ACUTE LEUKEMIAS

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Introduction

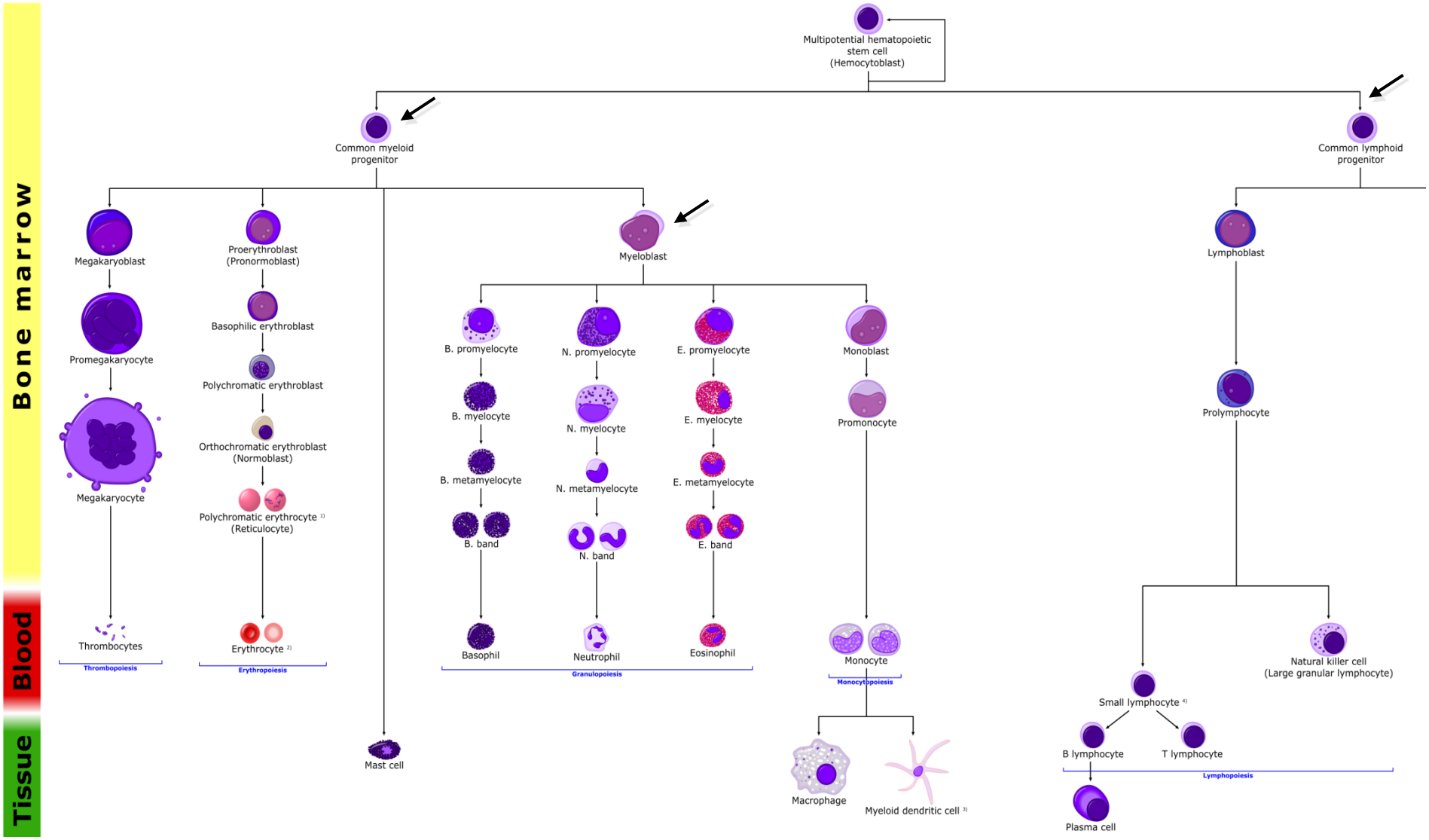
heterogeneous group of diseases

- malignant transformation of haemopoietic stem cell associated with total or partial loss of the ability to differentiate while maintaining the ability to proliferate

- accumulation of blasts in the bone marrow suppresses normal hematopoiesis and leads to granulopenia, anemia and thrombocytopenia symptoms

- leukemia transformation affects cells of myeloid or lymphoid lineage division into 2 basic groups: AML and ALL

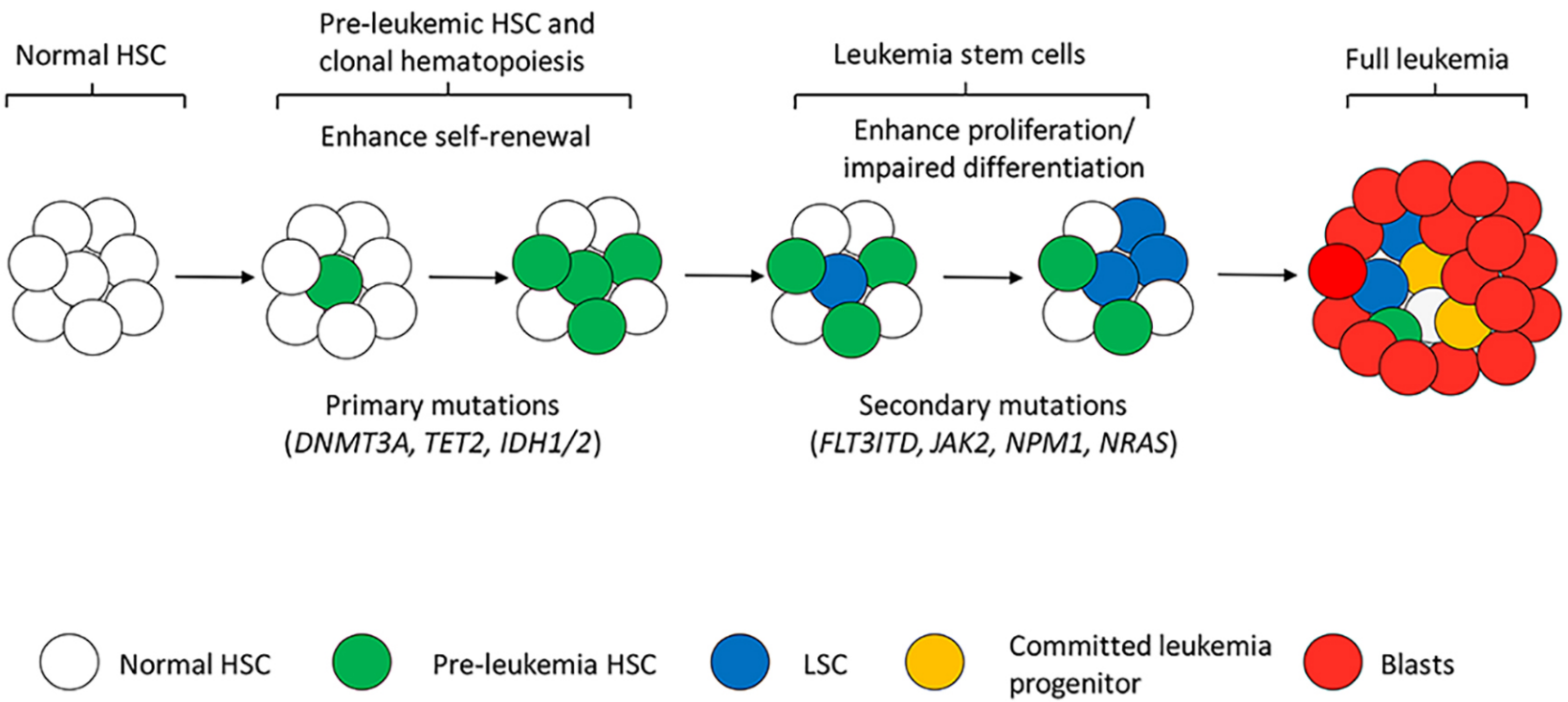
Myeloid and lymphoid differentiation



- leukemia transformation occurs at different degrees of differentiation

ACUTE MYELOID LEUKEMIA (AML)

Leukemogenesis

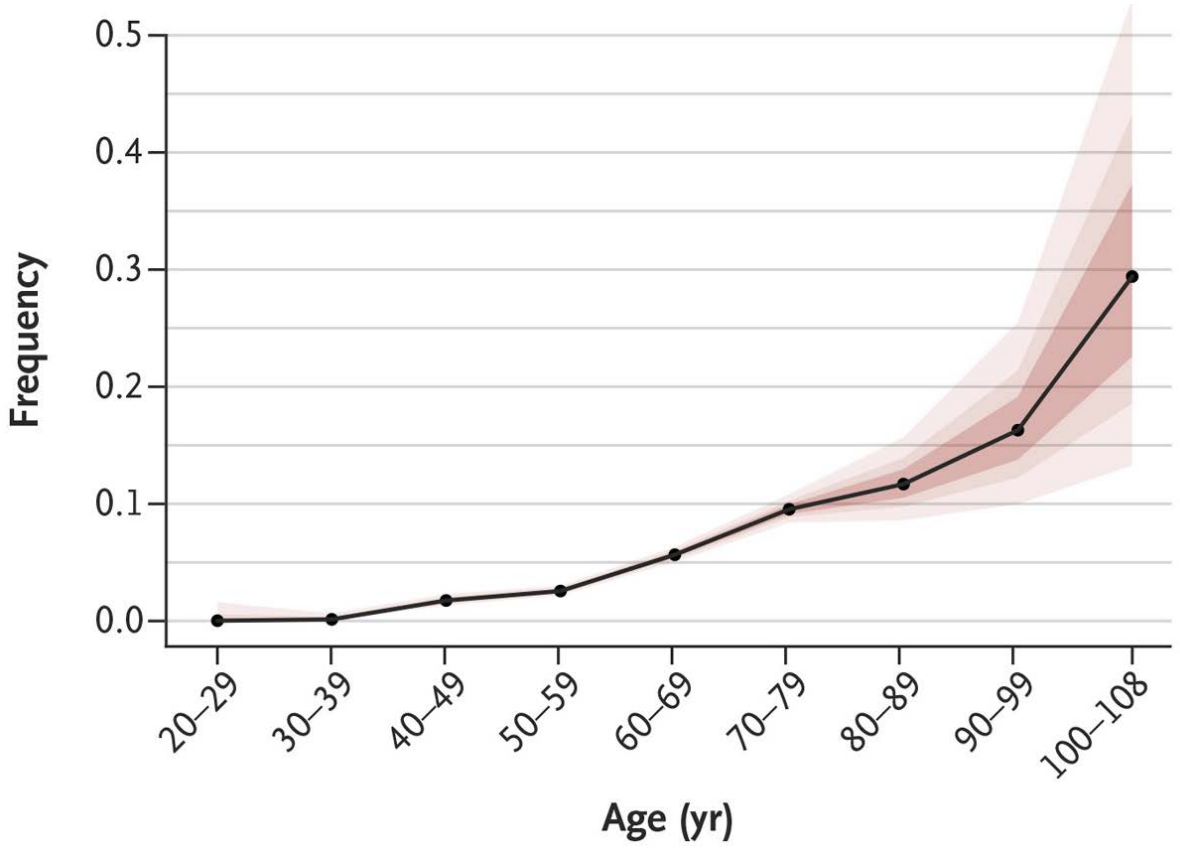


- mutations associated with myeloid malignancies develop in healthy individuals, resulting in clonal hematopoiesis of indeterminate potential (CHIP)
- the emergence of a secondary mutation will increase the proliferative capacity of preleukemic cells
- and allows the formation of leukemic stem cells and subsequently grows into a leukemic clone

Cellular and Molecular Medicine Research, 2018

Clonal hematopoiesis and age

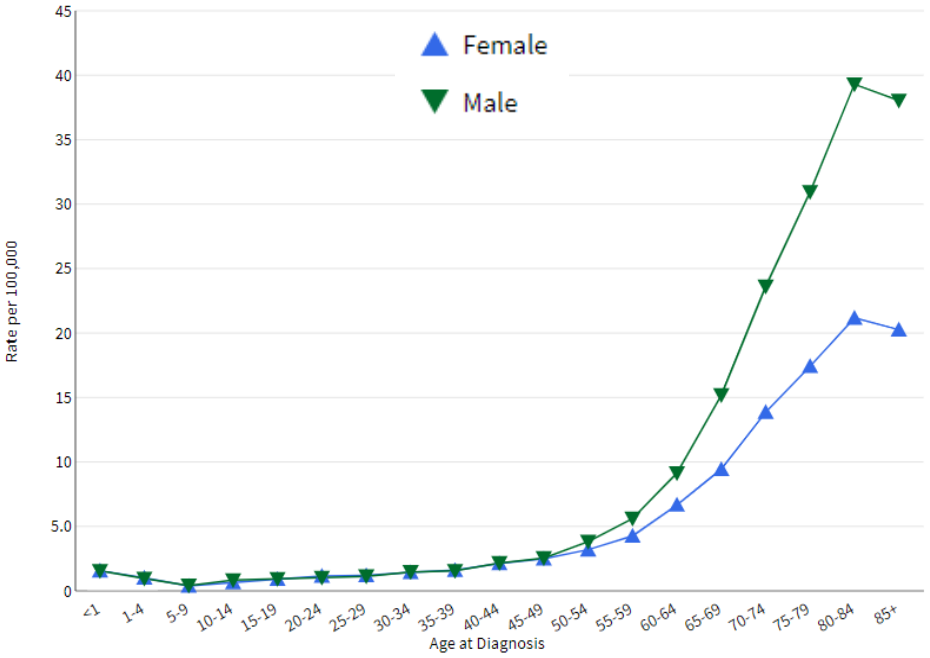
- somatic mutations are rare in people under 40 years of age, but in 70 years of age they occur in about 10%

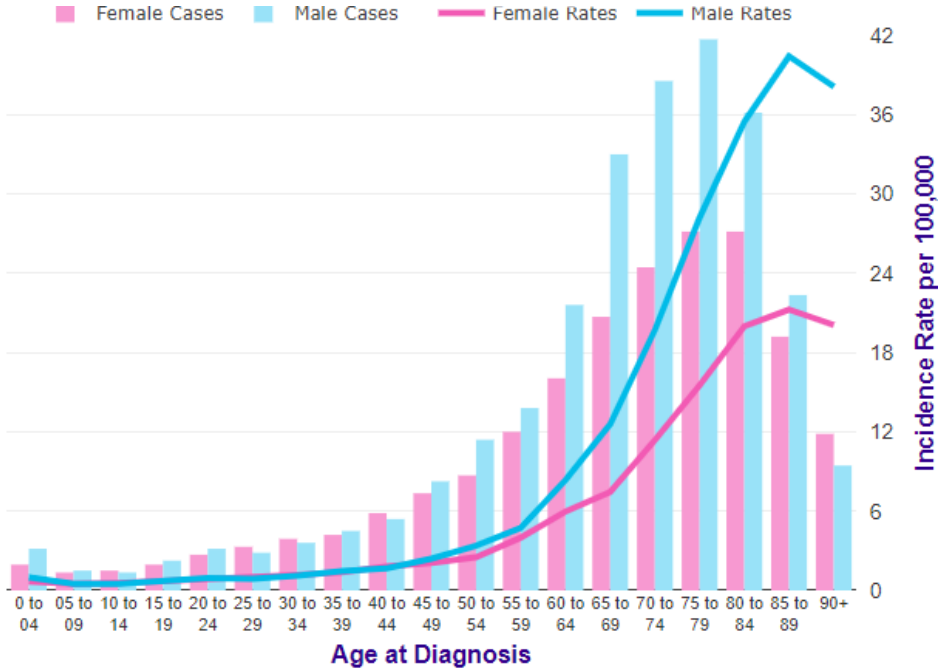


Jaiswal S, N Eng J Med 2014

Epidemiology

- incidence ca 3.5 - 4.0 per 100 000 / year
- CR: incidence - about 350 cases / year, prevalence - about 1500 cases / year
- the incidence increases with age, especially after 50 years
- the median age at the time of diagnosis is about 67 - 68 years



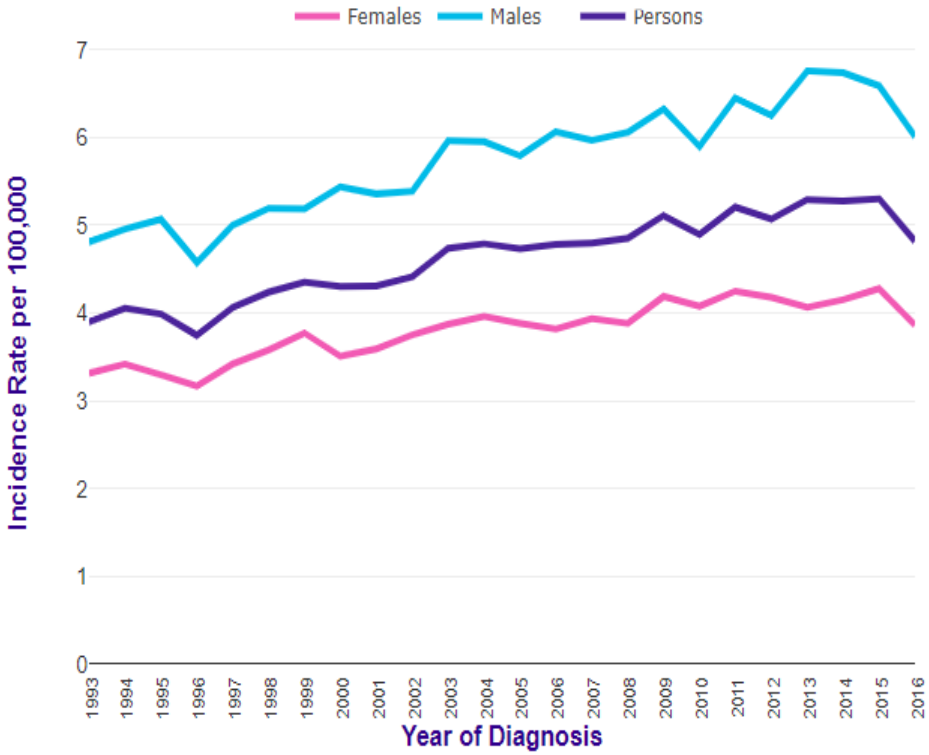


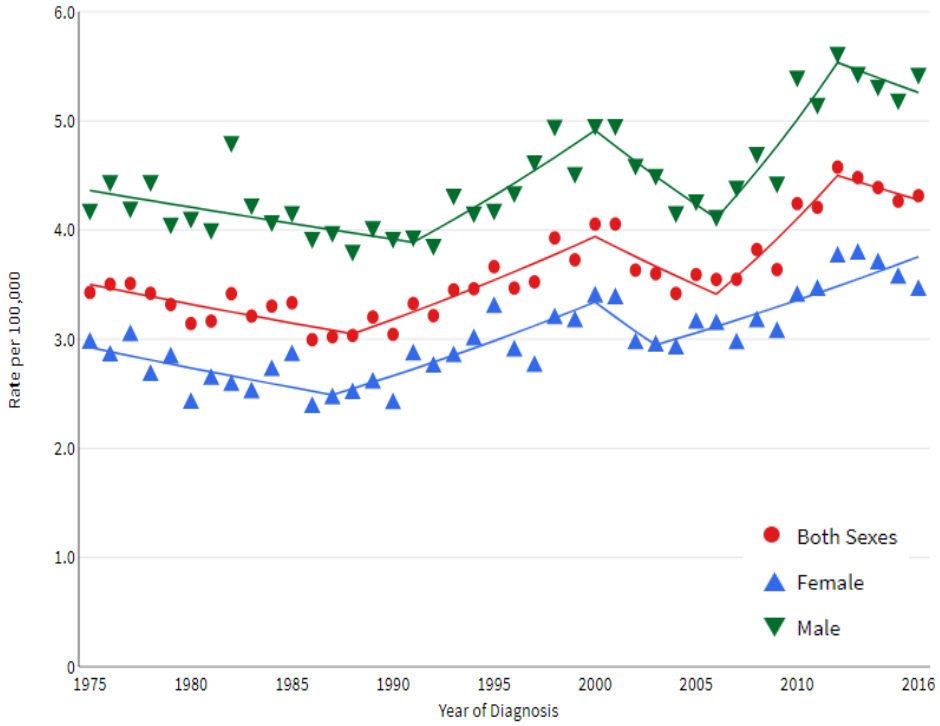
NIH, SEER data, USA

Cancer Research data, UK

Development of incidence over time

- incidence increases slightly





Cancer Research data, UK

NIH, SEER data, USA

AML classification

❶ etiology

⇨primary x secondary

❷ morphology

⇨ FAB

❸ etiopatogenetic

⇨ WHO

Etiology

I .: **mostly unknown:** "de novo" AML (= primary AML)

