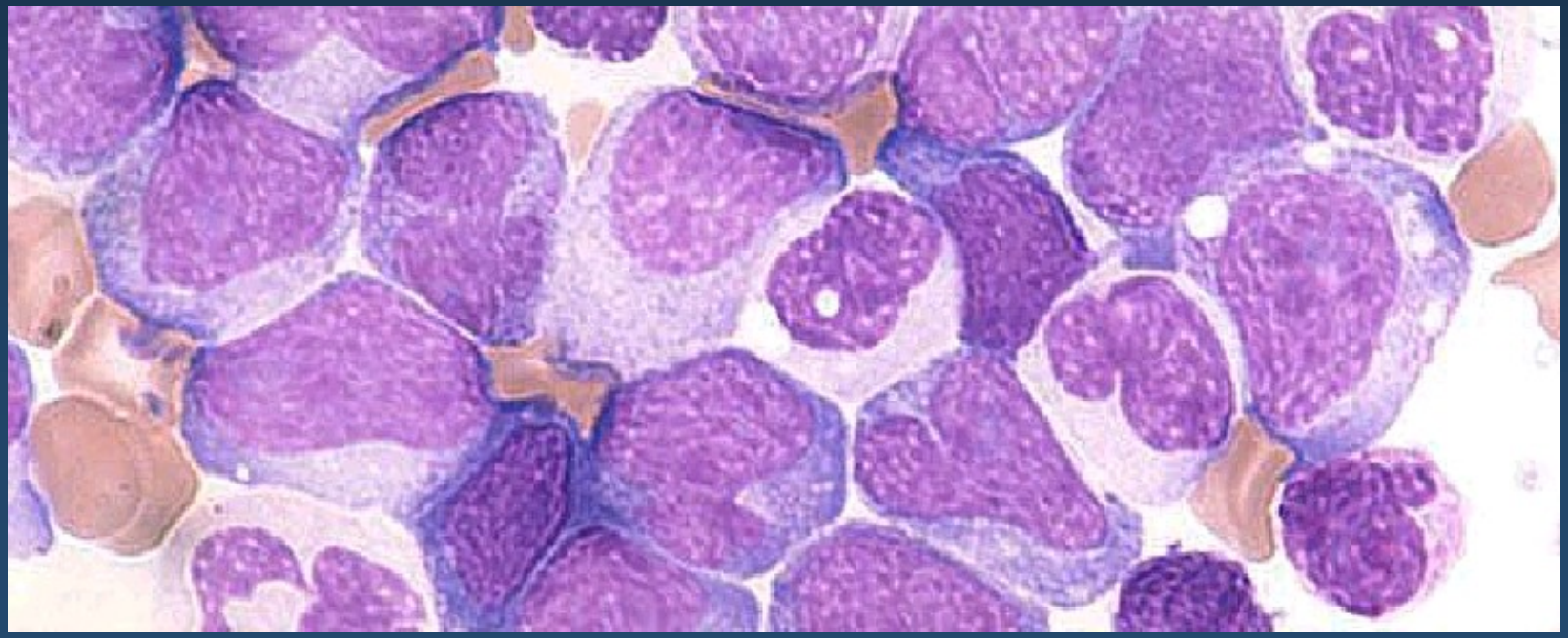
LEUKEMIAS AND MYELOPROLIFERATIVE DISEASES

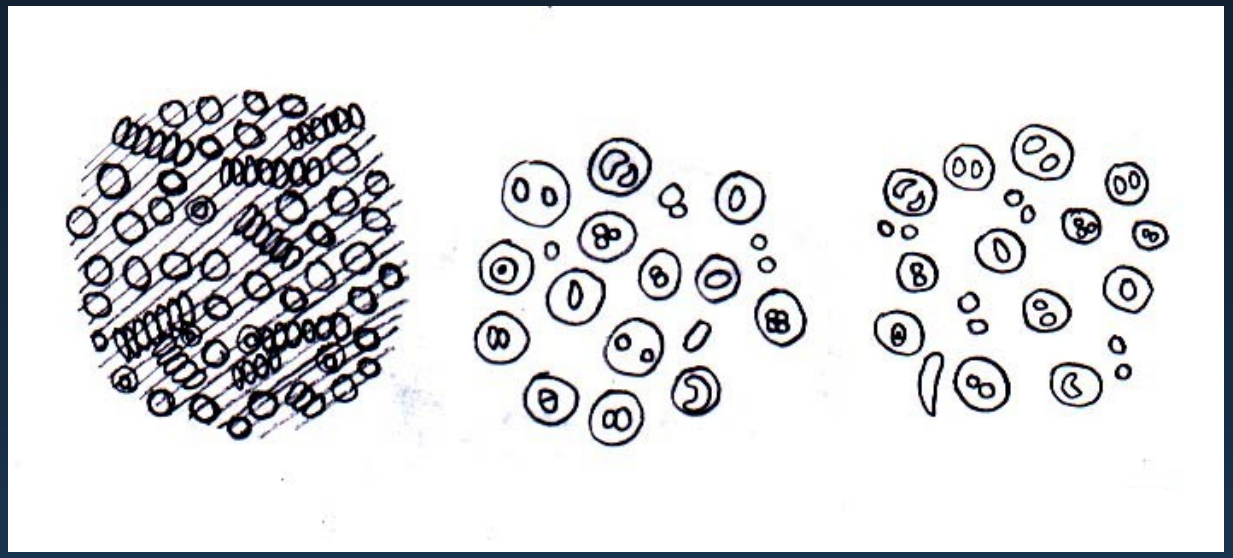


DEFINITION

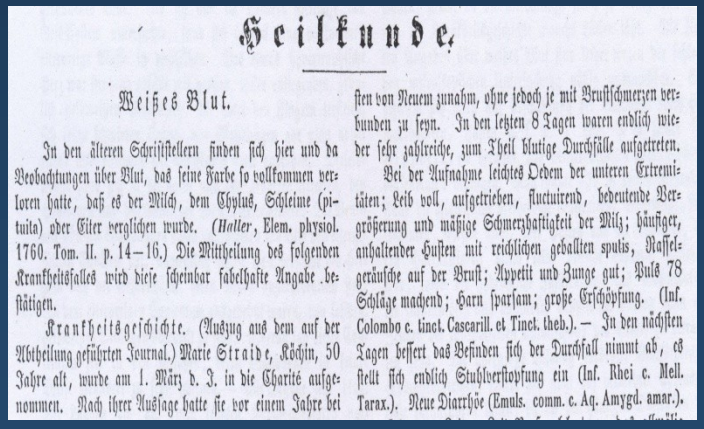
Leukemias and myeloproliferative diseases are CLONAL disorders resulting from a mutation of DNA within a pluripotent marrow stem cell or very early progenitor cell.

CLONAL POPULATION OF CELLS - cells with growth and/or proliferation advantage over against normal bone marrow cells.

Mutation of DNA can result in the expression of fusion genes that encode fusion proteins that are oncogenic or in the underexpression of genes that encode molecules critical to control of cell growth or progremmed cell death.



John Hughes Bennett: Two Cases of Disease and Enlargement of the Spleen, in which death took place from presence of purulent matter in the blood, 1845



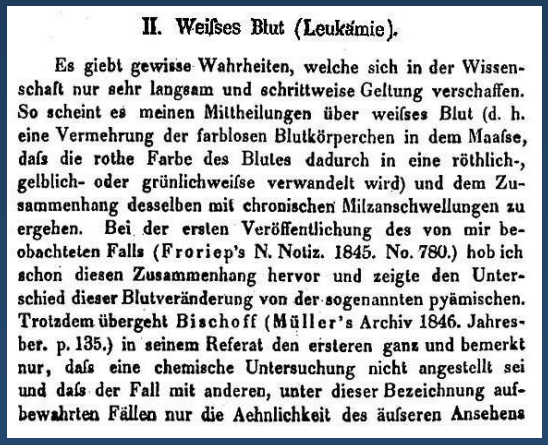
Heilkunde.

