-	++	+/-	+	-	+	+	-	-	-	-	-	-	-	Occ. CD14

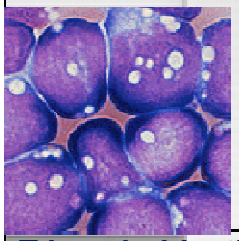
LEUKEMIA CLASSIFICATION

Classification	Morphology	Cytochemistry			General Markers		Myeloid Markers		B Cell Markers			T-Cell Markers			Platelet Marker	Other Markers
		MPO	NSE	PAS	HLA-DR	CD 34	CD 13	CD 33	CD 10	CD 19	kappa/ lambda	CD2	CD5	CD7	CD61	
AML M6 (erythroleukemia) 	Dysplastic erythroid precursors predominate, and within non-erythroid cells, > 30% are myeloblasts. "Chunky" PAS stain.	-	-	+	+/-	+/ -	-	-	-	-	-	-	-	-	-	Glyco-phorin A, CD71
AML M7 (megakaryo-blastic) 	Blasts of megakaryocyte lineage predominate. Blasts react with specific antibodies directed against GPIIb/IIIa or vWF.	-	-	+/-	+	+/ -	+ /-	+ /-	-	-	-	-	-	-	+	

LEUKEMIA CLASSIFICATION

Classification	Morphology	Cytochemistry			General Markers		Myeloid Markers		B Cell Markers			T-Cell Markers			Platelet Marker	Other Markers
		MPO	NSE	PAS	HLA-DR	CD 34	CD 13	CD 33	CD 10	CD 19	kappa/ lambda	CD2	CD5	CD7	CD61	
Pre-pre B ALL (lymphoblastic) 	L1 or L2 morphology – scant to moderate cytoplasm, few vacuoles.	-	-	-/+	+	+	-	-	+/-	+	-	-	-	-	-	TdT, hyper-diploidy
Pre-B ALL (lymphoblastic)	"Sting of pearls" PAS stain L1 or L2 morphology – scant to moderate cytoplasm, few vacuoles.	-	-	-/+	+	+/-	-	-	+	+	-	-	-	-	-	TdT, cytoplas-mic mu, t(1;19), t(11;23), t(9:22)

LEUKEMIA CLASSIFICATION

Classification	Morphology	Cytochemistry			General Markers		Myeloid Markers		B Cell Markers			T-Cell Markers			Platelet Marker	Other Markers
		MPO	NSE	PAS	HLA-DR	CD 34	CD 13	CD 33	CD 10	CD 19	kappa/ lambda	CD2	CD5	CD7	CD61	
Burkitt's leukemia/lymphoma (FAB type L3) 	Clonal kappa/lambda stain L3 morphology, w/ prominent vacuoles, abundant cytoplasm, deep basophilia	-	-	-	+	-	-	-	+/-	+	+	-	-	-	-	t(8;14), t(2;8), t(8;22)
T lymphoblastic Leukemia/ lymphoma	"String of pearls" PAS stain Often present with mediastinal mass.	-	-	-/+	+/-	-	-	-	-	-	-	+/-	+/-	+	-	TdT, CD1-/+, CD3-/+, CD4,8 double positive or double negative

Sources:
Cytochemistry, Immunophenotype, other markers: Laboratory Medicine, University of Washington, http://www.labmed.washington.edu/Division/Hematology/leuk.dx.html
Morphology: Handout, lecture notes; Robins *Pathologic Basis of Disease,* 6th edition, p 676

TREATMENT PHASES IN ACUTE LEUKEMIAS

I. Remission induction;

II. Postinduction intensification (remission consolidation);

III. Presymptomatic CNS therapy (is indicated in children with all morphological types of acute leukemias, in adults with acute myelomonoblastic (M4) and monoblastic (M5) leukemias, and in those with leukocyte count ≥ 50.0 x 10^9/l);