II .: **hereditary / "internal" disposition**: ➡ Down's syndrome, neurofibromatosis, sy ataxia - teleangiectasia, Fanconi anemia

III .: **external factors** ➡ ionizing radiation ➡ pesticides, benzene

IV .: **'treatment-related / induced'**: after chemo / radiotherapy (= secondary AML)

V. in the context of **ongoing hematological disease** ➡ blastic phase of chronic myeloid leukemia, myelofibrosis, etc.

Secondary („treatment induced“) AML

~ 10 (- 20) % of all AML

increasing incidence ← **cytostatic treatment** ←

- more frequent indications
- higher doses
- new indications
- elderly patients

↑ longer survival of patients

the consequence of progress and success in the treatment of malignancies

→ **secondary AML after chemo / radiotherapy**

= major adverse prognostic factor

AML classification

❶ etiology

⇨ primary x secondary

❷ morphology

⇨ FAB

❸ etiopatogenetic

⇨ WHO

FAB classification - 1985

M 0 - **undifferentiated**

M 1 - 2 - **myeloid without / with maturation**

M 3 - **promyelocytic**

M 4 - **myelomonocytic** **(Eo - with eosinofilia)**

M 6 - **erytroid** - **erytroleukemia**

M 7 - **megakaryoblastic**

diagnostic criteria: blast count, morphology, maturation
FAB classification is only of auxiliary importance today

AML classification

❶ etiology

⇨ primary x secondary

❷ morphology

⇨ FAB

❸ etiopatogenetic

⇨ WHO

WHO classification AML (since 1997)

I. AML with reccurent cytogenetic aberration
- ⇨ AML with t(8;21)
- ⇨ acute promyelocytic leukemia, AML with t(15;17)
- ⇨ AML with abnormal eosinophils, AML with (inv(16)
- ⇨ AML with 11q23 (MLL)

II. AML with multilineage dysplasia
- ⇨ with previous MDS
- ⇨ without previous MDS

III. AML and MDS, therapy induced
- ⇨ Alkylating cytostatics (melphalan)
- ⇨ topoisomerase II inhibitors (etoposid)

IV. AML otherwise uncategorized

WHO ➡ takes into account prognostic factors (cytogenetic abnormalities)

klasifikace ➡ distinguishes clinically and biologically different groups

AML and prognosis

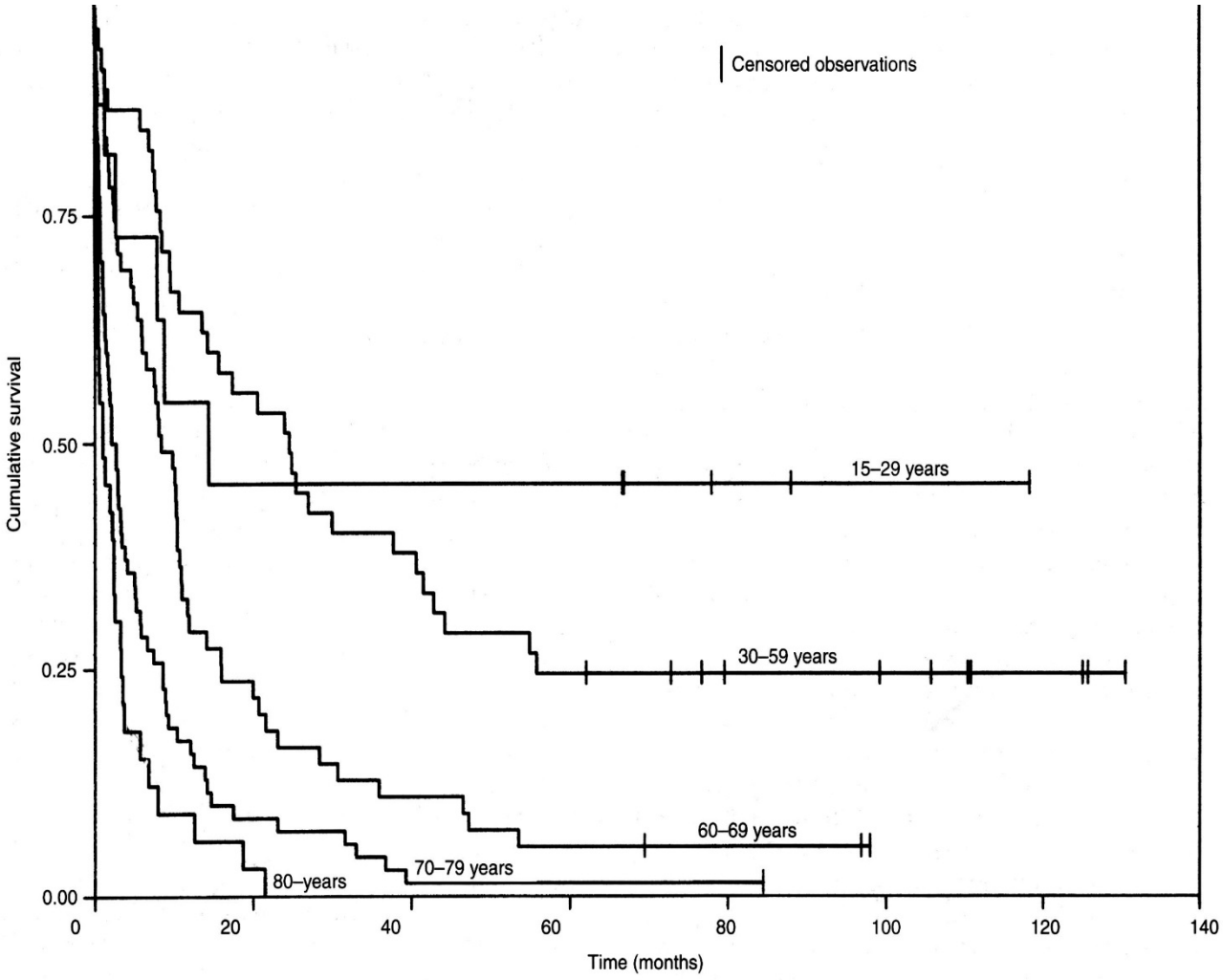
Patient side factors:

- age
- overall status
- comorbidity

Disease-related factors:

- cytogenetics and molecular genetics
- previous haematological disease (MDS)
- secondary etiology (after previous chemotherapy)

Dependence of overall survival on age



- age itself is a risk factor for AML

Aström M, Brit J Cancer 2000

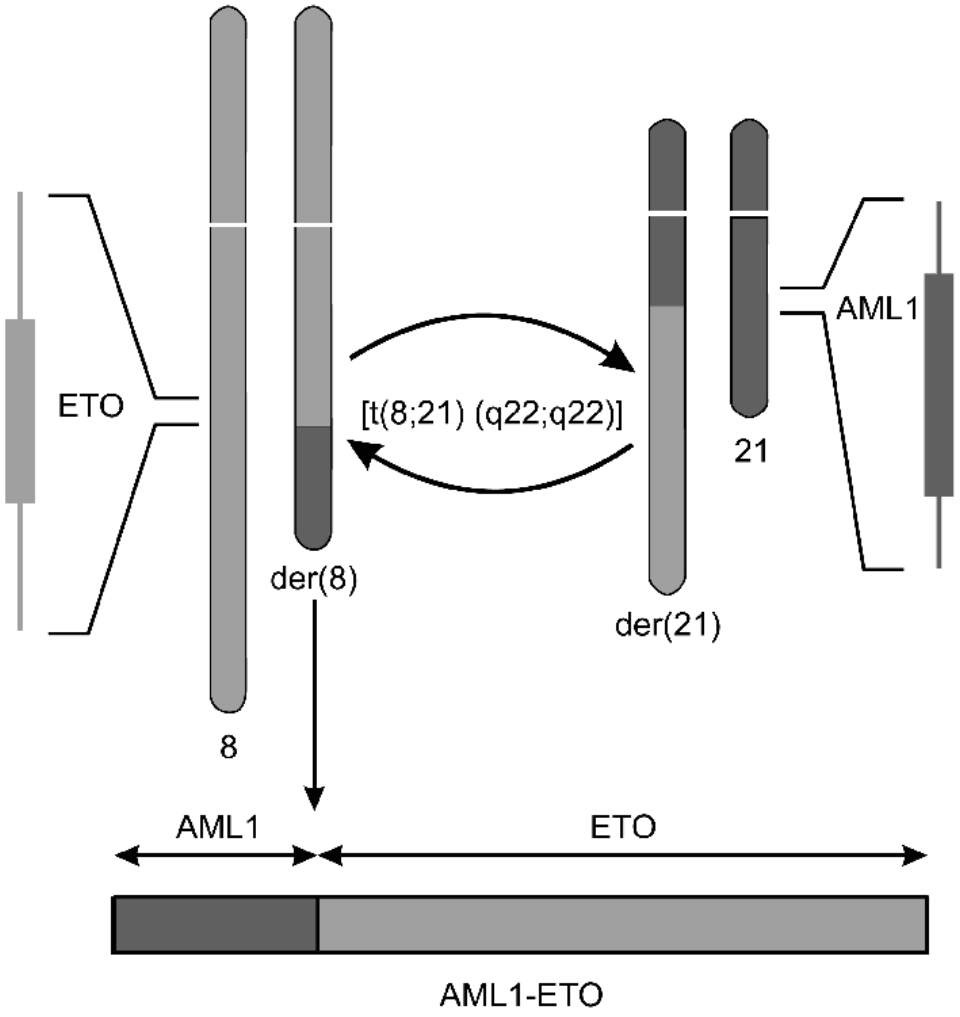
Cytogenetic stratification

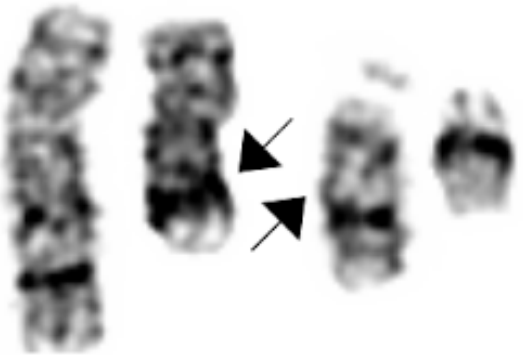
Risk group	**cytogenetic abnormalities**
low risk	inv(16), t(16;16), t(8;21), t(15;17)
Intermediate risk	normal cytogenetics +8 isolated t(9;11) other chromosomal abnormalities
high risk	komplex karyotype (≥ 3 abnormalities) monosomal karyotype -5, 5q-, -7, 7q-, 11q23 other than t(9;11) inv(3), t(3;3), t(6;9), t(9;22)

balanced aberration: translocation, inversion …
unbalanced: loss or recovery of part or all of the chromosome

NCCN Clinical Practice Guidelines, 2018

Example: chromosomal aberrations: AML t (8; 21)
(example of reciprocal "balanced" translocation)

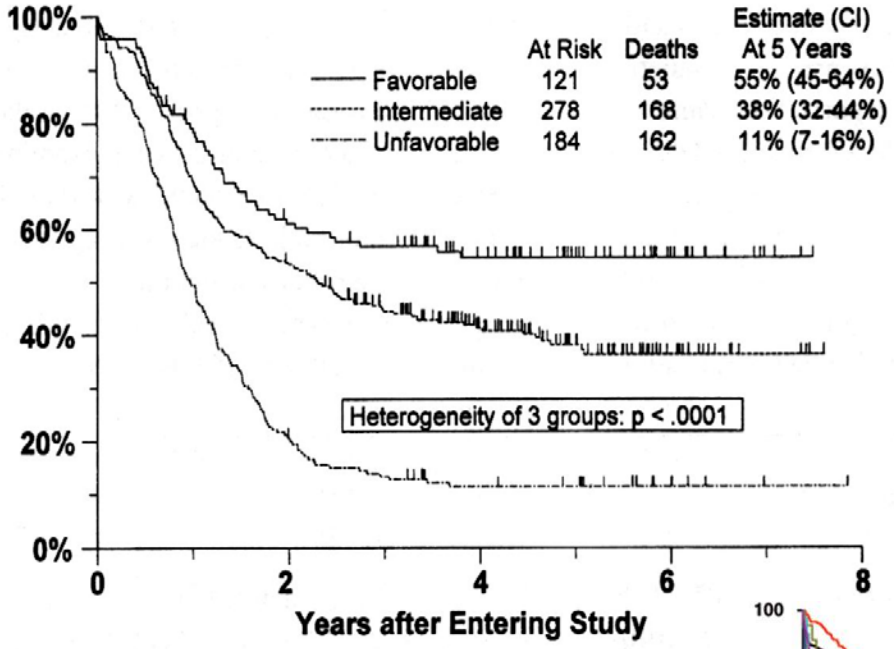


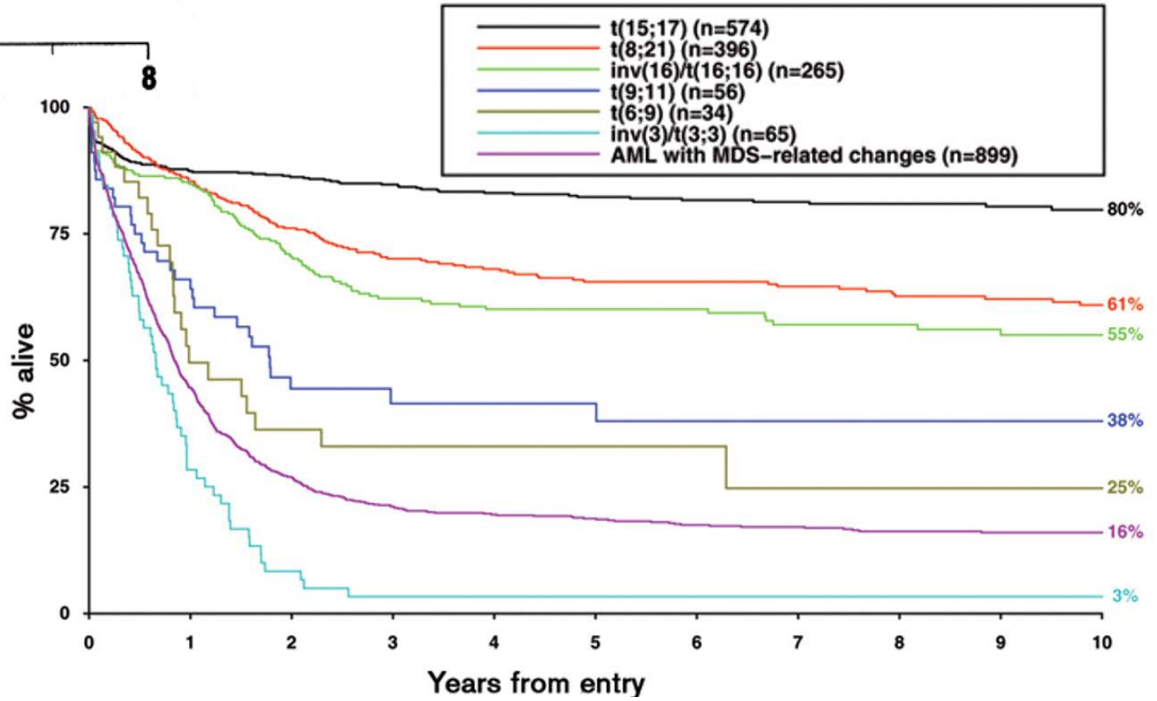


t(8;21)(q22;q22)

translocation results in the generation of the AML1-ETO fusion gene

Overall survival of AML by cytogenetic prognostic groups



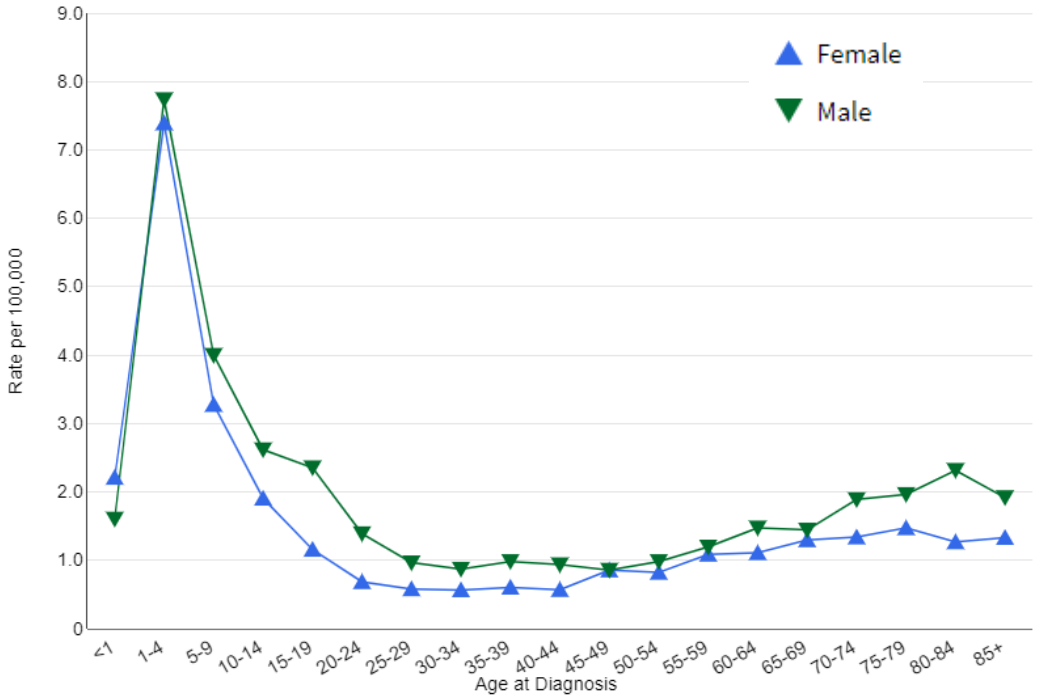


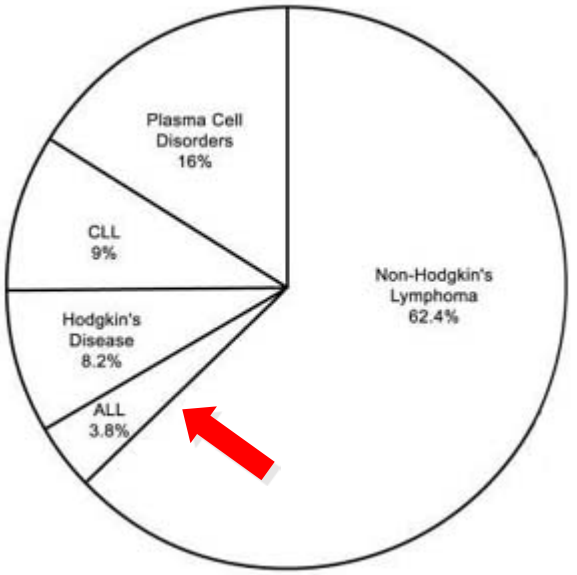
Slovak ML, Blood 2000; MRC AML10, AML12, AML15