Weißes Blut.

In den älteren Schriftstellern finden sich hier und da Beobachtungen über Blut, das seine Farbe so vollkommen verloren hatte, daß es der Milch, dem Chylus, Schleime (pituita) oder Eiter verglichen wurde. (*Haller*, Elem. physiol. 1760. Tom. II. p. 14–16.) Die Mittheilung des folgenden Krankheitsfalles wird diese scheinbar fabelhafte Angabe bestätigen.

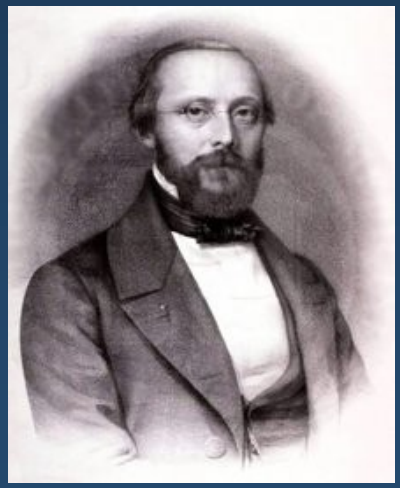
Krankheitsgeschichte. (Auszug aus dem auf der Abtheilung geführten Journal.) Marie Straide, Köchin, 50 Jahre alt, wurde am 1. März d. J. in die Charité aufgenommen. Nach ihrer Aussage hatte sie vor einem Jahre bei sten von Neuem zunahm, ohne jedoch je mit Brustschmerzen verbunden zu seyn. In den letzten 8 Tagen waren endlich wieder sehr zahlreiche, zum Theil blutige Durchfälle aufgetreten.

Bei der Aufnahme leichtes Oedem der unteren Extremitäten; Leib voll, aufgetrieben, fluctuirend, bedeutende Vergrößerung und mäßige Schmerzhaftigkeit der Milz; häufiger, anhaltender Husten mit reichlichen geballten sputis, Rasselgeräusche auf der Brust; Appetit und Zunge gut; Puls 78 Schläge machend; Harn sparsam; große Erschöpfung. (Inf. Colombo c. tinct. Cascarill. et Tinct. theb.). — In den nächsten Tagen bessert das Befinden sich der Durchfall nimmt ab, es stellt sich endlich Stuhlverstopfung ein (Inf. Rhei c. Mell. Tarax.). Neue Diarrhöe (Emuls. comm. c. Aq. Amygd. amar.).



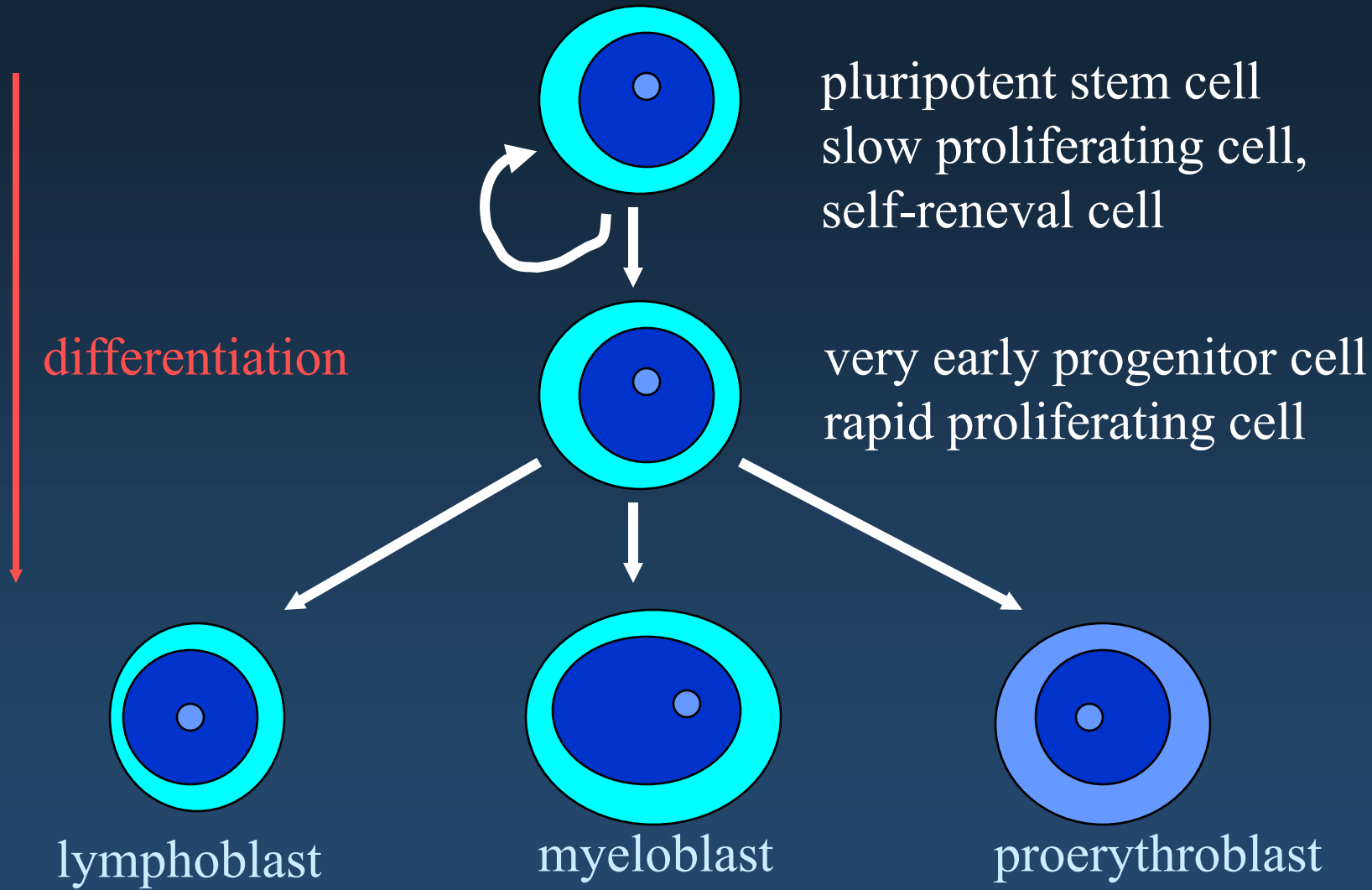
II. Weifses Blut (Leukämie).