IV. Maintenance therapy (3 – 5 years).

INDUCTION AND CONSOLIDATION CHEMOTHERAPY IN ACUTE MYELOBLASTIC LEUKEMIAS

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Induction		Consolidation	
AML induction and consolidation			
Ara-C	200 mg/m^2 IV as continuous infusion × 7 d	Ara-C[b]	3 g/m^2 q12h IV as 2- to 3-h infusion on days 1, 3, 5; repeat q28d × 4 cycles
IDA[a]	12 mg/m^2 IV on days 1-3		
ALSG regimen			
Ara-C[b]	3 g/m^2 IV q12h as 2- to 3-h infusion on days 1, 3, 5, 7 (8 doses)	Ara-C	100 mg/m^2 IV as continuous infusion × 5 d
Daun	50 mg/m^2 IV on days 1-3	Daun	50 mg/m^2 IV × 2 d
VP-16	75 mg/m^2 IV × 7 d	VP-16	75 mg/m^2 IV × 5 d

ALSG = Australian Leukemia Study Group; Ara-C = cytarabine; Daun = daunorubicin; IDA = idarubicin; VP-16 = etoposide

[a] Idarubicin has been substituted for Daun, 45 mg/m^2, which had been the prevalent anthracycline used in clinical trials prior to 1993. Mitoxantrone, 10 mg/m^2 × 5 days, has also been used as an alternative.

[b] For patients < 60 years of age

INDUCTION AND CONSOLIDATION CHEMOTHERAPY IN ACUTE PROMYELOCYTIC LEUKEMIA M3

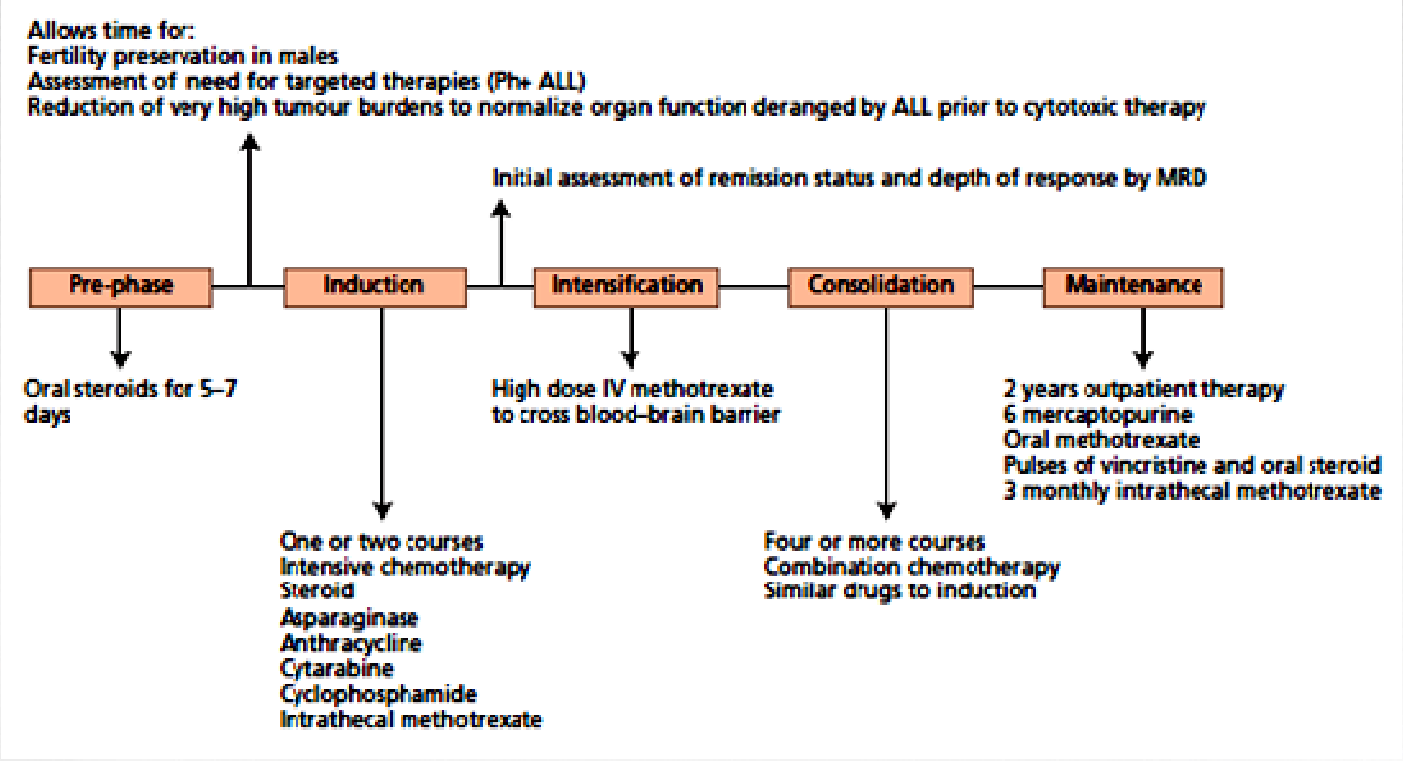
Induction		Consolidation	
European APL study			
ATRA	45 mg/m² PO daily in 2 divided doses for a minimum of 45 d and a maximum of 90 d	**Cycle 1** Repeat induction doses of Ara-C and Daun	
Ara-C	100 mg/m² IV as a continuous infusion × 7 d	**Cycle 2** Ara-C	2 g/m² IV infused over 1 h q12h × 8 doses (days 1-4)
		6-MP	90 mg/m²/d PO + MTX 15 mg/m²/wk PO × 2 years
		+/- ATRA	45 mg/m²/d for 15 d every 3 months
Daun	60 mg/m² IV × 3 d	Daun	45 mg/m² IV on days 1-3
or			
AIDA protocol		**Cycle 1**	
ATRA	45 mg/m² PO daily	Ara-C	1 g/m² IV infused over 6 h daily × 4 d
IDA	12 mg/m² IV on days 2, 4, 6, 8	*plus* IDA	5 mg/m²/d IV × 4 d (3 h after end of Ara-C infusion)
		Cycle 2 Mitox	10 mg/m²/d IV on days 1-5
		plus VP-16	100 mg/m² × 5 d by 1-h infusion 12 h after Mitox
		Cycle 3 IDA	12 mg/m² IV on day 1
		plus Ara-C	150 mg/m² SC q8h × 5 d
		plus 6-TG	70 mg/m² PO q8h × 5 d