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Epidemiology ALL

ALL - the most common tumor in childhood (1/3 of all tumors and about 75% of leukemias)
- but only 20% of adult leukemias





relative frequency of lymphoid malignancies

2 peaks of incidence: childhood (peak between 3 and 5 years)
~ from about 50 years with further growth with age

data seer.cancer.gov 2012 - 2016

Etiology

similar to AML but less frequently induced by treatment:

- genetic syndromes (Down sy, Fanconi anemia, neurofibromatosis… ..)
- external factors - radiation, benzene, pesticides
- infection (HTLV-1, EBV)

in adults (similar to AML), ALL develops most often obtained by somatic mutation

(genetic alteration of lymphoid precursor cell with dysregulation of proliferation and subsequent clonal expansion)

Leukemogenesis in ALL

mechanism similar to AML

2 principles:

a. activation of proto-oncogene by juxtaposition of specific gene promoter (IgH, TCR) ➡ deregulation of protein expression
= quantitative change - eg t (8; 14)

b. generation of a new fusion gene ➡ encodes transcription factors
= **qualitative change** - t (9; 22)

Morphological classification ALL

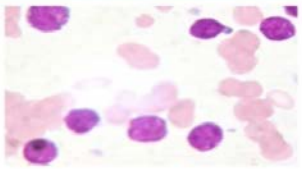
FAB: L1 - L3 according lymfoblasts morfology

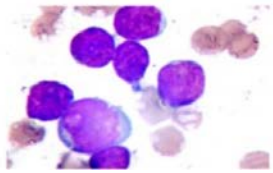
but: L1, L2 - no prediction of genetic abnormalities or clinical behavior

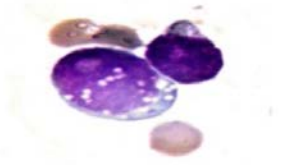
L3 - exclusively leukemising Burkitt's lymphoma

today: L1 - L3 nonerelevant, not used

	L1	L2	L3 (Burkitt)
Size:	Small	Large & small	Large cells
Heterogeneity:	Homogeneous	Heterogeneous	Homogeneous
Cytoplasm:	- Very thin rim. - Vacuoles +/-.	- Abundant cytoplasm. - Vacuoles +/-.	Deeply basophilic & vacuolated cytoplasm.
Nucleus:	Regular nuclear membrane and inconspicuous nucleoli	Irregular nuclear membrane and prominent nucleoli	Nucleus has loose arrangement of chromatin and inconspicuous nucleoli.
N/C ratio:	High nuclear cytoplasmic ratio	Lower N/C ratio	Lower N/C ratio







Immunophenotype ALL

20 - 25% T – ALL: younger age, significant leukocytosis, mediastinal tumor

70 - 75% B – ALL:

<u>immunophenotype allows:</u>

- division into T- or B-ALL
- division into subgroups according to the degree of blast differentiation

↓

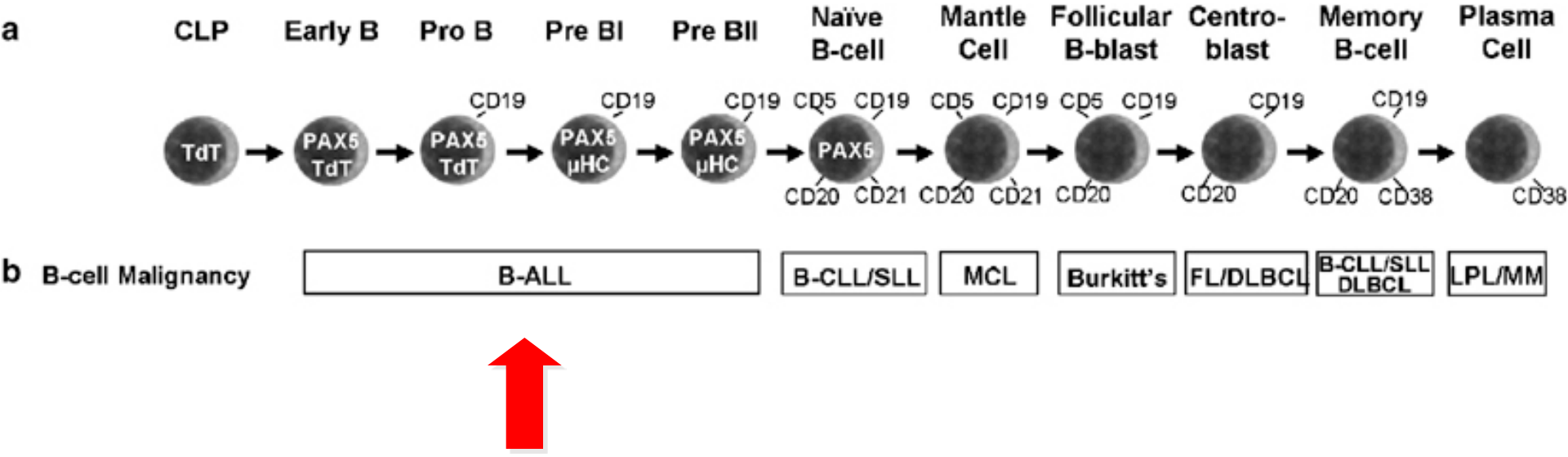
a number of "immunophenotypic" classifications (EGIL, GEIL)
(pro-B-pre-B-common-B-mature-B)

Lymphoid series differentiation

classification is based on normal lymphocyte differentiation

example: ⇨ normal stages of B-cell differentiation and their malignant counterparts

⇨ similarly for T-ALL



B-acute lymphoblastic leukemia is based on immature B-lymphocytes

WHO classification of immature (precursor) lymphoid malignancies

B-cell lymphoblastic leukemia/lymphoma, not otherwise specified
B-cell lymphoblastic leukemia/lymphoma, with recurrent genetic abnormalities
B-cell lymphoblastic leukemia/lymphoma with hypodiploidy
B-cell lymphoblastic leukemia/lymphoma with hyperdiploidy
B-cell lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2)[*BCR-ABL1*]
B-cell lymphoblastic leukemia/lymphoma with t(v;11q23)[*MLL* rearranged]
B-cell lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22)[*ETV6-RUNX1*]
B-cell lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3)[*TCF3-PBX1*]
B-cell lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32)[*IL3-IGH]*
B-cell lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (iAMP21)
B-cell lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases receptors (BCR-ABL–like ALL)
T-cell lymphoblastic leukemia/lymphomas
Early T-cell precursor lymphoblastic leukemia

Leukemia vs. lymphoma

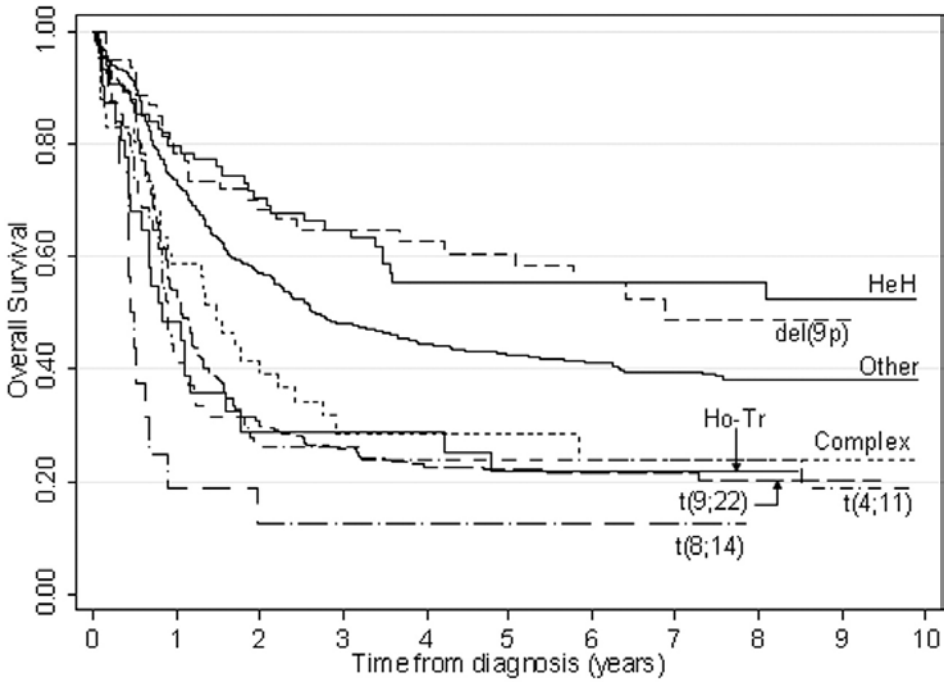
lymphoblastic leukemia vs. lymphoblastic lymphoma:

- in the prevalent involvement of bone marrow and peripheral blood, we define the disease as leukemia

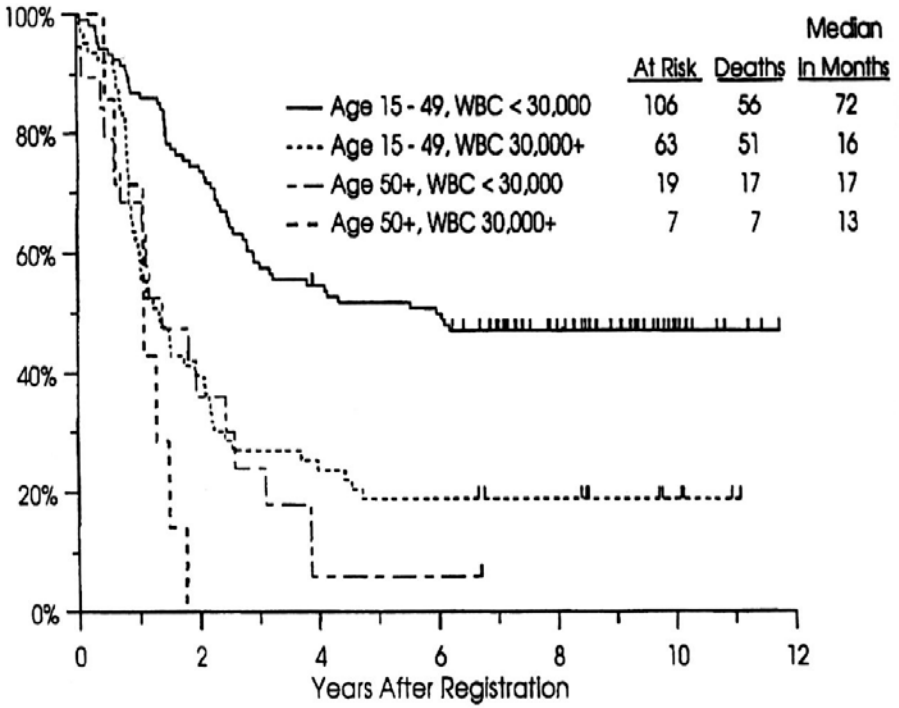
- if adenomegaly prevails without significant bone marrow infiltration (<20%), it is lymphoma

Influence of cytogenetics and age on survival

influence of cytogenetics



the effect of age and WBC levels



Moorman AV, Blood 2007; Leukemia 2000, Petersdorf SH

Ho = hypodiploid karyotype, HeH = hyperdiploid karyotype

Prognostic factors

input parameters:

- cytogenetics / molecular genetics
- age: risk is increasing steadily (> 30 years vs. <30 years)
- WBC:> 30 x 109 / l <30 x 10 9 / l
- CNS infiltration: yes vs. No

response to treatment:

- time to remission: <4 weeks vs. > 4 weeks
- presence of residual disease: positive vs. positive negative

➡ a combination of these factors determines the risk of ALL patients

Acute leukemia

1. clinical manifestation
2. diagnostics
3. therapy

Clinical manifestation

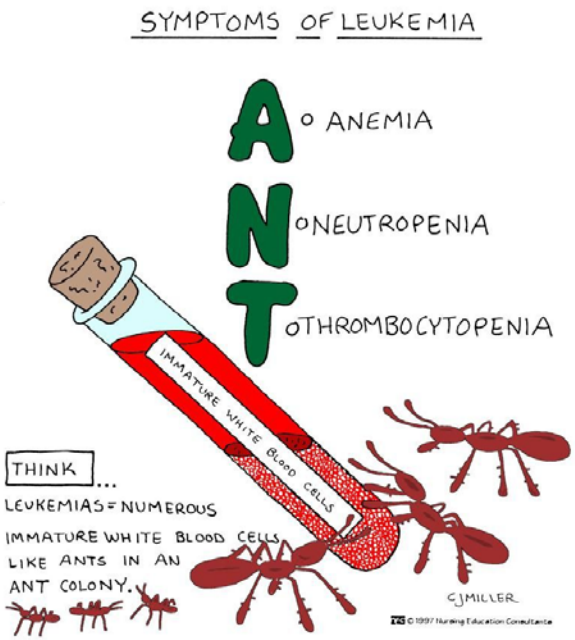
- development is usually fast - days to weeks (short history)

- **symptomatology is given by**:
  - changes in blood count (bone marrow infiltration with blasts)
  - temperatures with or without obvious infection
  - other general symptoms (weight loss, sweating, anorexia…)
  - bleeding symptoms (up to DIC)
  - bone pain
  - tissue infiltration (skin, gums…)
  - leukostasis

a patient with acute leukemia must be **immediately sent** to the center specialized haematological care

Bone marrow failure

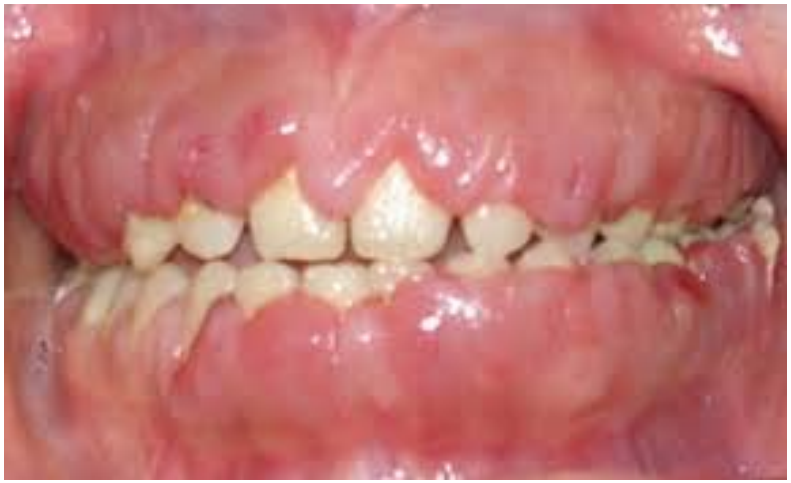
- neutropenia: febrile, infection, sepsis angina, stomatitis, HCD infection poorly responsive to common antibiotics
- anemia: fatigue, paleness
- thrombocytopenia: bleeding, petechiae, hematomas



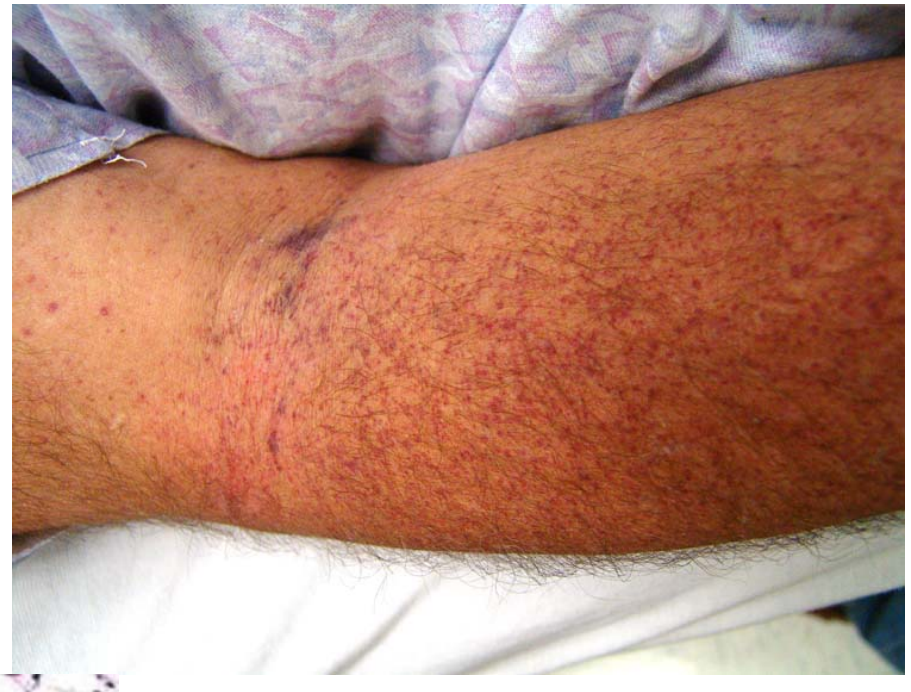
Tissue and organ infiltration

- hepatomegaly, splenomegaly, adenomegaly
- mediastinal tumor (ALL)
- gum hypertrophy
- skin infiltrates
- bone pain
- other organs: CNS, skin, testes, other (ALL)
- extramedullary leukemia (AML) = myeloid sarcoma (chloroma)