Es giebt gewisse Wahrheiten, welche sich in der Wissenschaft nur sehr langsam und schrittweise Geltung verschaffen. So scheint es meinen Mittheilungen über weifses Blut (d. h. eine Vermehrung der farblosen Blutkörperchen in dem Maafse, dafs die rothe Farbe des Blutes dadurch in eine röthlich-, gelblich- oder grünlichweifse verwandelt wird) und dem Zusammenhang desselben mit chronischen Milzanschwellungen zu ergehen. Bei der ersten Veröffentlichung des von mir beobachteten Falls (Froriep's N. Notiz. 1845. No. 780.) hob ich schon diesen Zusammenhang hervor und zeigte den Unterschied dieser Blutveränderung von der sogenannten pyämischen. Trotzdem übergeht Bischoff (Müller's Archiv 1846. Jahresber. p. 135.) in seinem Referat den ersteren ganz und bemerkt nur, dafs eine chemische Untersuchung nicht angestellt sei und dafs der Fall mit anderen, unter dieser Bezeichnung aufbewahrten Fällen nur die Aehnlichkeit des äufseren Ansehens



Rudolf Virchow: Weisses Blut. Frorieps Notizen, 36, s. 152 – 156, 1845

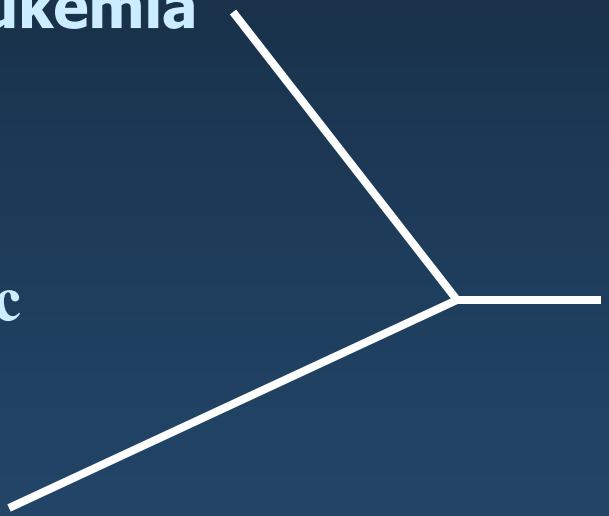
FIG.: SCHEME OF HEMATOPOIESIS



CLASSIFICATION OF MALIGNANT HEMATOPOIETIC DISEASES - shortened

Myeloproliferative disorders
- polycythemia vera
- essential thrombocytemia
- myelofibrosis
- chronic myeloid leukemia

Leukemias
- acute
  - myelogenous
  - lymphoblastic
- chronic
  - myeloid
  - lymphocytic
  - hairy cell



In reality, chronic myeloid leukemia is one of myeloproliferative disorders.

Myelodysplastic syndromes - „preleukemias“

Frequency of occurence

All leukemias affect
13/100 000 M 10/100 000 F

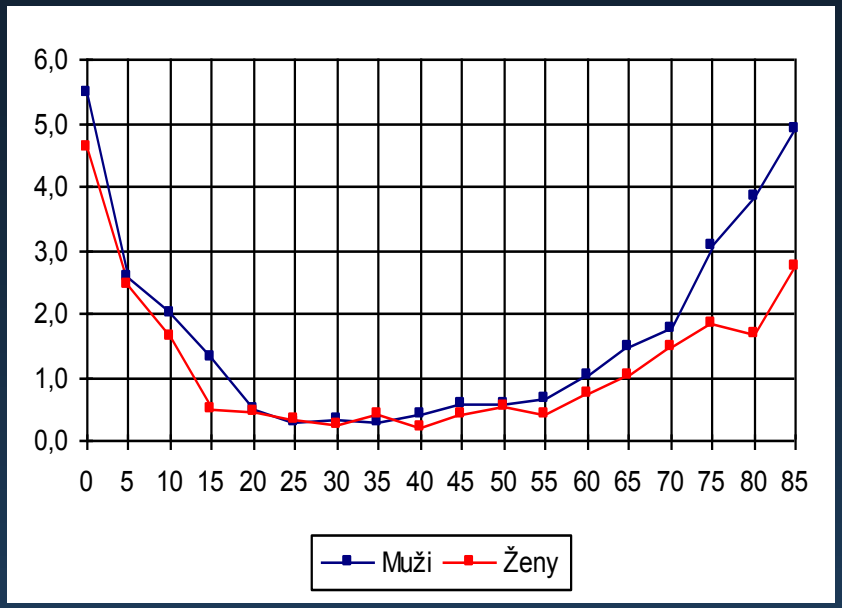
THERE IS A SLIGHT INCREASE COMAPRING WITH 70S.

40 % CLL (the most common leukemia of Caucasians)**,**
25 % AML, 15 % CML, 11 % ALL,
2 % HCL, 7 % other

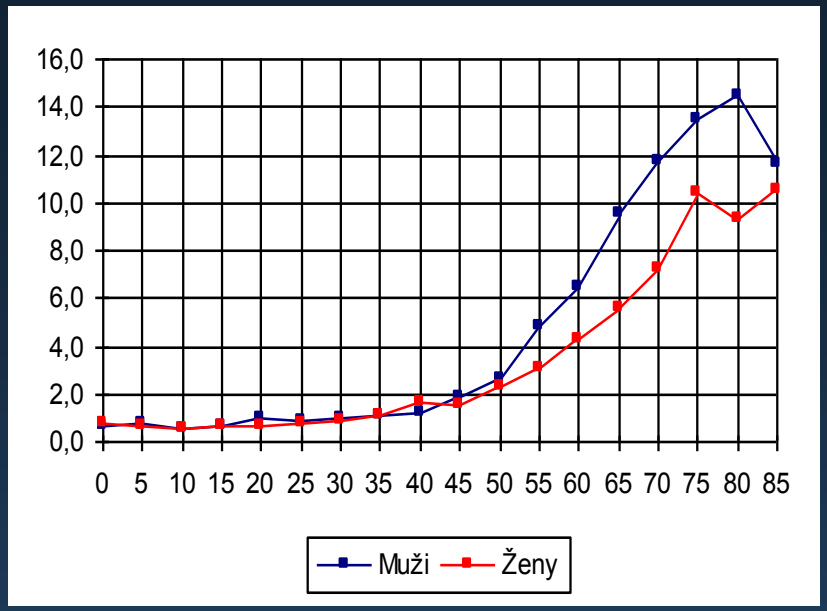
Myeloproliferative disorders without CML
1-3/100 000