Ara-C = cytarabine; ATRA = all-*trans*-retinoic acid; Daun = daunorubicin; IDA = idarubicin; Mitox = mitoxantrone; MTX = methotrexate; 6-TG = 6-thioguanine; 6-MP = 6-mercaptopurine; VP-16 = etoposide

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

TREATAMENT OF ACUTE LYMPHOBLASTIC LEUKEMIAS

(source: Postgraduate Haematology, Seventh Edition. Edited by A Victor Hoffbrand, Douglas R Higgs, David M Keeling and Atul B Mehta. © 2016 JohnWiley & Sons, Ltd. Published 2016 by JohnWiley & Sons, Ltd.)



INDUCTION AND CONSOLIDATION CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIAS: M.D. ANDERSON REGIMEN (HYPER-CVAD)

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Cyclophosphamide	300 mg/m^2 infused over 3 hr q12h × 6 doses (days 1-3)
Doxorubicin	25 mg/m^2/d continuous infusion over 24 hr × 2 days to begin 12 hr after last cyclophosphamide (days 4 and 5)
Vincristine	1.4 mg/m^2 (max 2 mg) IV on days 4 and 11
Dexamethasone	40 mg/d days 1-4 and 11-14
Alternate q21d with	
Methotrexate (MTX)	1 g/m^2 continuous infusion over 24 hr (day 1)
Ara-C	3 g/m^2 over 2 hr q12h × 4 doses (days 2 and 3)
Leucovorin rescue	50 mg PO at end of MTX infusion and then 25 mg PO q6h × 48 hr

INDUCTION AND CONSOLIDATION CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIAS

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Induction	Consolidation	CNS prophylaxis	Maintenance
BFM REGIMEN (*Blood* 85:123-131, 1988)			
Phase I	**Phase I[a]**	**Weeks 5-8**	6-MP 60 mg/m² PO on weeks 10-18 and 29-130
VCR 2 mg IV on days 1, 8, 15, 22	VCR 2 mg IV on days 1, 8, 15, 22	MTX 10 mg IT on days 31, 38, 45, 52	MTX 20 mg PO or IV weekly on weeks 10-18 and 29-130
DNR 25 mg/m² IV on days 1, 8, 15, 22	Adria 25 mg/m² IV on days 1, 8, 15, 22	Cranial RT[c] 2,400 cGy (given along with phase II induction)	
PSE 60 mg/m² PO on days 1-28	Dex 10 mg/m² PO on days 1-28		
L-Asp 5,000 IU/m² IV on days 1-14			
Phase II	**Phase II**		
CTX 650 mg/m² IV on days 29, 43, 57 (maximum, 1,000 mg)	CTX 650 mg/m² IV on day 29		
	Ara-C 75 mg/m² IV on days 31-34, 38-41		
Ara-C 75 mg/m² IV on days 31-34, 38-41, 45-48, 52-55	6-TG 60 mg/m² PO on days 29-42		
6-MP 60 mg/m² IV on days 29-57			