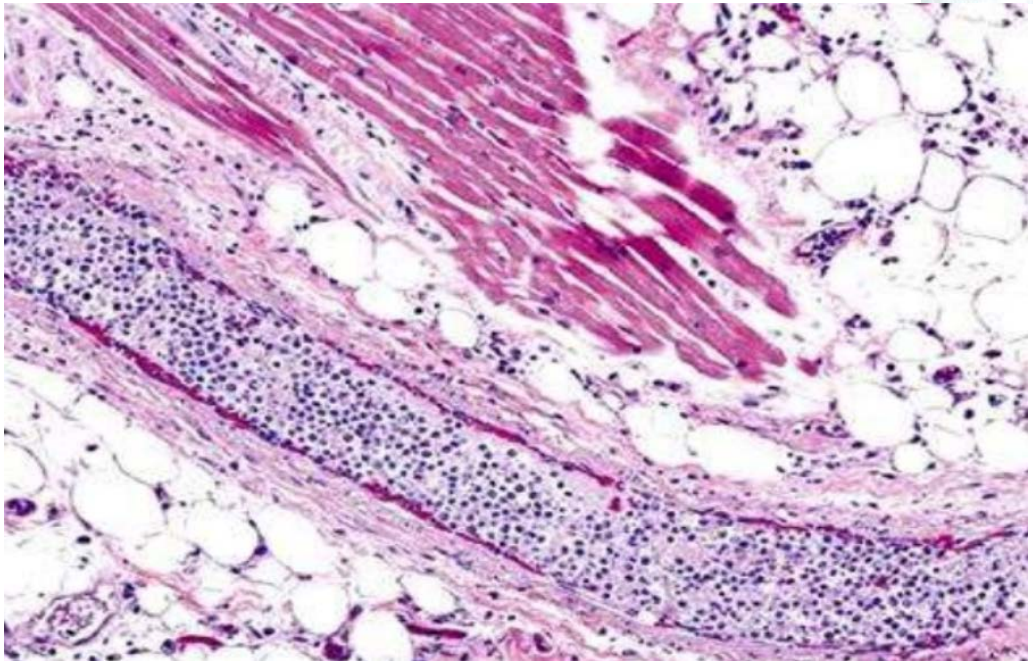
gum hyperplasia



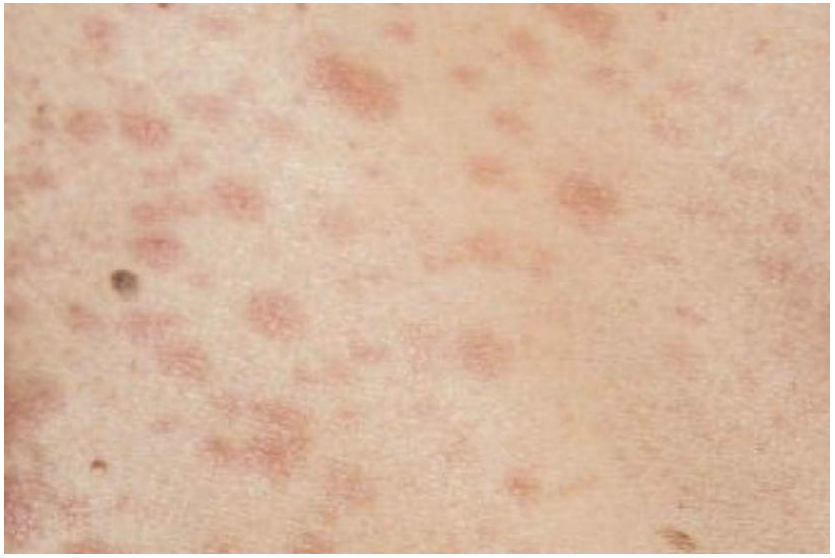
petechia



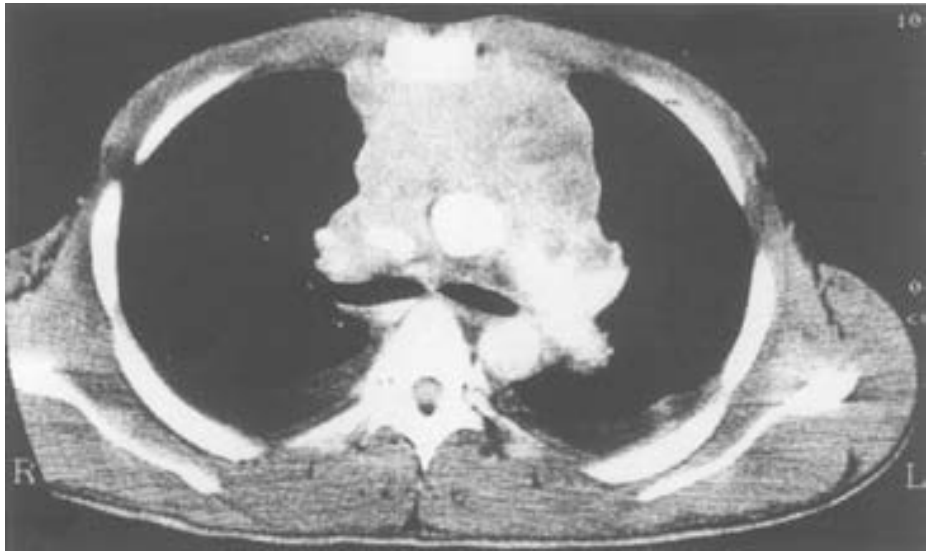
leukostasis



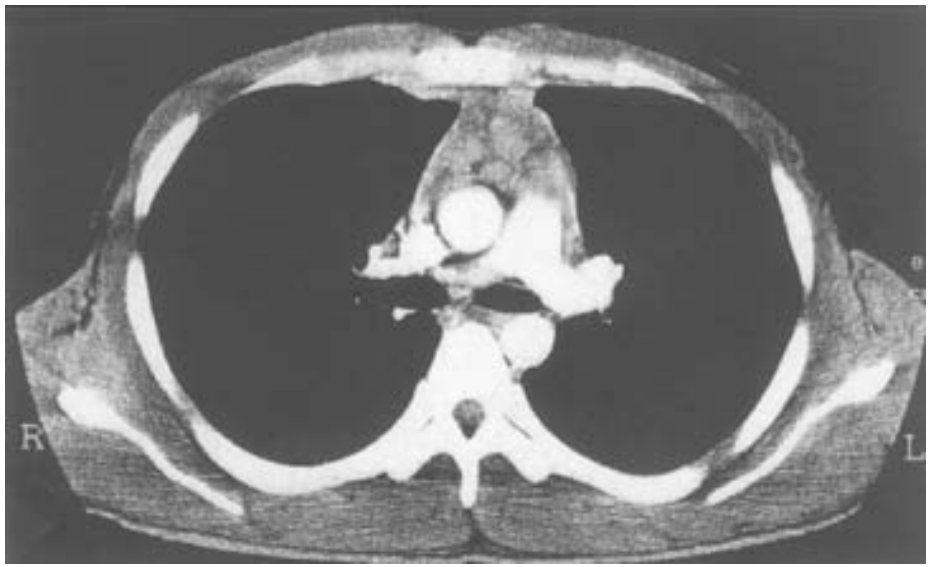
Skin infiltrates



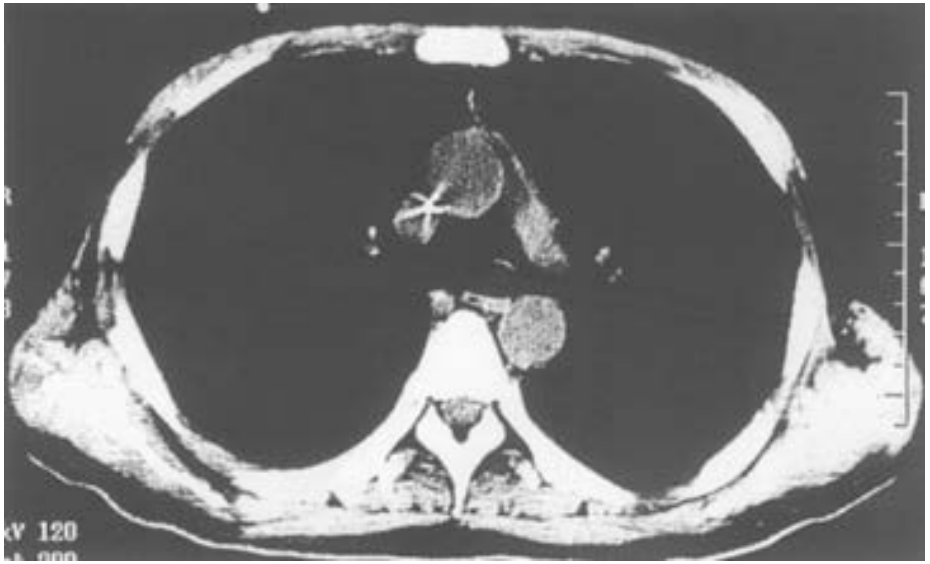
T-ALL – mediastinal tumor



before treatment



before transplant



after transplant

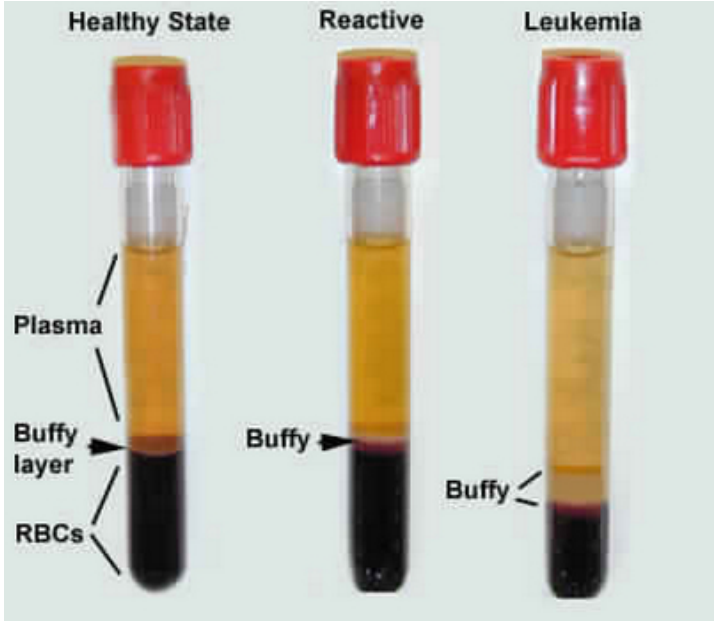
Leukostasis

- blast accumulation in microcirculation damages perfusion
- lungs: dyspnoea, hypoxemia, pulmonary infiltrates
- CNS: neurological symptomatology, consciousness disorder, ictus
- vascular system: limb ischemia, myocardial infarction, renal vein thrombosis, retinal haemorrhage, DIC
- usually at leukocyte levels above 50-100 x 10 9 / L, especially in AML

part of the treatment - leukapheresis!

Blood count

- WBCs are generally elevated but may be normal or leukopenia blasts in peripheral blood
- lack of developmental stages of granulocytes ("hiatus leucaemicus")
- (normocytic) anemia, thrombocytopenia



B--Le	206,20	-	4 - 10	10^9/l
B--Ery	2,84	-	4 - 5,8	10^12/l
B--Hb	95	-	135 - 175	g/l
B--HTK	0,291	-	0,4 - 0,5	1
B--Obj ery.	102	-	82 - 98	fl
B--Hb ery	33,4	>	28 - 34	pg
B--Hb konc	326	-	320 - 360	g/l
B--Erytr.křivka	18,7	-	10 - 15,2	%
B--Trombo	76	-	150 - 400	10^9/l
B--shluky trombo	nejsou			
Dif mikr.				
B--Seg	0,01		0,47 - 0,7	1
B--Ly	0,06		0,2 - 0,45	1
B--MMc	0,01		0 - 0	1
B--Blasty	0,92		0 - 0	1

ALL

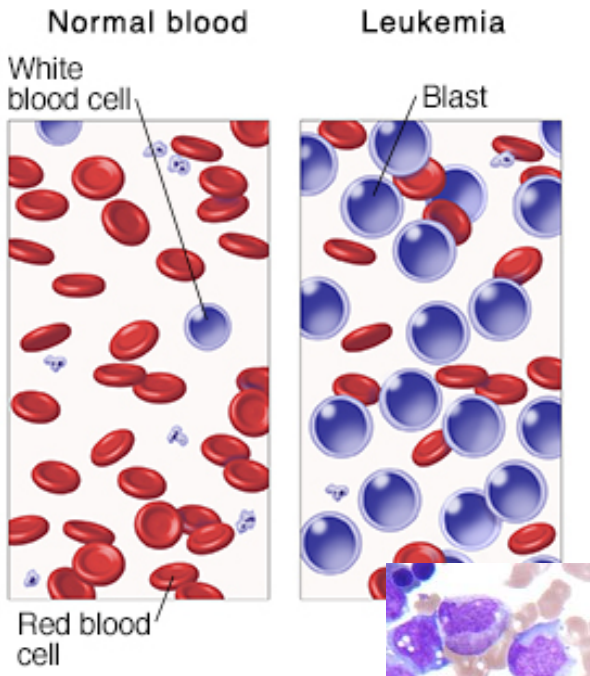
Krevní obraz				
B-Le	71,80	normální	4 - 10	10^9/l
B-Ery	4,01		3,5 - 5,6	10^12/l
B-Hb	116		130 - 173	g/l
B-HTK	0,352		0,42 - 0,53	1
B-Hb ery	29,1		26 - 35	pg
B-Hb konc	331		310 - 370	g/l
B-Obj ery.	88		80 - 98	fl
B-Trombo	14		150 - 400	10^9/l
B-Ret př. rel				1
Diferenciál				
B-Seg				1
B-Tyc	0,01		0 - 0,04	1
B-Ly	0,23		0,2 - 0,45	1
B-Mo	0,01		0,02 - 0,1	1
B-Ba				1
B-Eo				1
B-PMc				1
B-Mc	0,01		0 - 0	1
B-MMc				1
B-Blasty	0,74		0 - 0	1

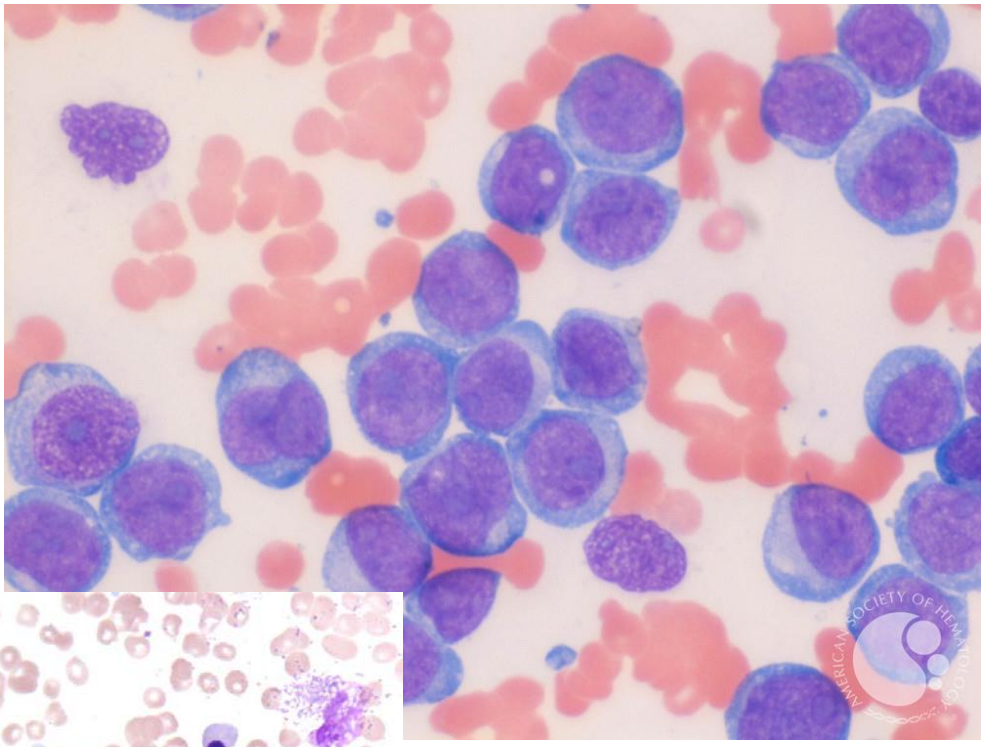
AML

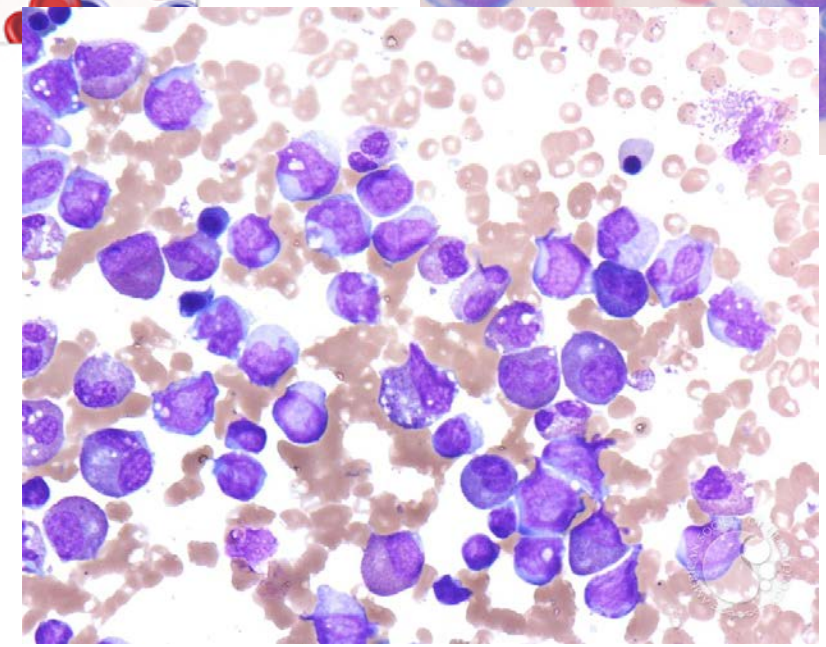
Krevní obraz				
B-Le	73,00		4 - 10	10^9/l
B-Ery	2,28		3,5 - 5,6	10^12/l
B-Hb	94		130 - 173	g/l
B-HTK	0,279		0,42 - 0,53	1
B-Hb ery	41,1		26 - 35	pg
B-Hb konc	336		310 - 370	g/l
B-Obj ery.	122		80 - 98	fl
B-Trombo	279		150 - 400	10^9/l
B-Ret př. rel				1
Diferenciál				
B-Seg	0,01		0,47 - 0,7	1
B-Tyc	0,04		0 - 0,04	1
B-Ly				1
B-Mo				1
B-Ba				1
B-Eo				1
B-PMc				1
B-Mc				1
B-MMc				1
B-Blasty	0,95	B_Blasty	0 - 0	1

Hiatus leukemicus

Peripheral blood smear







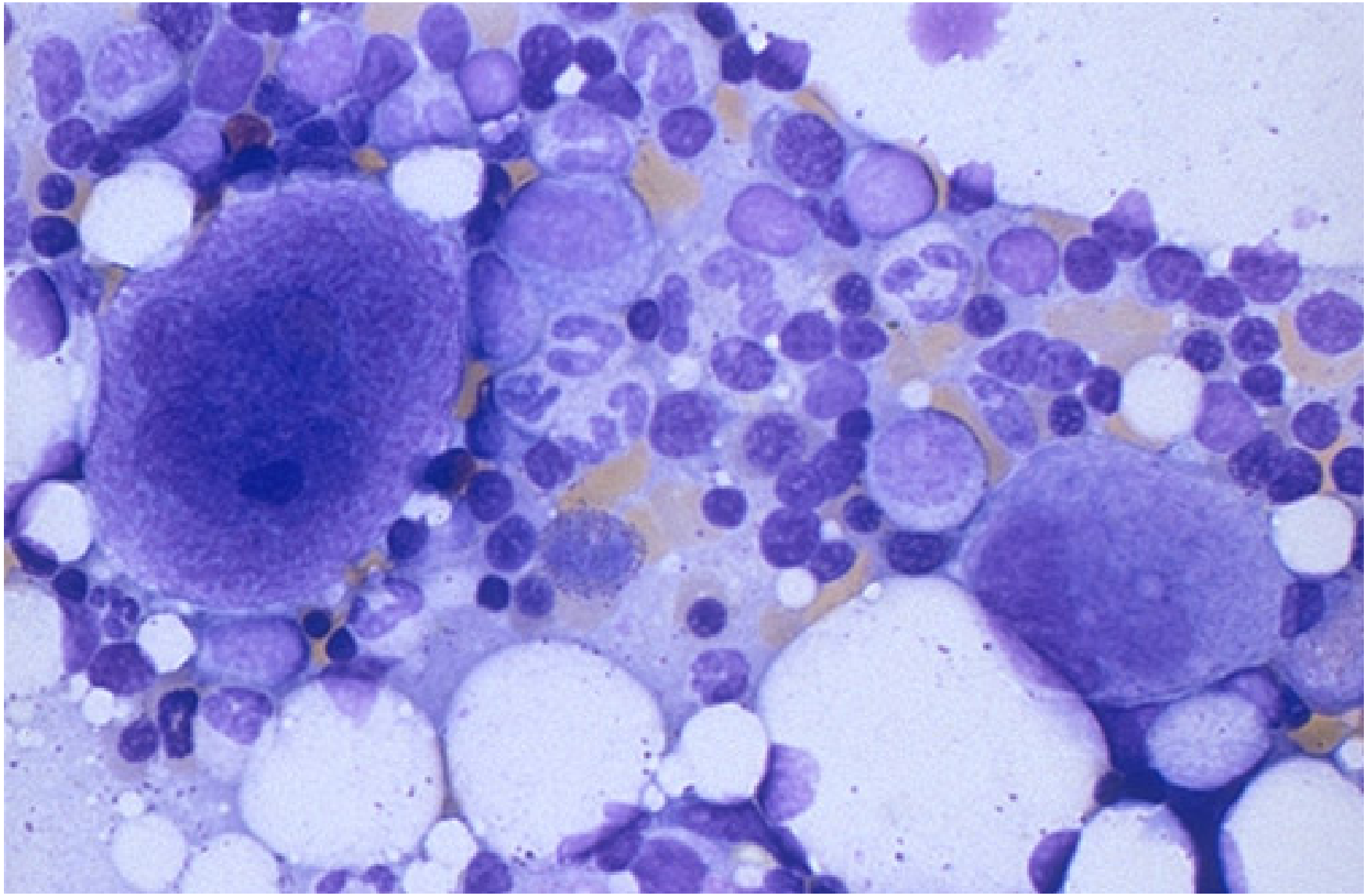
Examination of bone marrow

- necessary for diagnosis
- important for determining the type of leukemia (AML x ALL)
- important for determining prognostic factors

morphology
immunophenotyping (flow cytometry)
cytogenetics / FISH
molecular genetics / NGS