Myelodysplastic syndromes
1-3/100 000

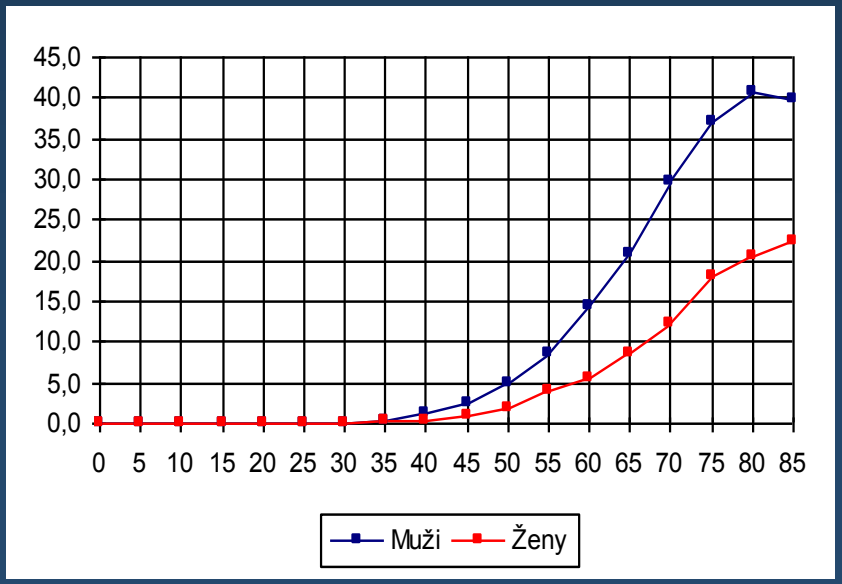
ALL per 100 000



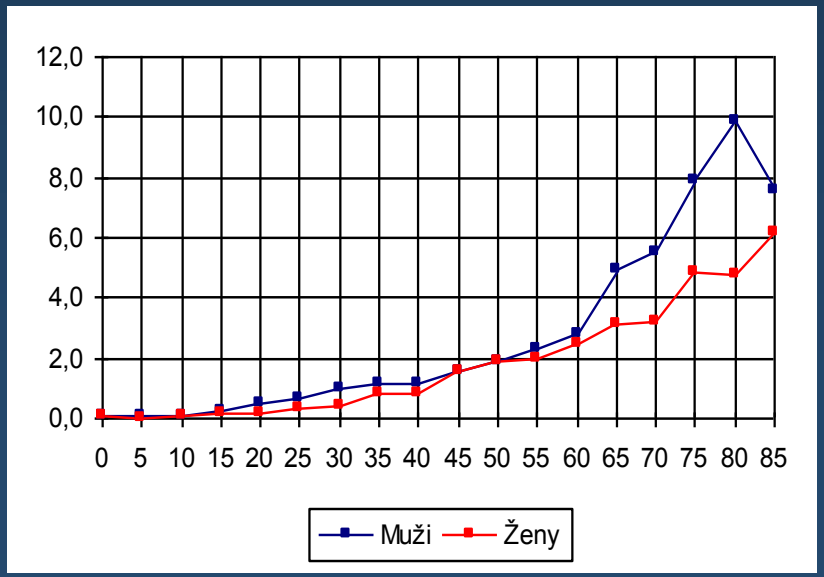
AML



CLL



CML



Clinical symptoms of malignant diseases of blood and bone marrow

Symptoms affecting patients	Frequency
infection, fever	36 % (all)
bleeding	33 % (APL, AML)
thrombosis, DIC	10 % (APL, ET, PV)
lymph nodes enlargement	57 % (ALL, CLL)
splenomegaly	56 % (CML, CLL, PV, MF)
hepatomegaly	47 % (CML, AML)
mediastinal tumor	14 % (ALL, CLL)
CNS involvemet	7 % (ALL, AML M5)
involvement of another organs	9 % (all)

CAVE: All symptoms of hematologic diseases are non-specific!

Differential diagnosis

SPLENOMEGALY

Myelofibrosis, CML, HCL
CLL, CML
ALL (occasionally)

LYMPHADENOPATHY

CLL, ALL
(CML, AML)

ON SOME

MORBID APPEARANCES

OF

THE ABSORBENT GLANDS

AND

SPLEEN.

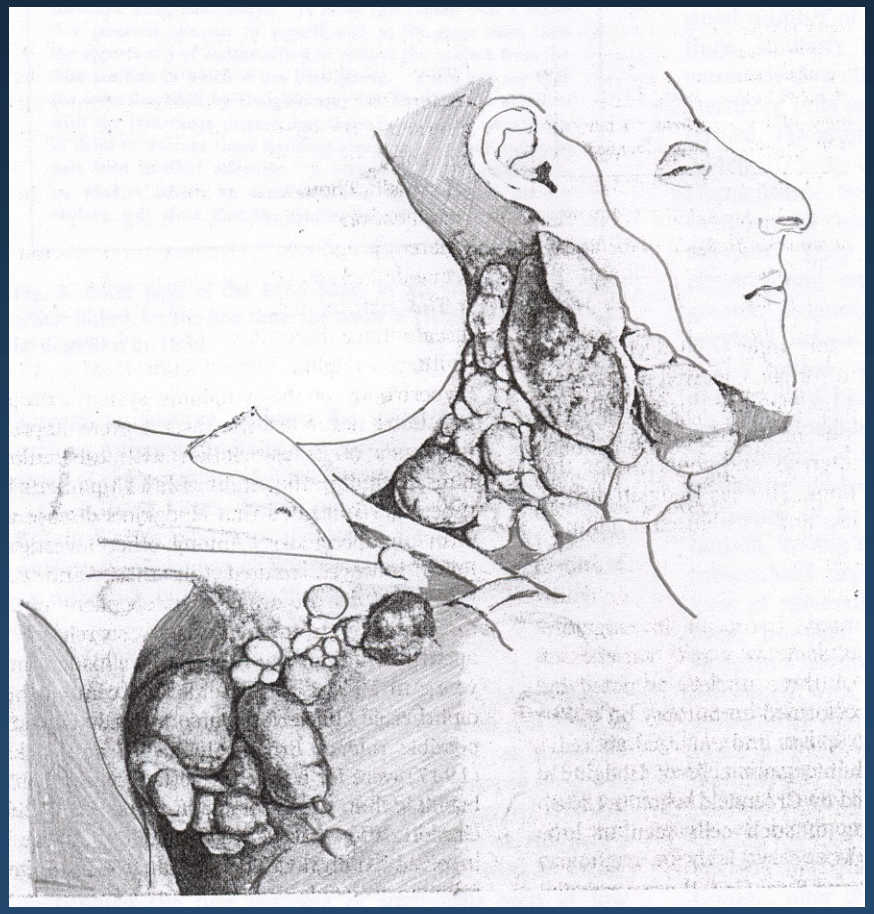
BY DR. HODGKIN.

PRESENTED

BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

THE morbid alterations of structure which I am about to describe are probably familiar to many