Adria = Adriamycin; Ara-C = cytarabine; BFM = Berlin-Frankfurt-Munster; CTX = cyclophosphamide; Dex = dexamethasone; DNR = daunorubicin; Dox = doxorubicin; L-Asp = L-asparaginase; 6-MP = 6-mercaptopurine; MTX = methotrexate; PSE = prednisone; RT = radiation therapy; 6-TG = 6-thioguanine; VCR = vincristine

[a] Begin week 20 [b] For patients > 60 years old, modify doses as follows: CTX, 800 mg/m² on day 21; DNR, 30 mg/m² on days 1-3; PSE, 60 mg/m² on days 1-7

[c] Cranial RT dose for prophylaxis is reduced to 1,800 cGy if patient is being considered for allogeneic BMT while in first CR

[d] Weeks 5-12 [e] Weeks 13-25 [f] Begin week 26 [g] Until 24 months from diagnosis

INDUCTION AND CONSOLIDATION CHEMOTHERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIAS

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Induction and early intensification	CNS prophylaxis and interim maintenance	Late intensification	Prolonged maintenance

CALGB REGIMEN (*Blood* 85:2025-2037, 1995)

Course I: Induction (4 wk)

CTX	1,200 mg/m^2 IV on day 1[b]
DNR	45 mg/m^2 IV on days 1-3[b]
VCR	2 mg IV on days 1, 8, 15, 22
PSE	60 mg/m^2/d PO/IV on days 1-21[b]
L-Asp	6,000 IU/m^2 SC on days 5, 8, 11, 15, 18, 22

Course II: Early intensification[d] (4 wk; repeat once)

MTX	15 mg IT on day 1
CTX	1,000 mg/m^2 IV on day 1
6-MP	60 mg/m^2/d PO on days 1-14
Ara-C	75 mg/m^2/d SC on days 1-4, 8-11
VCR	2 mg IV on days 15, 22
L-Asp	6,000 IU/m^2 SC on days 15, 18, 22, 25

Course III: CNS prophylaxis and interim maintenance[e] (12 wk)

Cranial RT	2,400 cGy on days 1-12
MTX	15 mg IT on days 1, 8, 15, 22, 29
6-MP	60 mg/m^2/d PO on days 1-70
MTX	20 mg/m^2 PO on days 36, 43, 50, 57, 64

Course IV: Late intensification[f] (8 wk)

Dox	30 mg/m^2 IV on days 1, 8, 15
VCR	2 mg IV on days 1, 8, 15
Dex	10 mg/m^2/d PO on days 1-14
CTX	1,000 mg/m^2 IV on day 29
6-TG	60 mg/m^2/d PO on days 29-42
Ara-C	75 mg/m^2/d SC on days 29, 32, 36-39

Course V: Prolonged maintenance[g]

VCR	2 mg IV on day 1 of q4wk
PSE	60 mg/m^2/d on days 1-5 of q4wk
MTX	20 mg/m^2 PO on days 1, 8, 15, 22
6-MP	80 mg/m^2/d PO on days 1-28

RESPONSE CRITERIA FOR TREATMENT OF ACUTE LEUKEMIAS

Complete remission: **the disappearance of clinical and hematological evidence of acute leukemia; in the bone marrow aspirates the blast cells count does not exceed 5%, lymphocytes ≤ 30%.**

Partial remission: **the disappearance of clinical symptoms of the disease, normalization of the blood count; in the bone marrow aspirates the blast cells count does not exceed 20%.**

Clinical and hematological improvement: **the significant regression of main clinical syndromes; hemoglobin exceeds 90g/l, mature granulocytes constitute ≥2.0 x 10^9/l, thrombocyte count is ≥ 50.0 x 10^9/l, the absence of positive changes in the bone marrow aspirates.**

Response failure.

THANK YOU FOR YOUR ATTENTION!