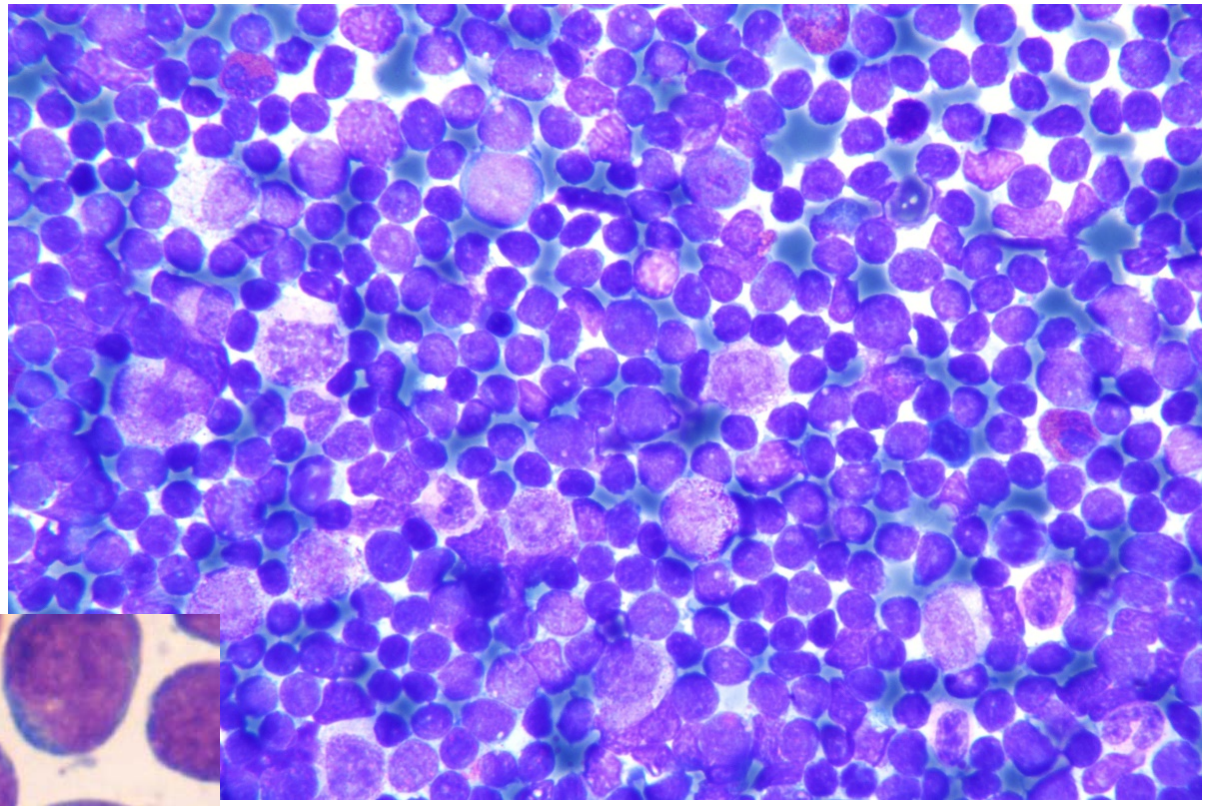
not only for diagnosis but also for investigation of response to treatment and minimal residual disease

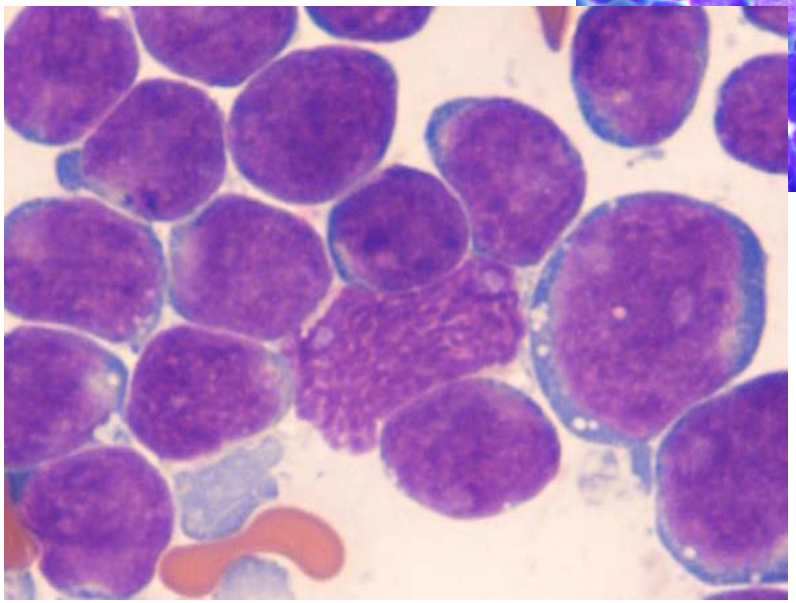
Morphology - bone marrow



normal bone marrow

Morphology - bone marrow

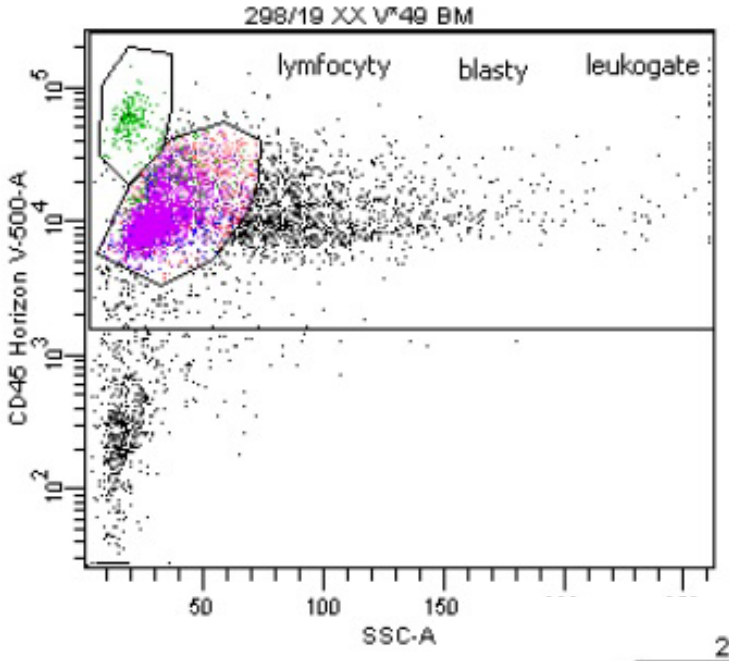




bone marrow smear:

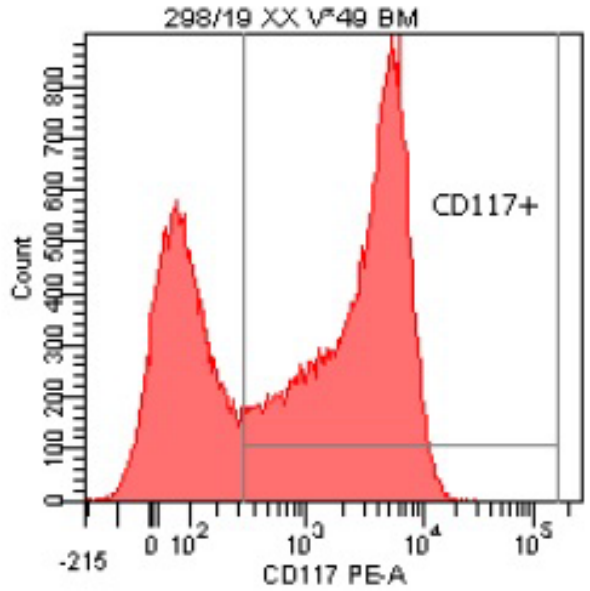
AML leukemia defined by the presence of> 20% blasts in the bone marrow

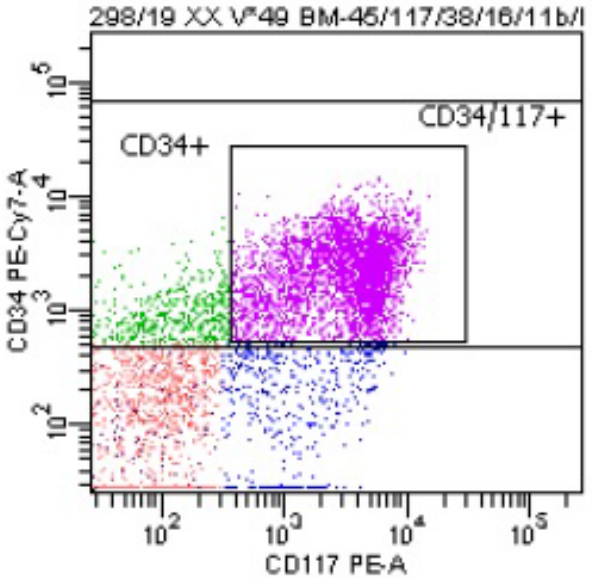
Flowcytometry



Population	#Events	%Parent	%Total
All Events	100,000	####	100.0
leukogate	88,052	88.1	88.1
lymfocyty	3,450	3.9	3.4
blasty	55,796	63.4	55.8
CD33+	51,212	89.2	51.2
CD33/117+	34,869	60.7	34.9
cMPO+	17,489	30.5	17.5
CD117+	35,931	64.4	35.9
CD34+	36,550	65.5	36.6
CD34/117+	31,150	55.8	31.2
CD13+	29,438	52.1	29.4
CD38+	52,976	94.9	53.0
HLA-DR	51,330	92.0	51.3

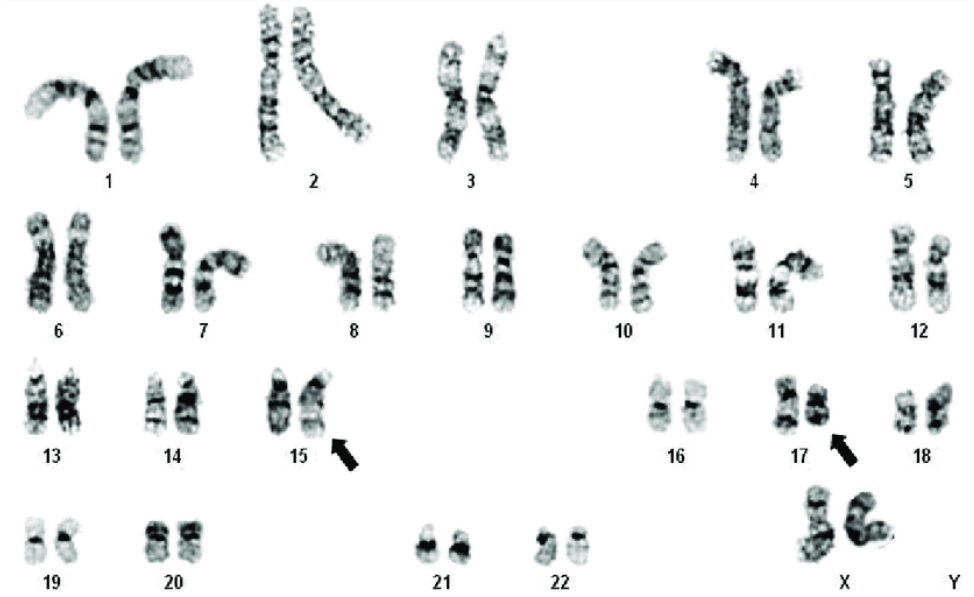
- antigenic profile of blasts
- leukemia-associated immunophenotype (LAIP)



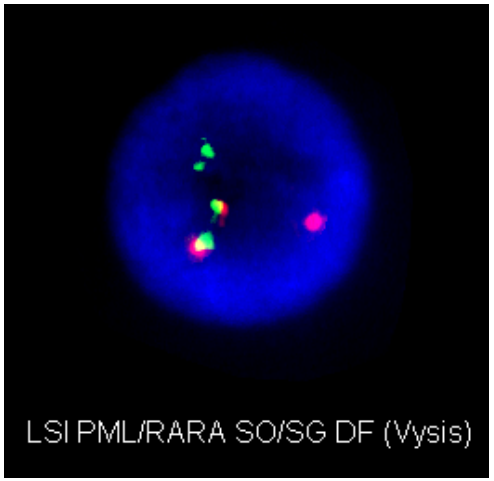


Cytogenetics

karyotype



FISH



example AML: translocation 15,17
fusion gene PML/RARA

Differential diagnostics

leukocytosis:

- infectious mononucleosis (atypical lymphocytes in peripheral blood)
- infection (leukemoid reaction after infection)
- myeloproliferative diseases (CML)
- leukemizing lymphomas

pancytopenia:

- aplastic anemia
- severe deficiency of vitamin B12 or folic acid
- bone marrow infiltration in carcinomas
- drug-related bone marrow damage (methotrexate in rheumatology)

Treatment

is intended:

- type of disease (AML, ALL)
- prognostic factors
- age and general condition of the patient

Chemotherapy

induction:

- the first step is to achieve remission of the disease (eradication of the leukemia clone and regeneration of healthy hemopoiesis)
- complicated by transient bone marrow aplasia and pancytopenia
- the same in most patients
- does not remove all blasts - residual disease of varying size

➡

post-remission treatment (intensification, consolidation):

- to destroy residual disease and cure the patient
- prevents relapse
- individualized according to risk factors, age, etc.

maintenance therapy:

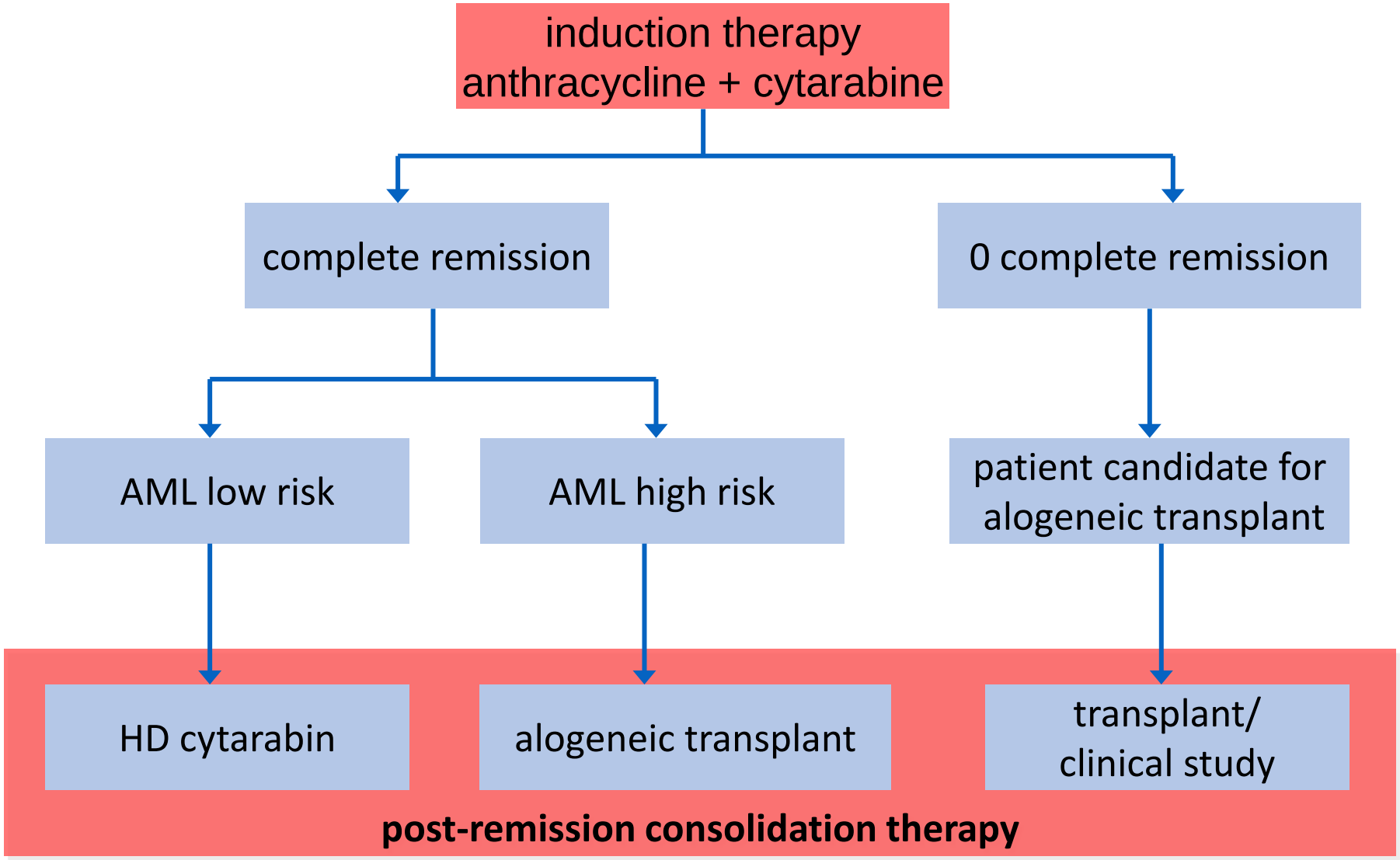
- small doses of cytostatics to maintain remission

CNS prophylaxis

- intrathecal application

} **ALL**

AML treatment algorithm



Complete remission ?