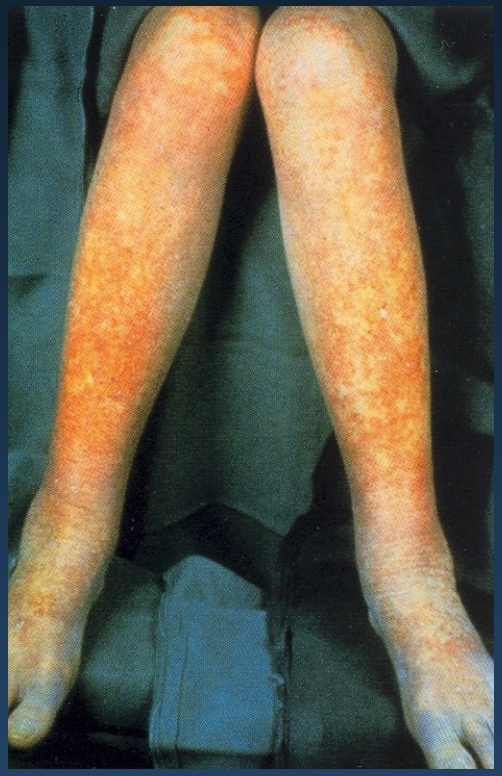
Differential diagnosis

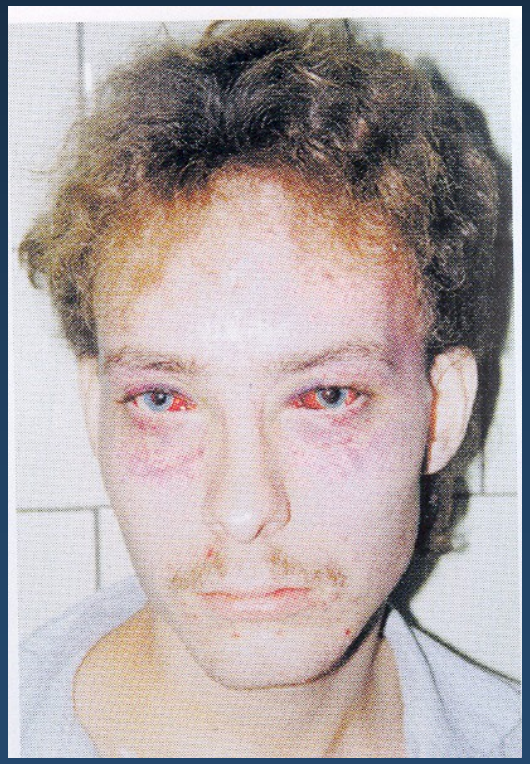
THROMBOCYTHEMIA

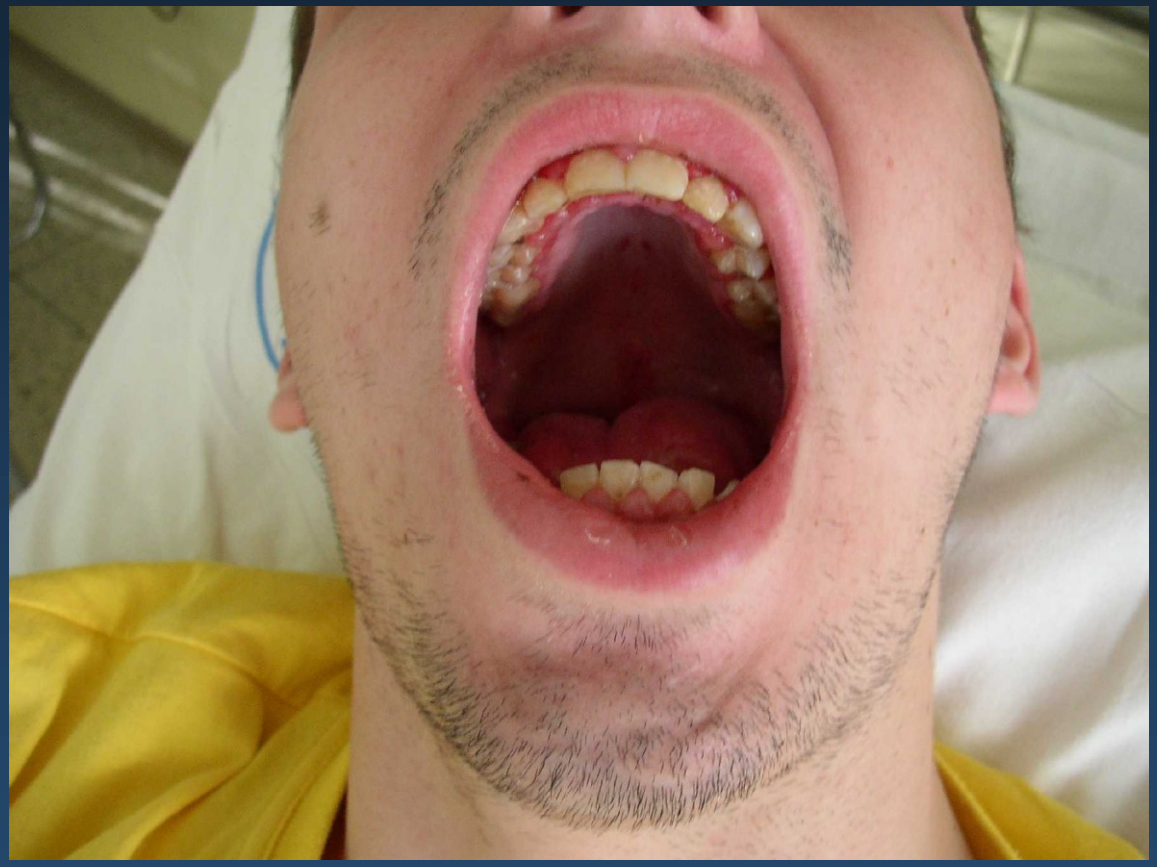
PMF, ET, PV, CML
MDS (5q-), MDS/MPS