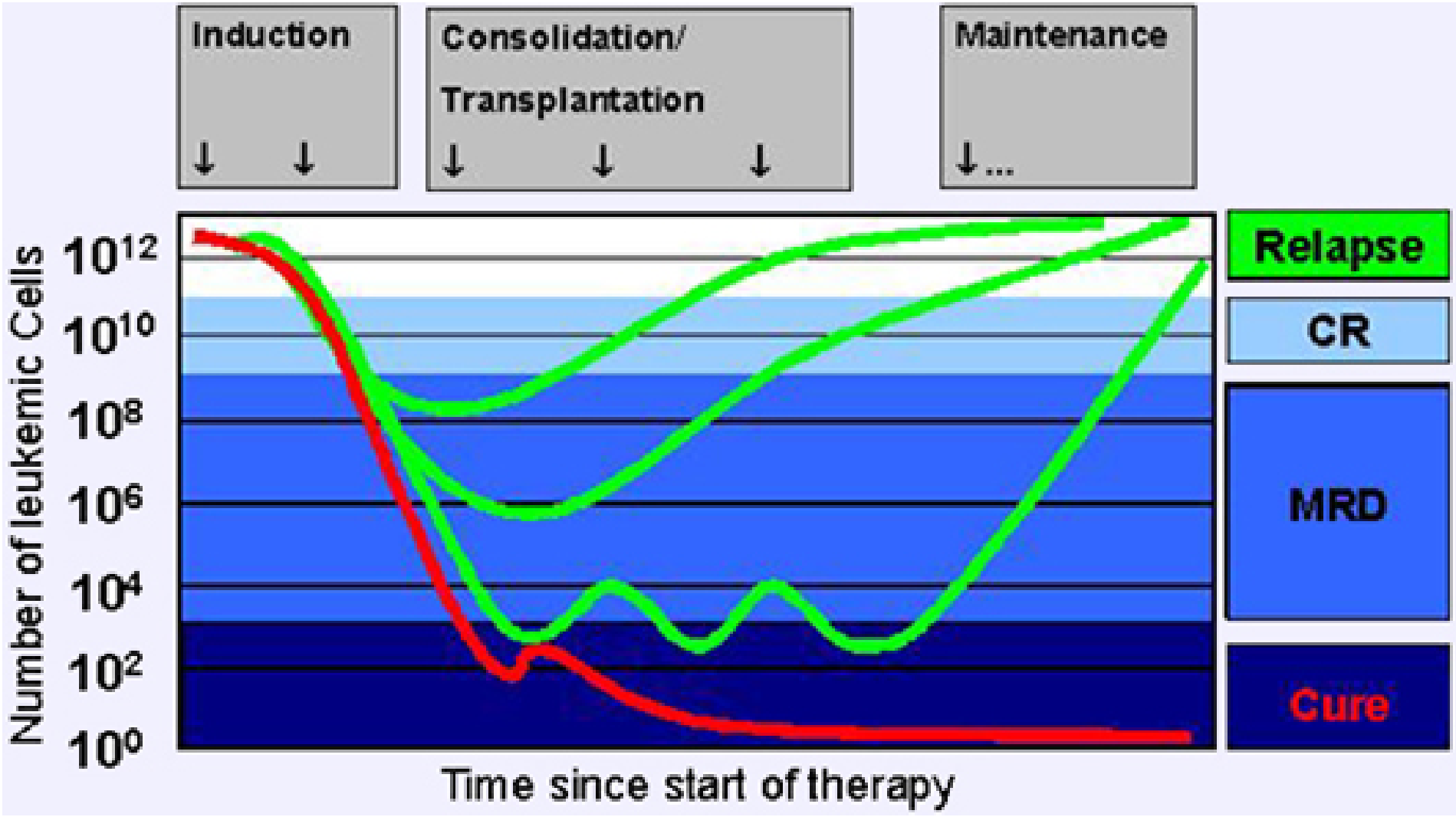
CR is defined by:

- neutrophils in PB ≥ 1.0 x 109 / L
- platelets ≥ 100 x 109 / L
- no circulating blasts in peripheral blood
- bone marrow blasts <5%
- no extramedullary leukemia

other more sensitive methods to detect residual disease:

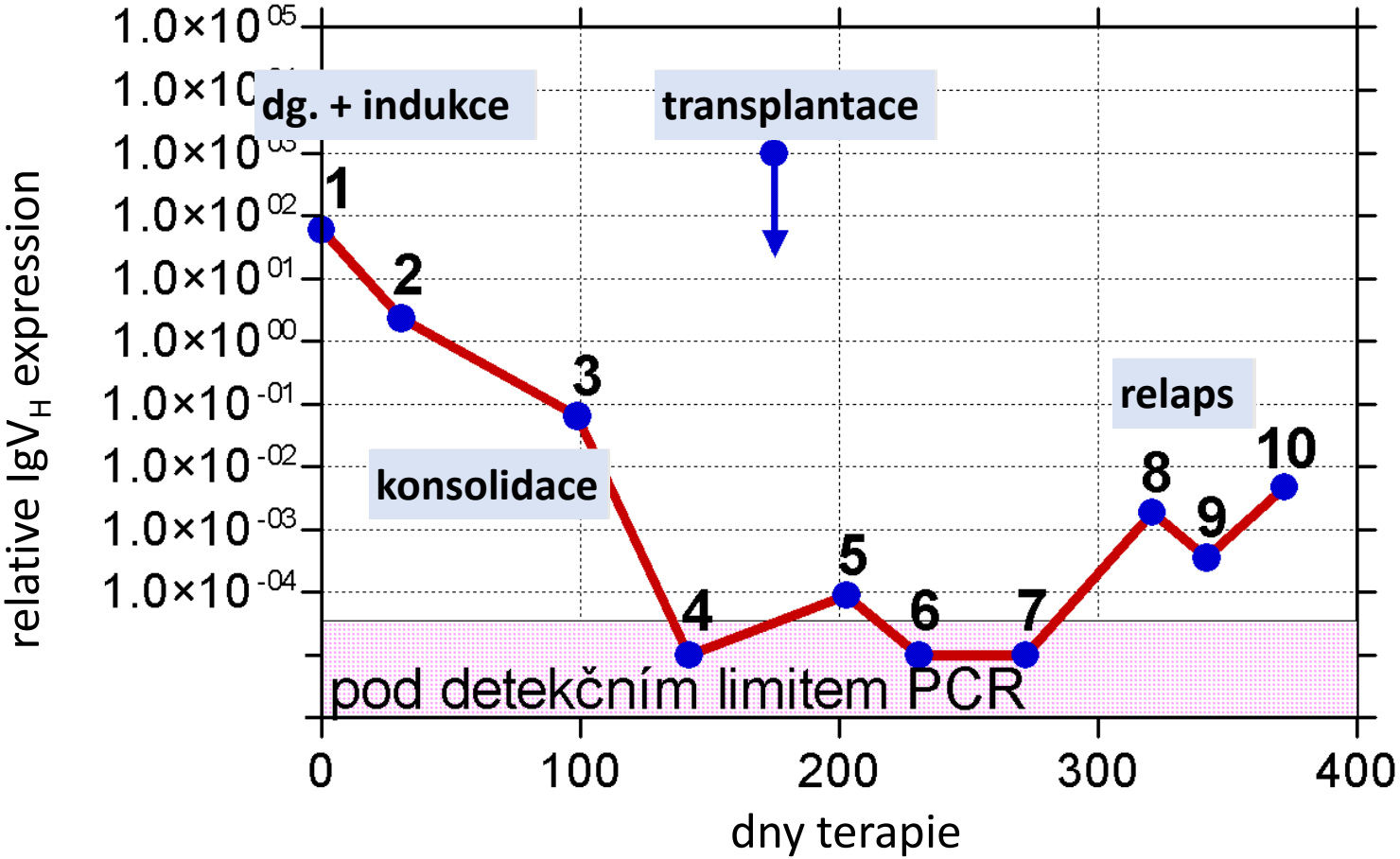
- flow cytometry
- cytogenetics / FISH
- molecular genetics

} $10^{-4} – 10^{-6}$



- several cycles of treatment required to eradicate the leukemia clone

PCR monitoring after aloSCT - example



clonal rearrangement of the IgV$_H$ gene in B-ALL

Treatment - others

supportive treatment

- transfusion, antibiotics, nutrition, growth factors

actinotherapy

- CNS in ALL, extramedullary leukemia
- whole body irradiation before transplantation

psycho-social support

- patient and family

symtomatic treatment

- old patients, insoluble relapse
- substitution, pain treatment, antibiotics

Supportive treatment

substitution:

- thromboconcentrates, ERY resuspension
- irradiated and deleukotized (prevention of TA-GVHD and alloimmunization)

antibiotics, antifungals:

- predisposition (neutropenia, mucosal barrier disorder, immunosuppression)
- prophylaxis and treatment of infectious complications

nutrition:

- mucositis, enterocolitis
- parenteral nutrition

granulopoiesis growth factors (G-CSF):

- shortens neutropenia time

regime measures:

- reverse insulation, air filtration (HEPA)
- low microbial diet, barrier treatment

Allogeneic transplantation hemopoietic stem cells

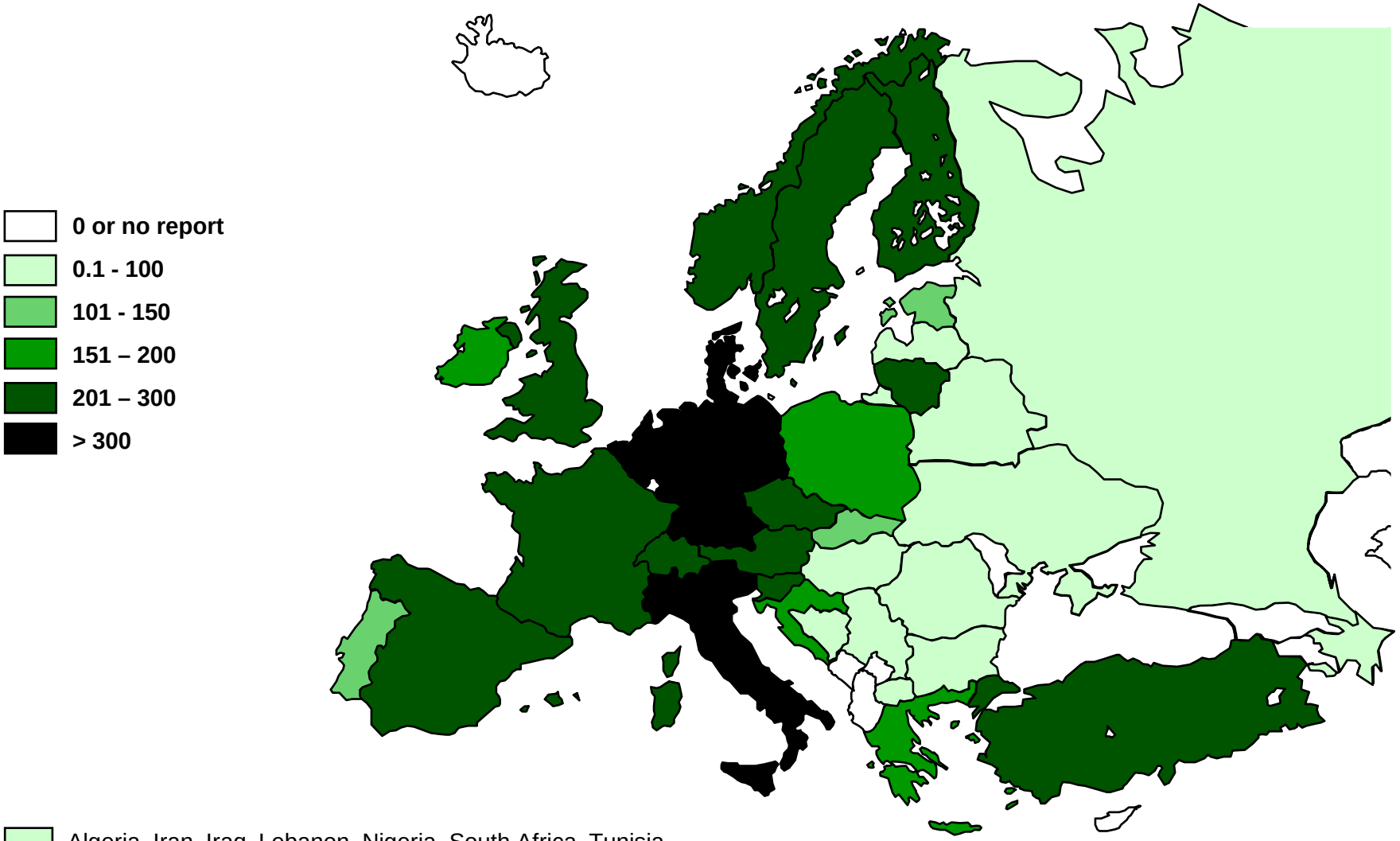
Type of transplants

different types of transplants ➡ classification by:

1. **by donor**
   - autologous, allogeneic, related, unrelated, haploidentic…
2. **by stem cell source** (graft type)
   - bone marrow, peripheral stem cells, cord blood
3. according to **pre-transplant conditioning**
   - myeloablative, non-myeloablative

different combinations of these types

Transplant activity in Europe

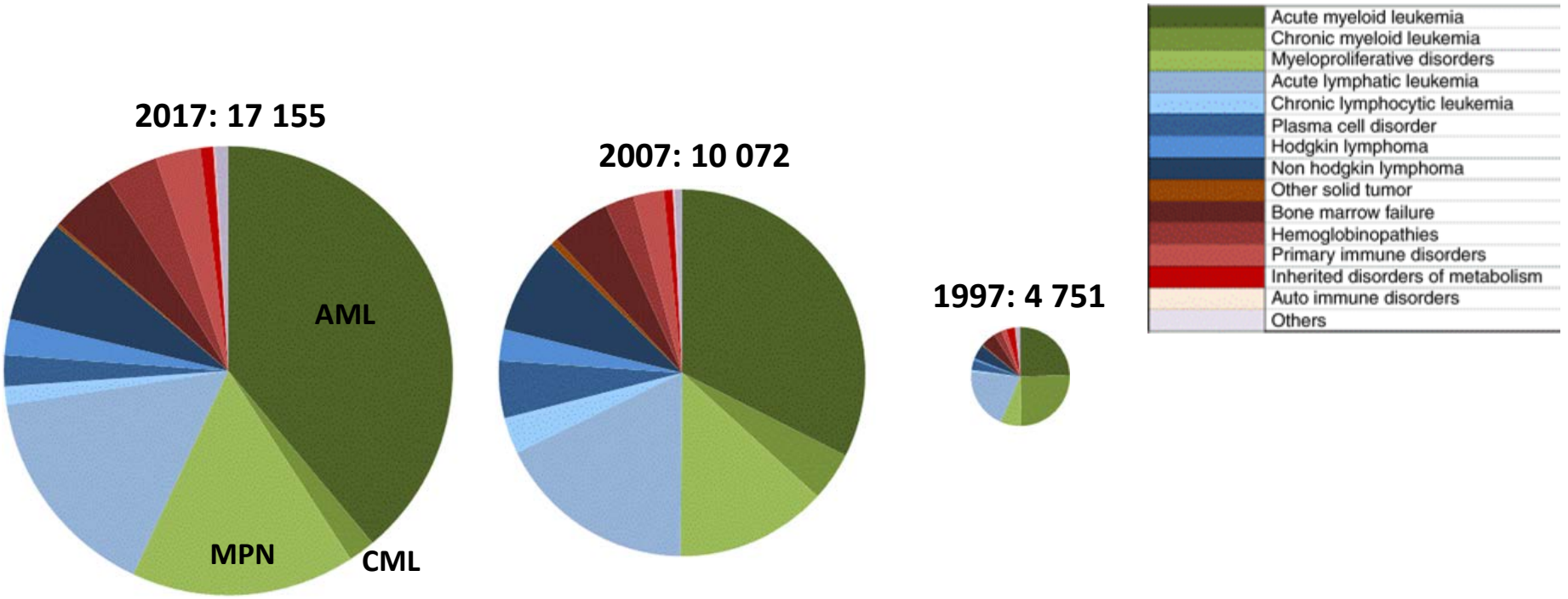


Numbers of allogeneic transplant per 10 millions inhabitans (2017)

Passweg JR, BMT 2019

Transplant statistics (2017)

- 17 155 allogeneic transplant in Europe
- main indications: acuute leukemia, myeloproliferative disease



Absolute number of aloTx a indications – last 20 years

AML: 24 % ➡ 39 %

CML: 25 % ➡ 2 %

MPN: 7 % ➡ 16 %

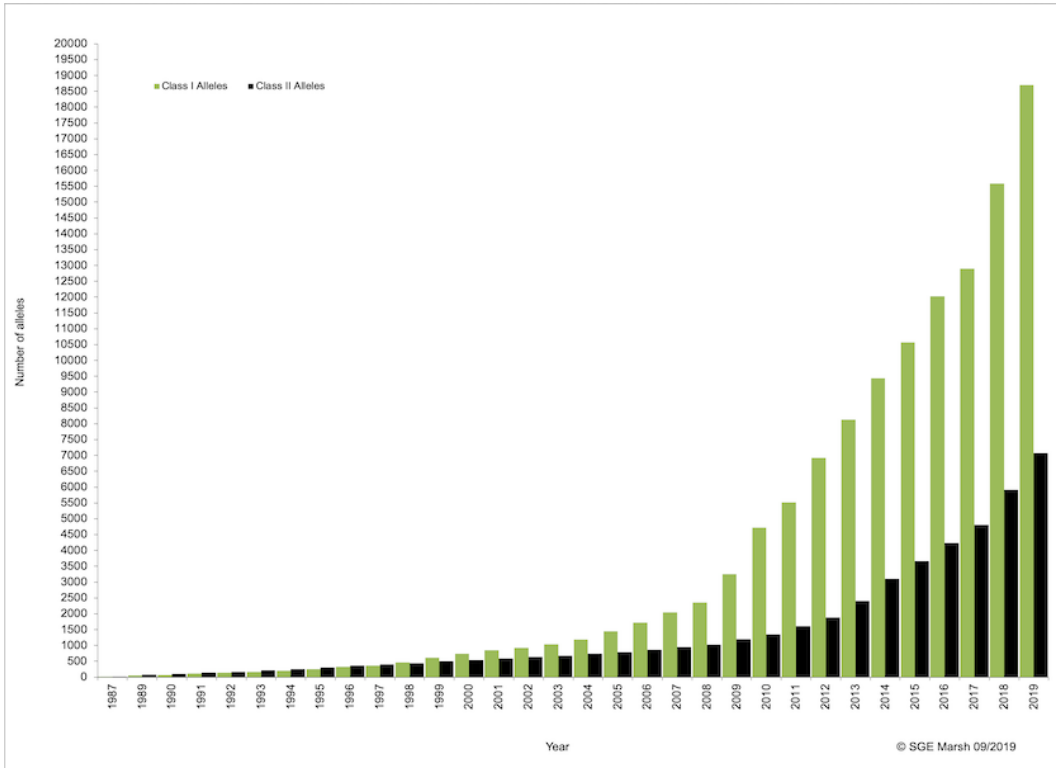
Passweg JR, Bone Marrow Transplant 2019

Transplantation procedure

1. **donor selection**
2. preparation of the patient - so-called **conditioning** (chemotherapy)
3. **collection and administration of hematopoietic stem cells**
4. **post-transplantation period**
   - post-transplant immunosuppression
   - engraftment and hematopoiesis recovery
   - post-transplant complications
   - immunotherapy (eg donor lymphocytes)