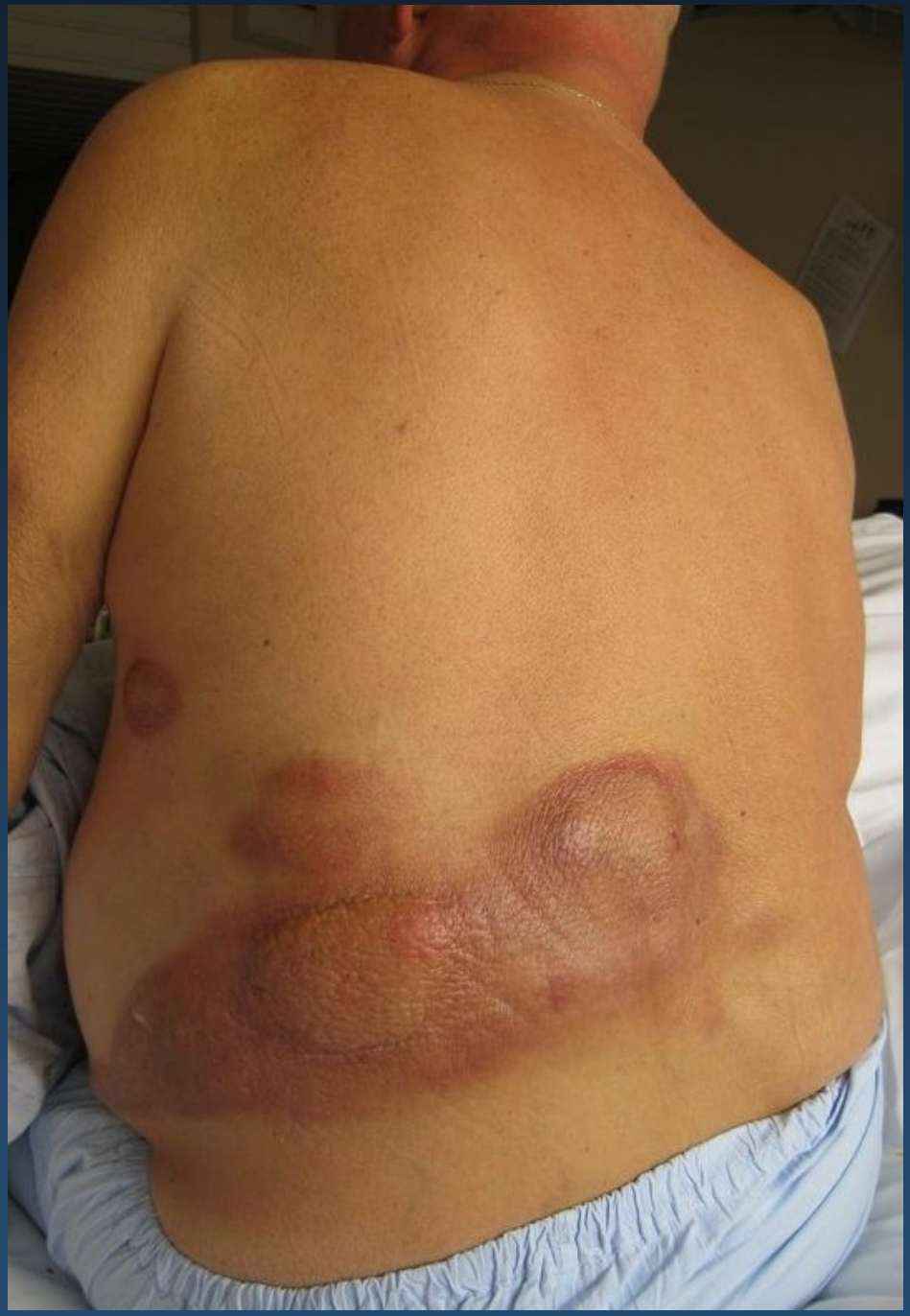
THROMBOCYTOPENIA

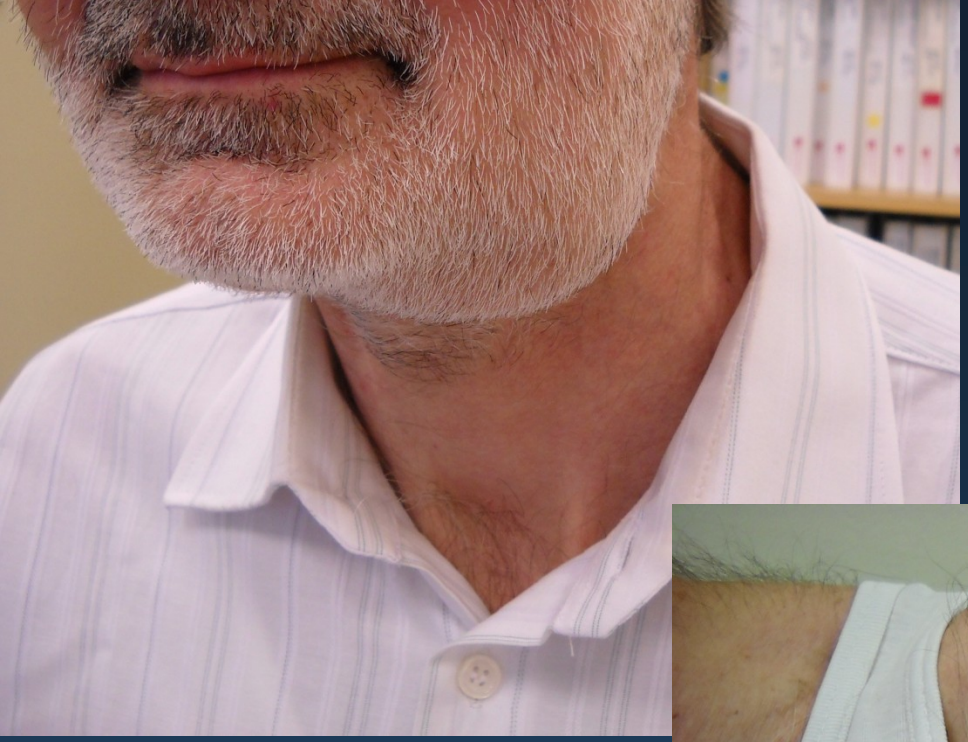
ALL, AML, HCL, MDS
myelofibrosis
CLL (autoimmune phenomenon)
CML (accelerated phase, blast crisis)