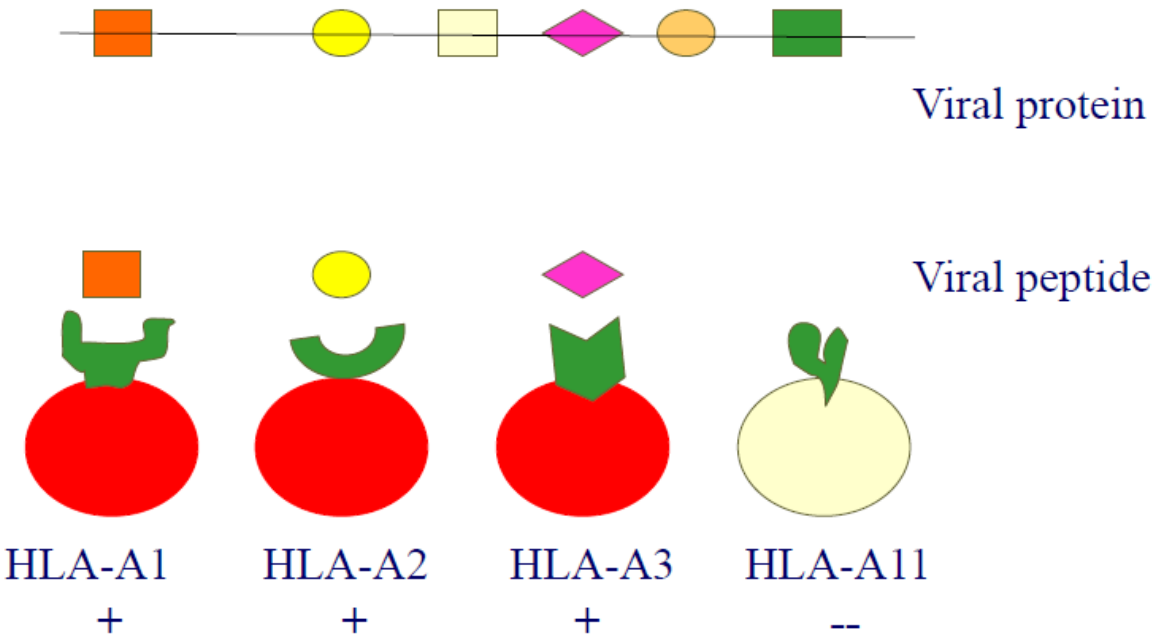
HLA polymorfism

- HLA genes are the most polymorphic of all known systems to respond to all different peptides (antigens)
- hundreds of allelic variants of each HLA antigen are currently known
- 2019: total alleles 25 756, HLA-A, HLA-B - 5735, 7053 alleles ……
- of these variants each inherit 2 alleles, this makes thousands of possible combinations
- polymorphisms are specific to different populations, ethnicities



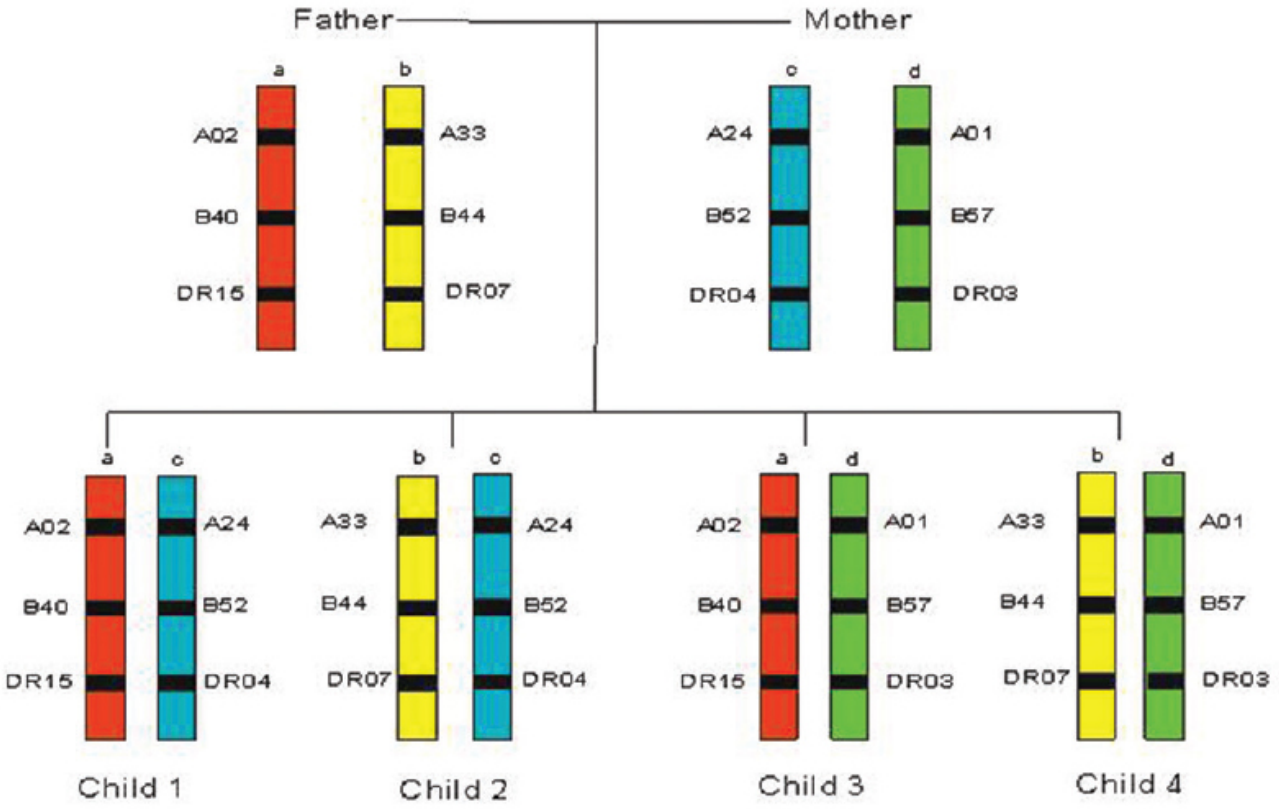
HLA diversity

- guarantees the presentation of the maximum spectrum of foreign ("infectious") peptides ➡ protects the human population from epidemic infection
- more different HLA molecules ➡ different types of antigenic peptide binding to HLA molecules and different immune responses… ➡ pressure of selection and migration
- genetic diversity ensures that a pathogen always survives



Inheritance of HLA antigens

- the HLA allele assembly encoded on one chromosome is called a haplotype
- we each have two haplotypes, one from each parent, the haplotype is inherited as a whole
- the resulting phenotype is given by the combined expression of both haplotypes (co-dominance)



HLA ANTIGENAS ARE INHERITED AS HAPLOTYPES

A1
B8
DR17

A11
B55
DR7

A B

A23
B60
DR 4

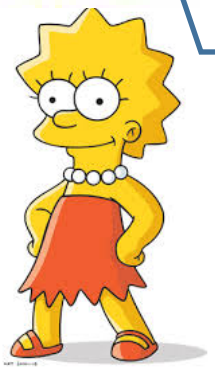
A2
B7
DR15

C D

A1
B8
DR17

A2
B7
DR15

A D



HAPLO - IDENTIC
(only 1 inherited haplotype is shared)
50%

A1
B8
DR17

A23
B60
DR 4

A C

GENO - IDENTIC
(both inherited haplotypes are
25%

A1
B8
DR17

A23
B60
DR 4

A C

COMPLETE MISMATCH (no shared haplotype)
25 %

A23
B60
DR 4

A11
B55
DR7

D E

What are donor registers?

a **database** of (young and healthy) people willing to give anonymously to a patient with identical HLA hematopoietic stem cells

What does the database contain?

- basic donor transplantation (HLA) features
- age, sex, blood type, donor weight
- donor contact

Probability of finding a donor

- only about 20 - 25% of patients have HLA identical donor in the family (sibling)
- around 80% of patients need an unrelated donor ➡ **from donor registers**
- the probability of finding an unrelated donor in the registers is min. 80%
- it really depends:
  - ethnicity (80% whites □ 40% Hispanics □ less than 20% Asians, African Americans)
  - belonging to a minority (Roma, Vietnamese) - they are not represented in the registers
  - and on the urgency of transplantation (takes up to 4 months to find a donor)

Variables affecting survival after allogeneic transplantation

pre-Tx conditioning

age P/D

gender P/D

diagnosis, status in the time of SCT P

type of stem cells D

Time from dg. ->Tx P/D

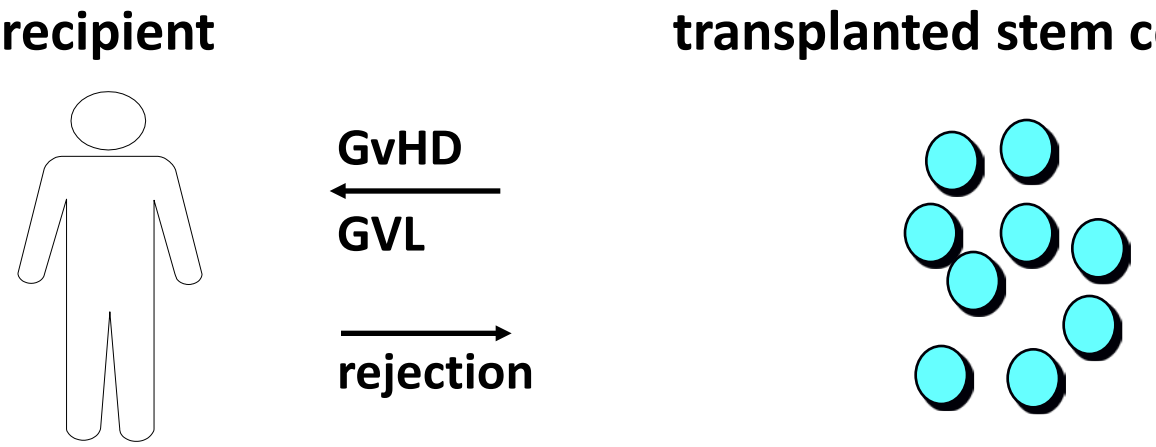
polymorfism non-HLA genes P/D

CMV status P/D

HLA match:
A, B, C, DRB1, DQB1, DPB1

P = patient
D = donor

Immune aspects of transplantation



☹ **GvHD** - reaction graft x host (graft versus host disease)

⇨the donor's immune system damages the recipient's cells

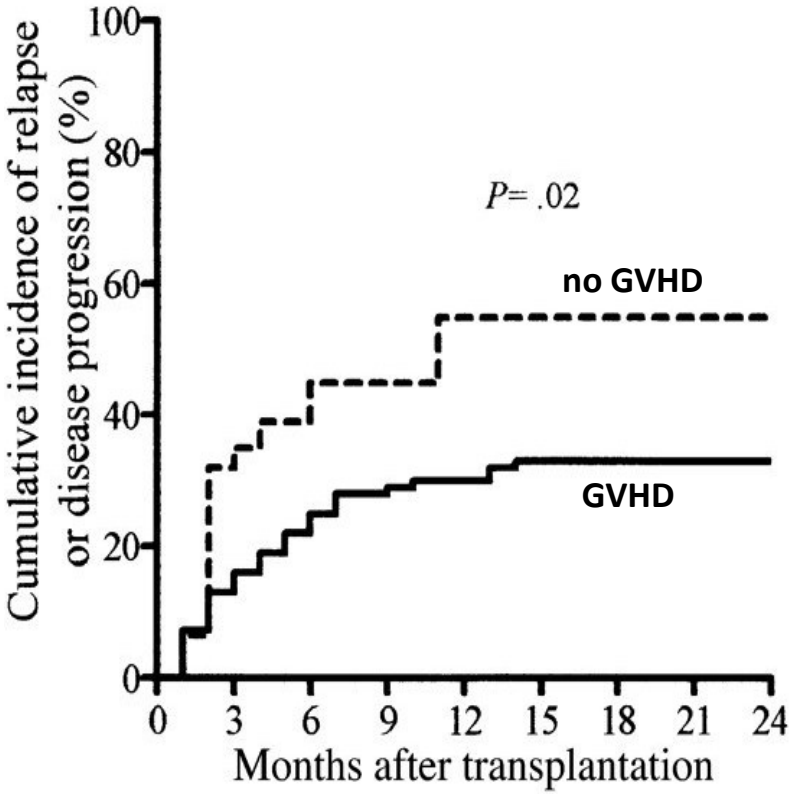
☺ **GVL** - reaction graft x leukemia (graft versus leukemia)

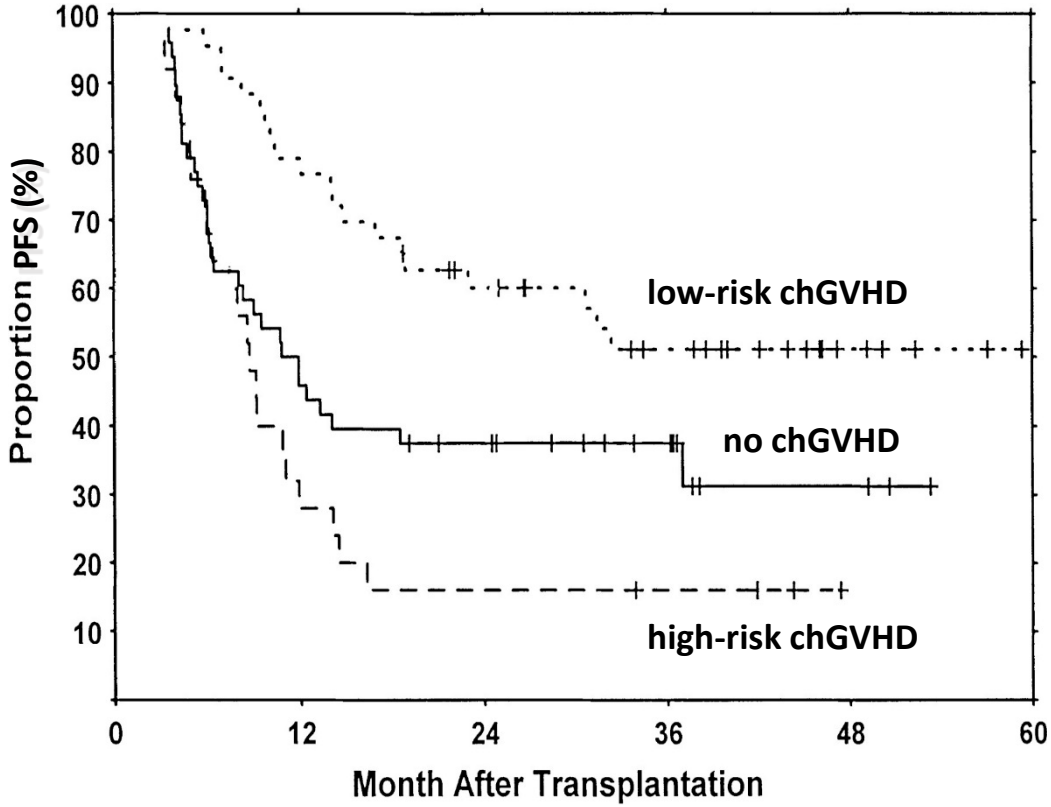
⇨the donor's immune system eliminates residual tumor cells

😐 **graft rejection**

⇨the recipient's immune system eliminates the transplanted donor cells

Influence of GVHD on relapse





presence of GVHD reduces the risk of relapse (clinically light GVHD is OK)
but in case of severe GVHD, survival is worse (not due to relapse but complications of GVHD)

Mohty M, Blood 2003

Przepiorka D, Blood 2001

What is the GVL effect?

GVL = graft versus leukemia

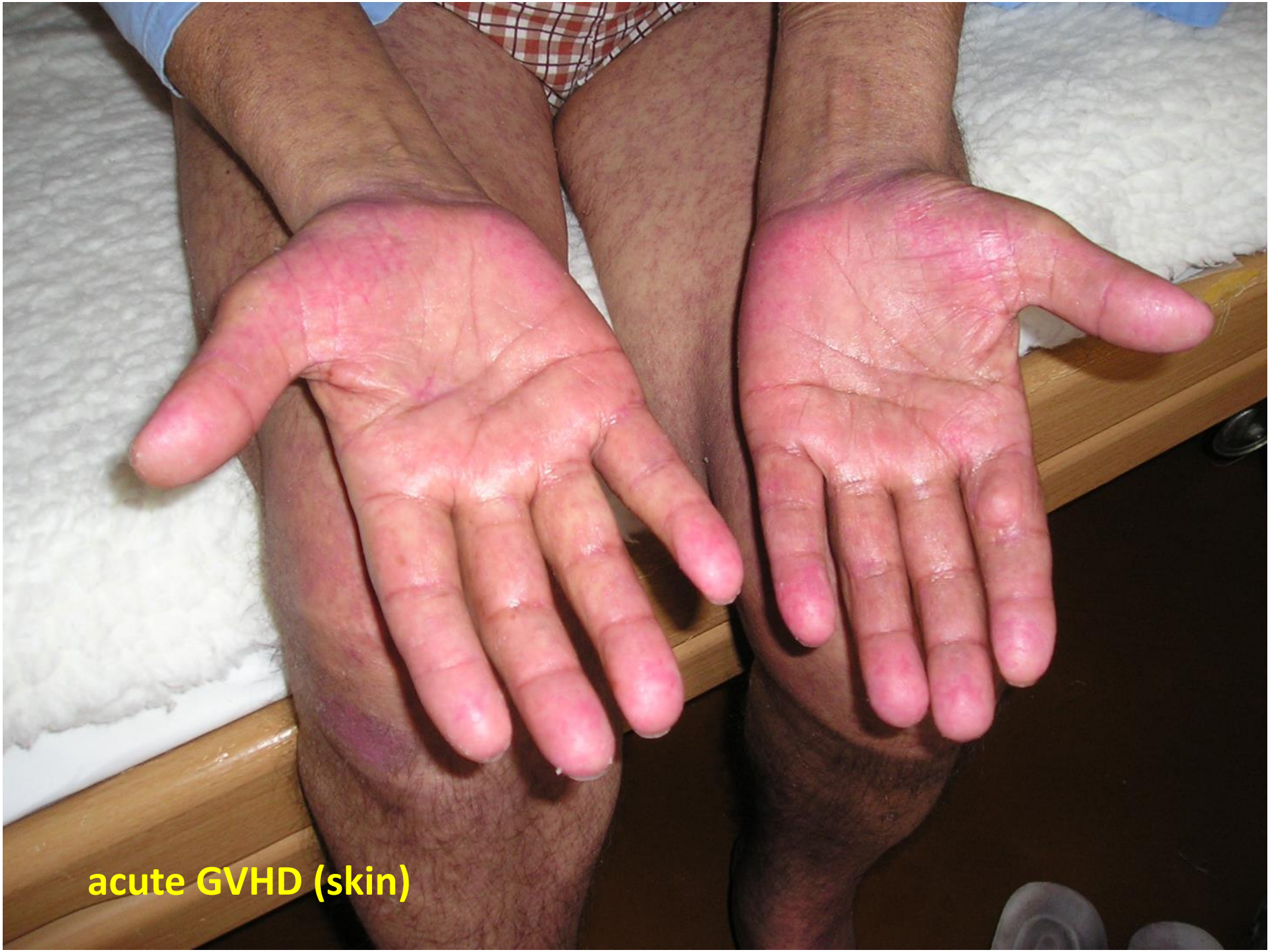
- how foreign hematopoietic stem cells can identify recipient tissues as foreign and damage them ➡ GVHD
- even the remaining leukemia cells of the patient are recognized as foreign and may interfere with ➡ GVL