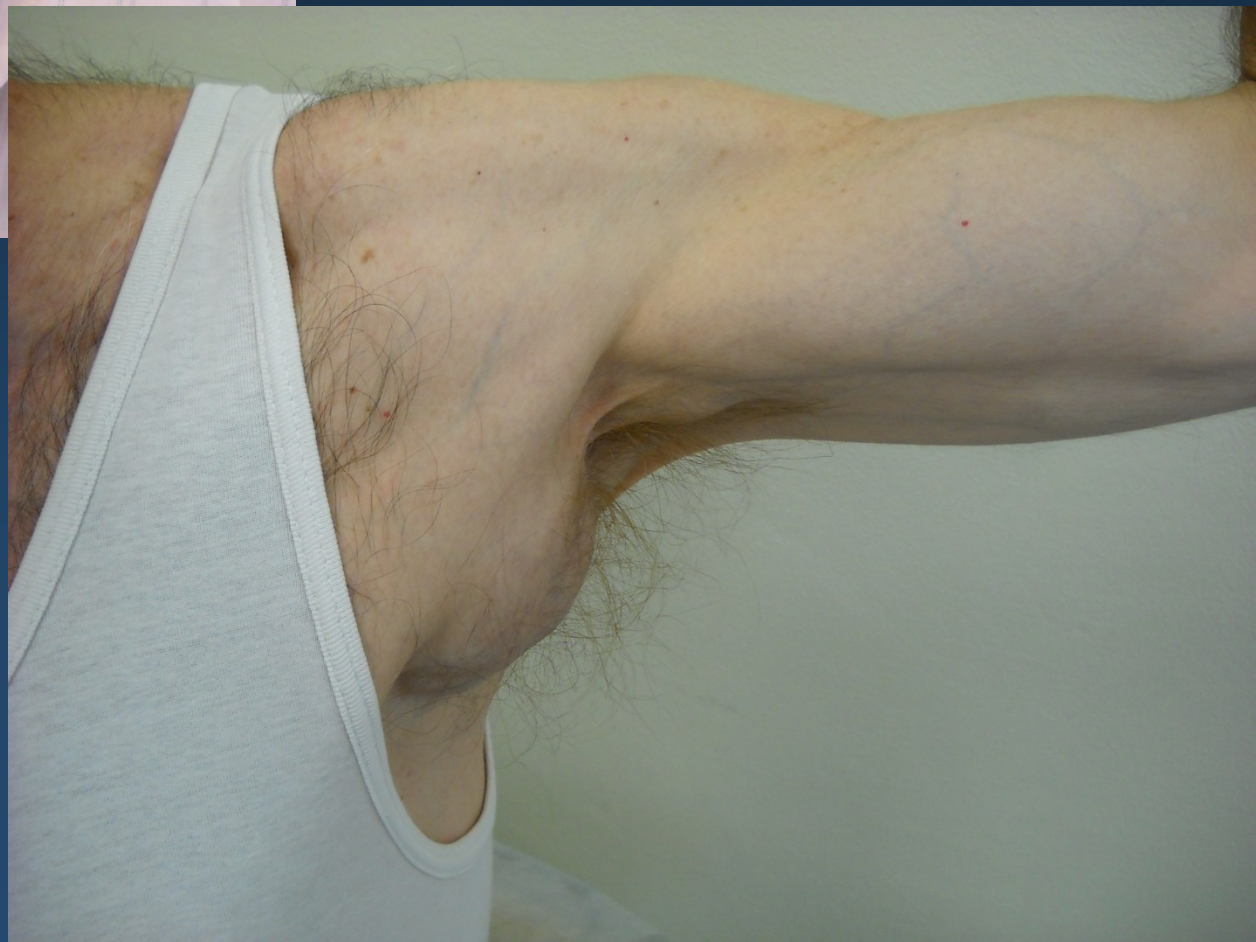












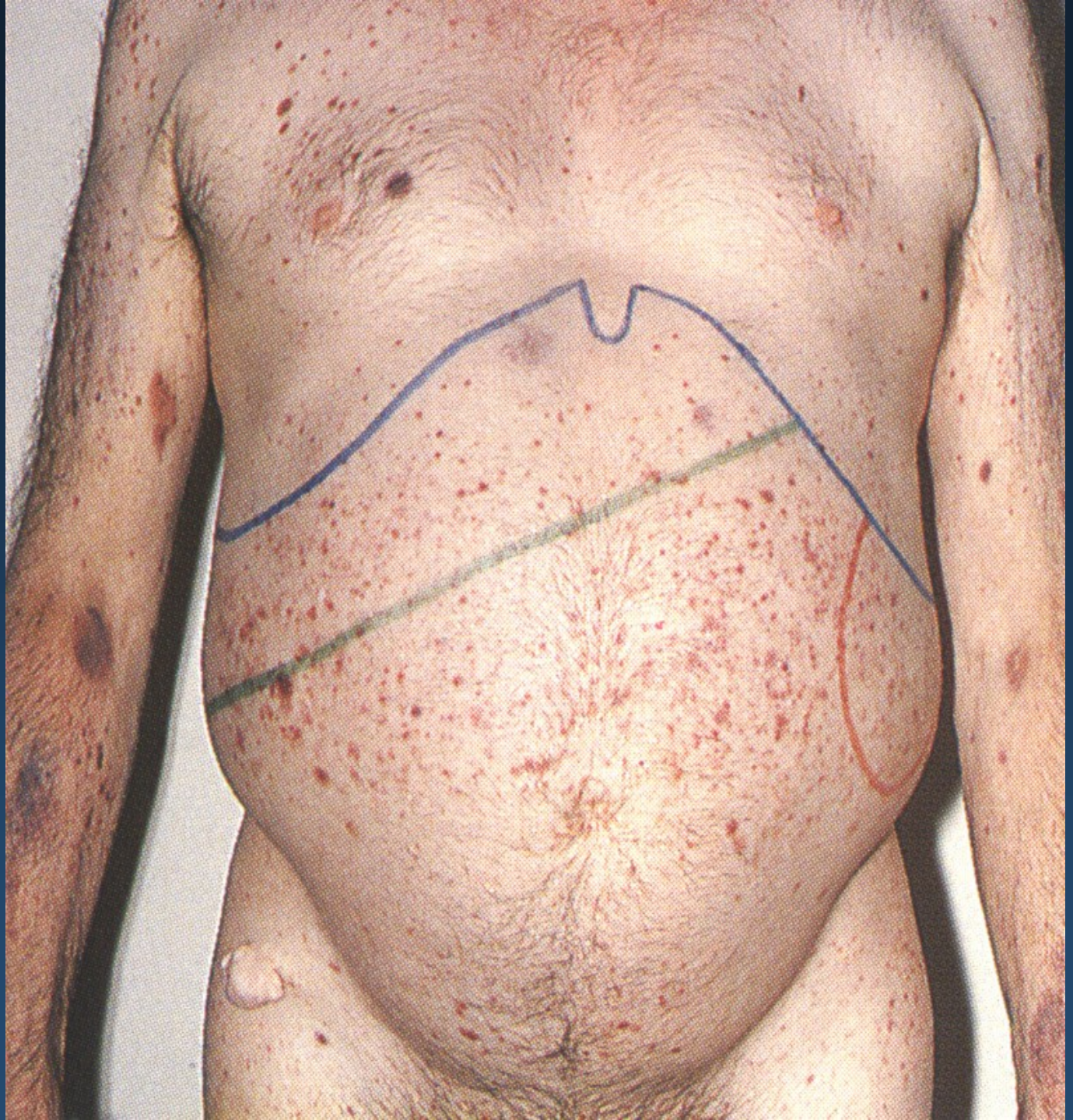


TABLE II. Time from the First Symptoms (Analysis Only Performed Among Patients that Presented Symptoms) and from the First Medical Visit to a Definitive Diagnosis

	ALL	AML	APL	CLL	CML	HCL	Acute leukemias	Chronic leukemias	Total
				Time from the first symptoms to a definitive diagnosis[a]					
No. of analyzed pts.	90	305	59	125	68	22	454	215	669
Days—median (range)	25 (3–194)	22 (0–226)	14 (3–90)	27 (3–274)	21 (1–256)	34.5 (4–370)	21 (0–226)	27 (1–370)	22 (0–370)
Days—25–75% interval	14–43	12–36	8–22	14–52	11.5–48	14–77	12–35	13–60	12–42
				Time from the first medical visit to a definitive diagnosis					
No. of analyzed pts.	106	366[b]	74	293	123	41	546	457	1003
Days—median (range)	9 (0–108)	7 (0–171)	5.5 (0–71)	12 (0–343)	6 (0–119)	20 (0–355)	7 (0–171)	10 (0–355)	8 (0–355)
Days—25–75% interval	3–16	3–16	2–12	4–22	2–16	8–36	3–15	3–23	3–19

LEUKEMIAS

Do you know differences between acute and chronic leukemias?

Briefly:

Acute leukemia - there is defect of proliferation, proliferation of young bone marrow cells (blasts) is increased!

Chronic leukemia - there is defect of apoptosis (programmed cell death), apoptosis of mature cells is decreased, mature cells are accumulated in the body!

CAVE: CL can switch to AL (CML in blast crisis, CLL in Richter´s syndrome)

LEUKEMIAS – PREDISPOSING FACTORS

Increased risk of leukemia is in:

Genetic syndromes – M. Down, FA, ataxia telangiectasia

Drugs (chemotherapy, alkylating agents)

Radiation (can cause all leukemias except CLL)

Socioeconomic factors

(increased incidence of childhood ALL in industrial countries, probably due to later contact of children with alergens or banal childhood infections)

Viruses (EBV, HTLV I, HIV)

Benzene, toluene, etc.

LEUKEMIAS – ETIOLOGY

	Autonomní buněčná proliferace	Blok diferenciace	Porucha apoptózy	Zvýšená sebeobnova	Ztráta kontroly buněčného cyklu	Diseminace maligních buněk
Lesion						
Molecular lesion	Aktivační mutace FLT3, JAK2, c-kit. Inaktivace NF1.	PML-RARα PZLF-RARα AML1-ETO (RUNX1-MTG8), CBFβ MYH11, translokace MLL genu. Mutace PU.1, C/EBPα	Mutace p53 a NPM. Nadměrná exprese Bcl-2.	Aktivace a mutace cateninu.	Dysfunkce P15 a P16.	Sekrece TNF. Vysoká exprese selektinů, kadherinů a integrinů.

LEUKEMIAS AND MYELOPROLIFERATIVE DISEASES Blood and bone marrow features

What can we found in periperal blood (WBC, RBC, platelets)?

- acute leukemia
- chronic leukemia
- myeloproliferative diseases

What can we found in bone marrow?

- acute leukemia
- chronic leukemia
- myeloproliferative diseases

Laboratory diagnostics

Peripheral blood count with differential WBC

Bone marrow

Flow cytometry (analysis of CD antigens)
(ALL, CLL, LGL)
Cytogenetic analysis (CML, AL, MDS, CLL - ?)
Molecular genetic analysis (CML, APL)
Cytology a cytochemistry
Histology (necessary in myeloproliferative diseases)

Do you know differences between trephine biopsy and sternal puncture?

Sternal puncure - we can collect only marrow blood. SP fits for diagnostics of leukemias.

Laboratory diagnostics

Biochemical analysis of blood (elevated LD in myeloproliferative diseases)

Coagulation – DIC, thrombophilia, bleeding
fibrinogen, aPTT, PT, AT III, DD, EGT

Other
(Chest X ray, abdominal sonography, ECG, heart sonography, serology – CMV…)
- we have to exclude focal infections and to evaluate function of heart, kidneys, liver and lungs (chemotherapy is nephrotoxic, hepatotoxic or cardiotoxic)