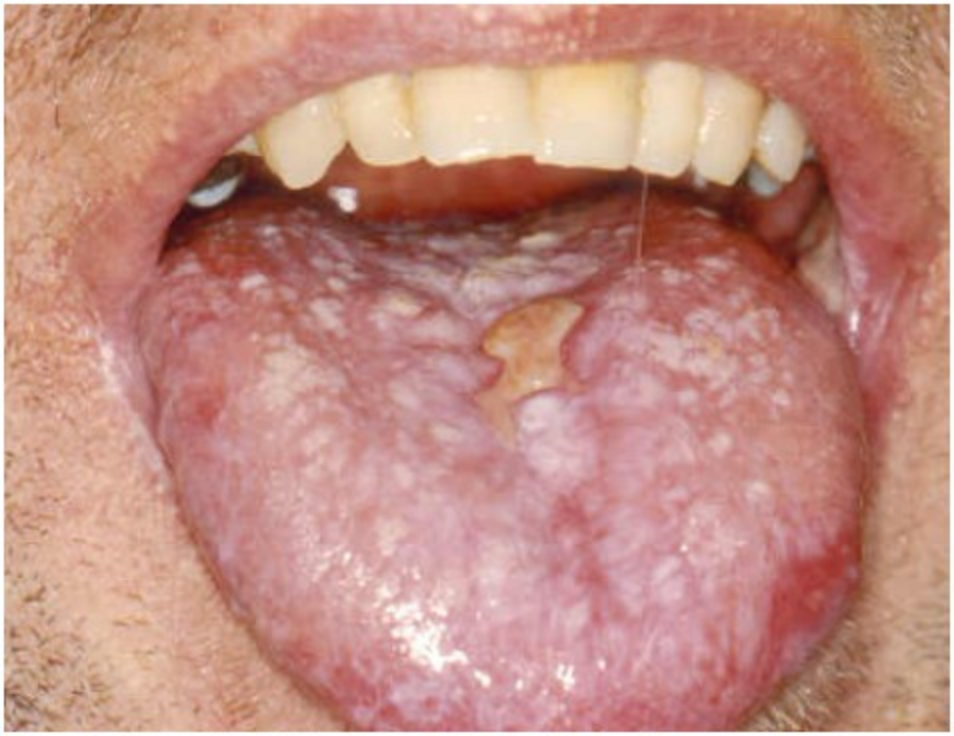
patients with GVHD (and thus GVL) have a significantly lower risk of leukemia relapse than patients without GVHD

Late complications of transplantation

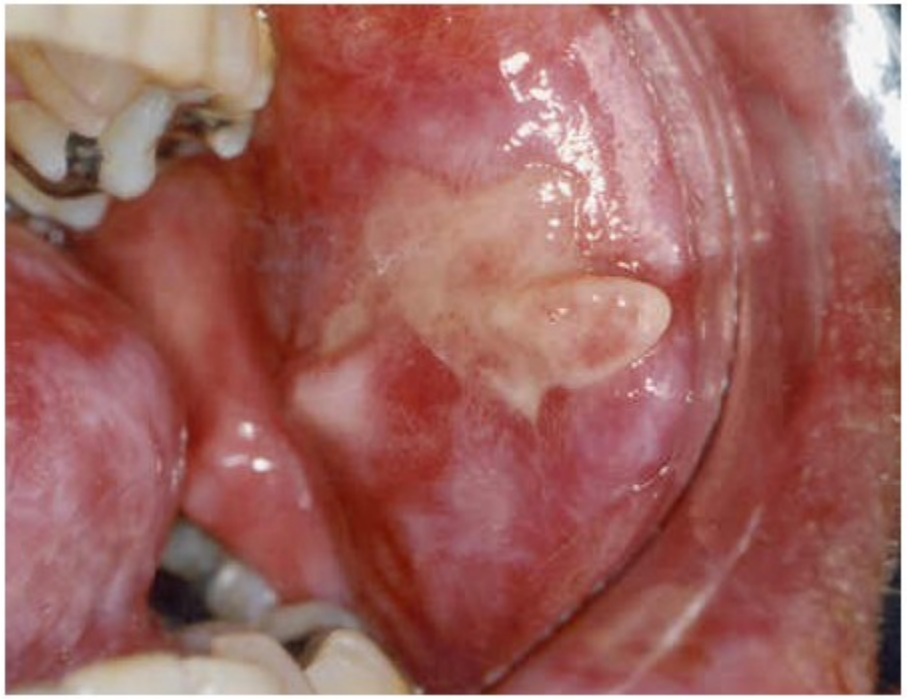
- **eyes**: cataract, conjunctivitis
- **lung**: chronic obstructive pulmonary disease, pulmonary fibrosis
- **bones, joints**: osteoporosis, avascular necrosis
- **endocrine function**: hypothyroidism, gonad dysfunction
- **muscles**: myopathy
- **kidney**: nephropathy
- **nervous system**: peripheral neuropathy, encephalopathy
- **immunity**: infection, autoimmune disease

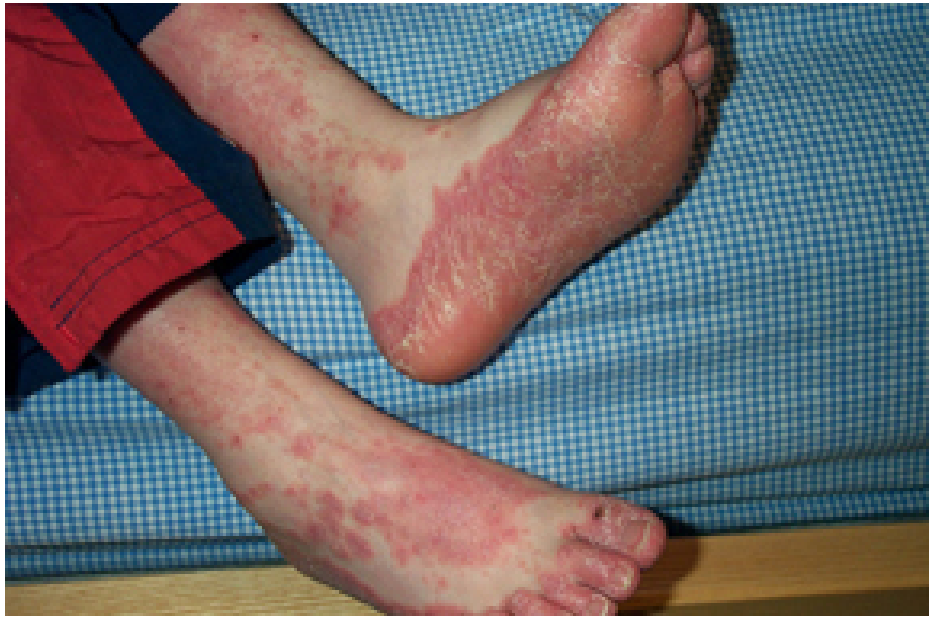
mostly associated with chronic GVHD and its treatment


acute GVHD (skin)

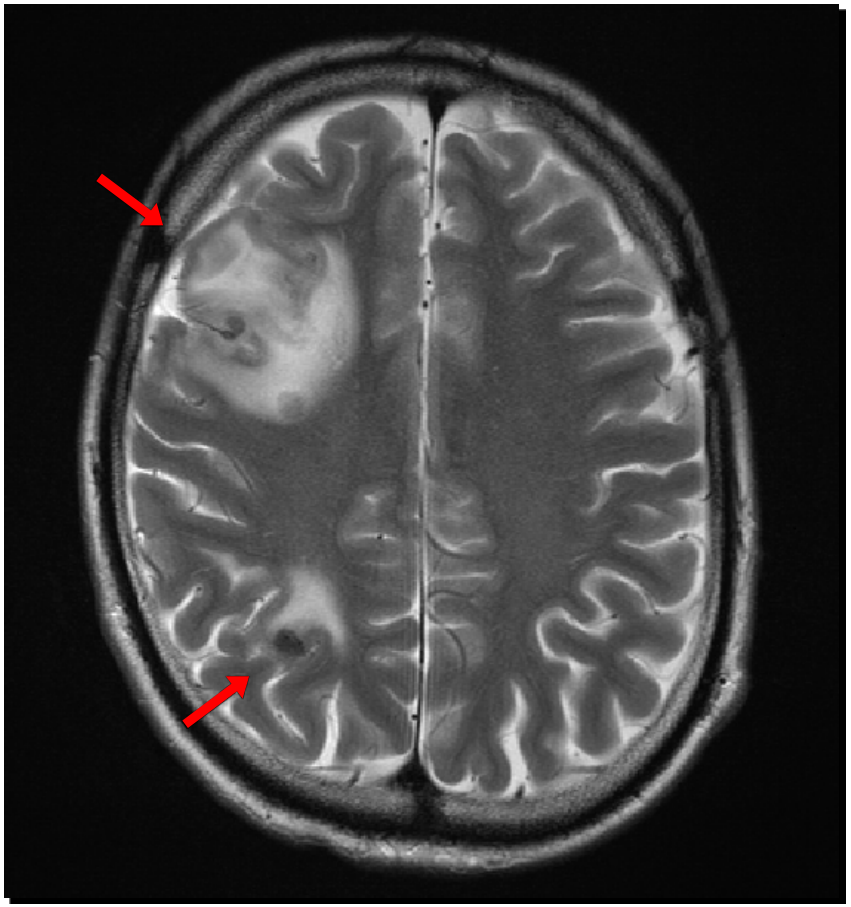


chronic GVHD
(skin, mucosae)

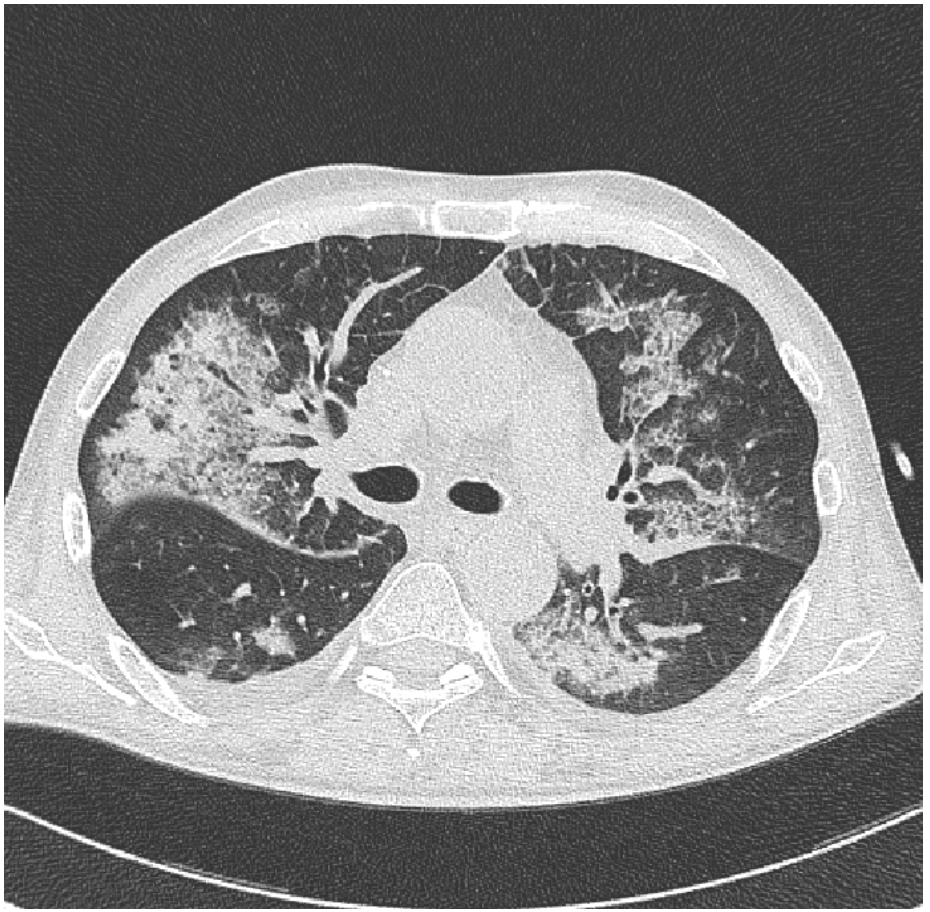




Infectious complications after transplantation

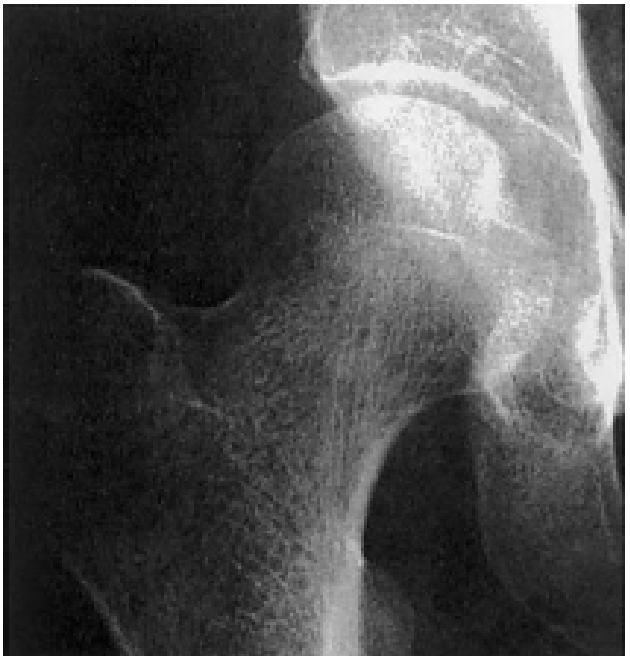


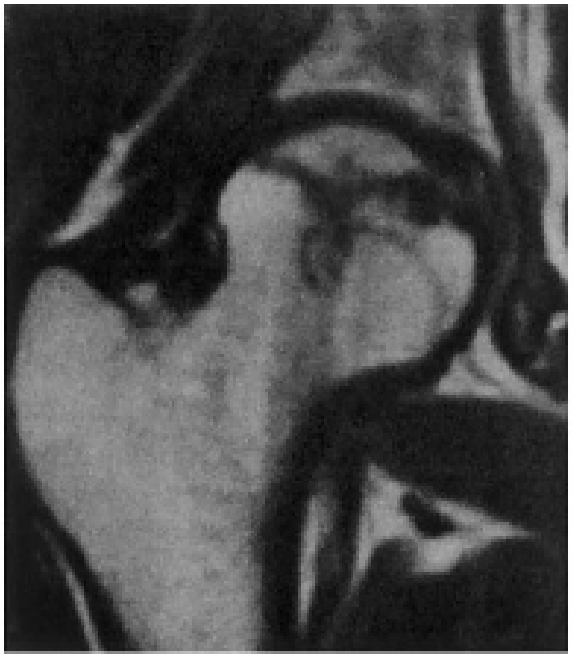
angioinvasive aspergilosis
with CNS involvement

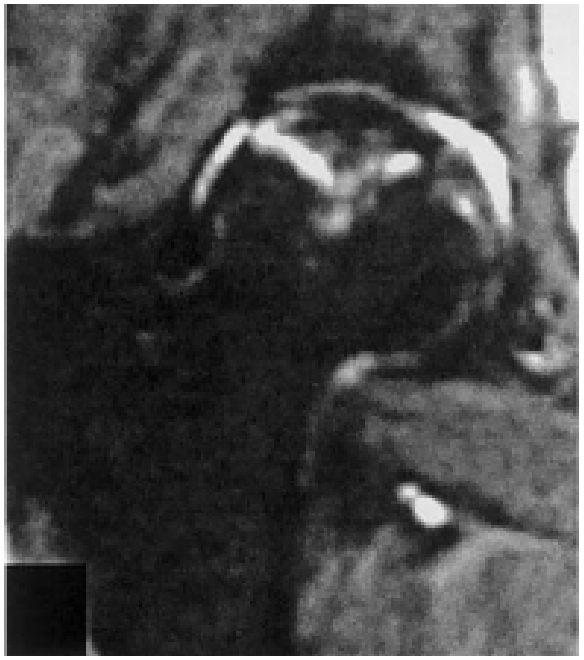


cytomegalovirus pneumoniae

X-ray **MRI**



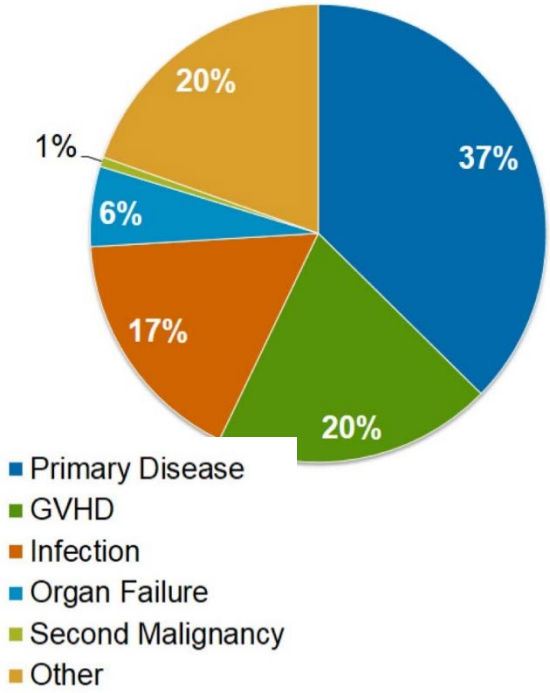




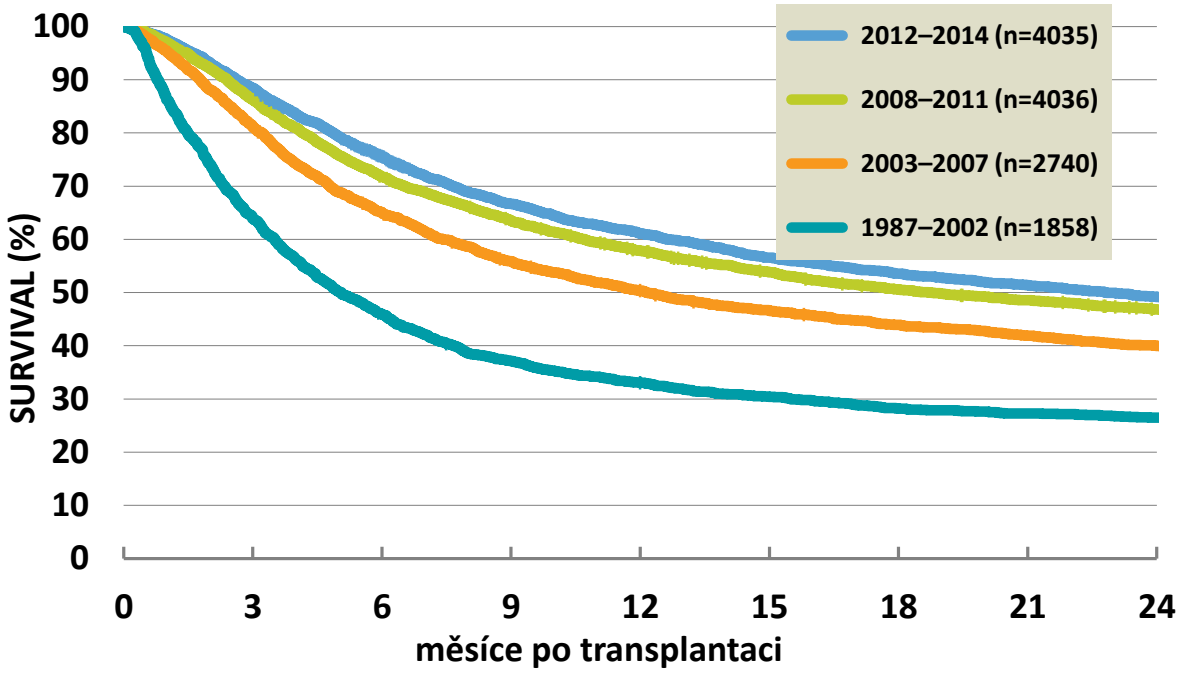
avascular necrosis of the hip joint (AVN)

Survival after allogeneic transplantation

causes of death after unrelated transplantation (2012-2013)



survival patients with AML (1987-2014)



- patient survival is continually improving
- main causes of death: relapse, GVHD, infection

zdroj www.CIBMTR.org

Allogeneic transplant

- indicated in patients with high-risk leukemia (cytogenetics)
- the risk of relapse after aloTx is relatively small (less than after standard treatment)
- but the toxicity of treatment is higher (infection, GVHD, organ toxicity)
- the advantage is the presence of graft-versus-leukemia effect (GVL) - reduces the risk of relapse

greater anti-leukemia effect - but at the cost of greater toxicity

THANKS FOR YOUR ATTENTION