Differential diagnosis of malignant hematologic diseases

LEUKOPENIA is typical finding in

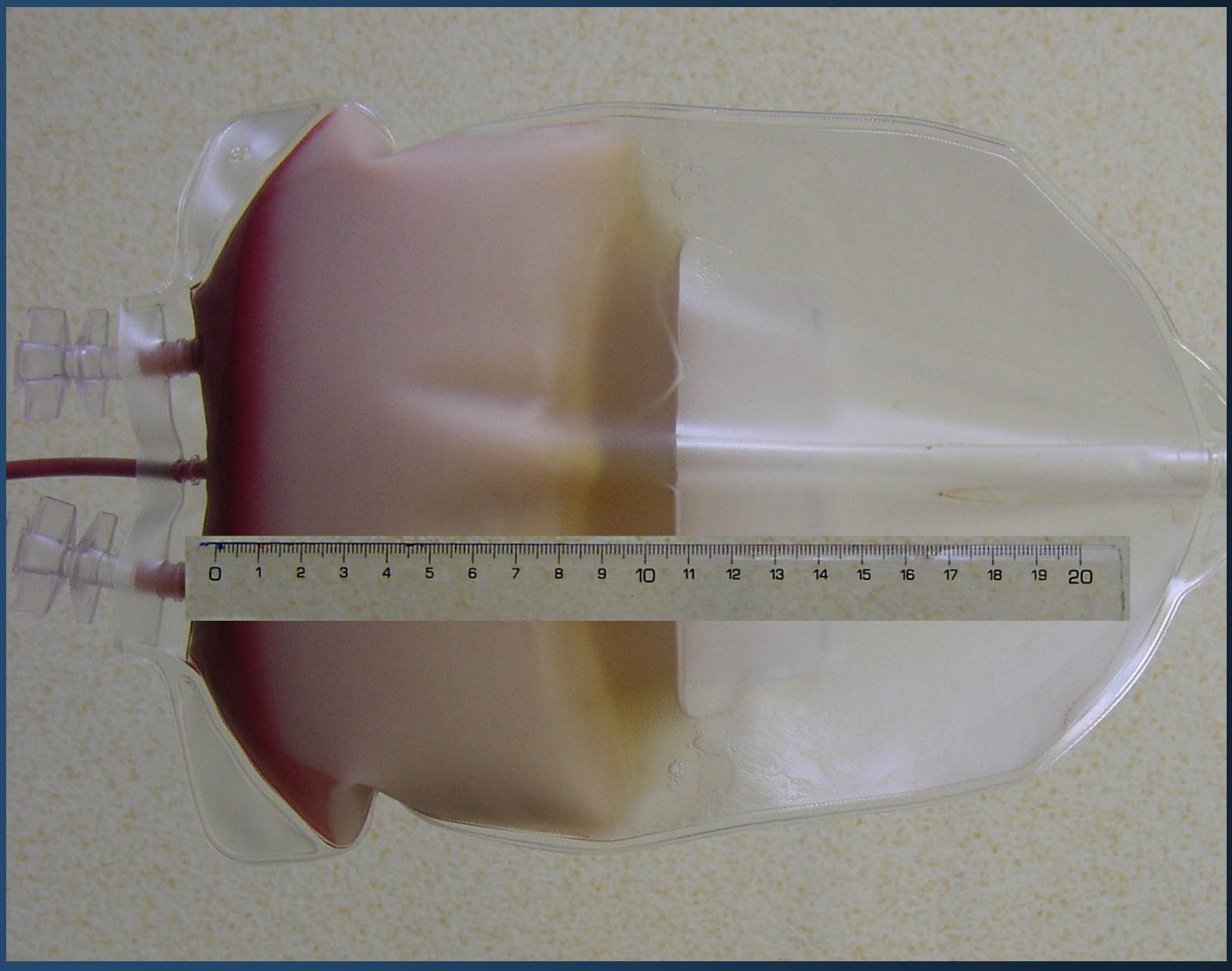
hairy cell leukemia
acute leukemias (ALL, AML M3, secondary or treatment related AL)
myelofibrosis
LGL (T-LGL)
MDS (RA, RC, RCMD, RARS, RAEB)

Differential diagnosis of malignant hematologic diseases

LEUKOCYTOSIS

variant hairy cell leukemia
acute leukemias (worse prognosis)
CML, CLL
ET, PV
myelofibrosis
MDS, MDS/MPS

Hyperleukocytic syndrome
develops when WBC is over 200 leu/uL in CML or AL, or over 500 leu/uL in CLL (smaller cells in CLL).
The circulation of CNS, lungs, retina or penis is most sensitive to the effect of leucostasis. There are hemorrhage, dyspnea, priapism, vascular oclusion and disruption.
Treatment: leukapheresis and or cytoreduction chemotherapy.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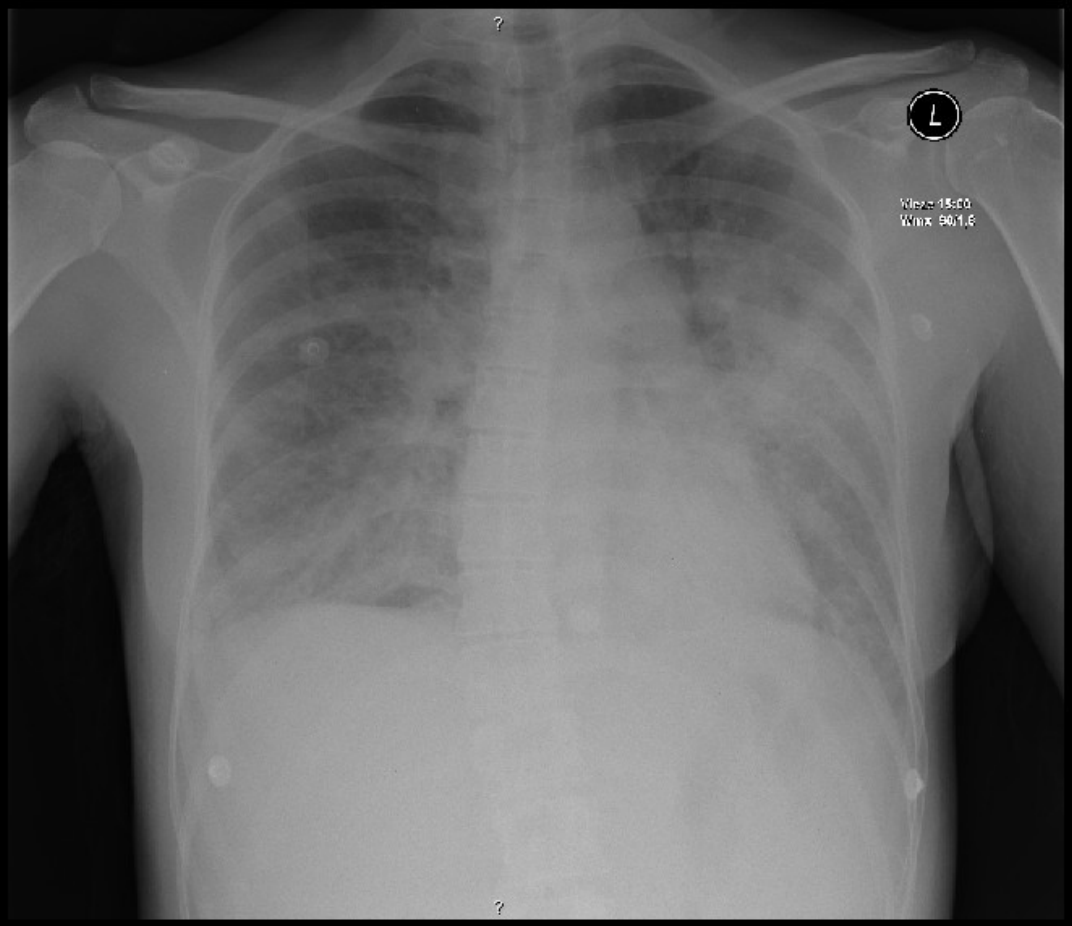
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Classification of leukemias

FAB (1982)

Classification according to morphology of malignant cells

WHO (1999-)

Classification according to morphology, cytogenetic features, flow cytometry, and molecular genetic features

Classification of AML

FAB (1982) divides AML among

AML M0, M1, M2, M3, M4, M5, M6, M7

WHO (1999-) divides AML among

AML with recurrent chromosomal abnormality

t(8,21), t(15,17), t(16,16), translocation of 11q23

AML developed from MDS

Treatment related AML – topoisomerase II inhibitors, alkylating agents

Remainder AML – see FAB

Classification of ALL

FAB (1982)

ALL L1, L2, L3

WHO (1999) includes ALL in malignancies from B or T precursor cells

EGIL classification divides ALL among

T ALL
pro T, pre T, thymic T, mature T
B ALL
pro B, common B, pre B, mature B

Classification of chronic lymphoproliferative diseases

WHO (1999-)

includes CLL, PLL, HCL, and plasma cell leukemia in malignancies from B or T peripheral cells

Classification of myeloproliferative diseases

FAB (1982)

CML, PV, ET, MF

WHO (1999-)

CML, CNL, HES/CEL, ET, PV, MMM

Myeloproliferative/myelodysplastic disorders

atypical CML, JMML, CMML

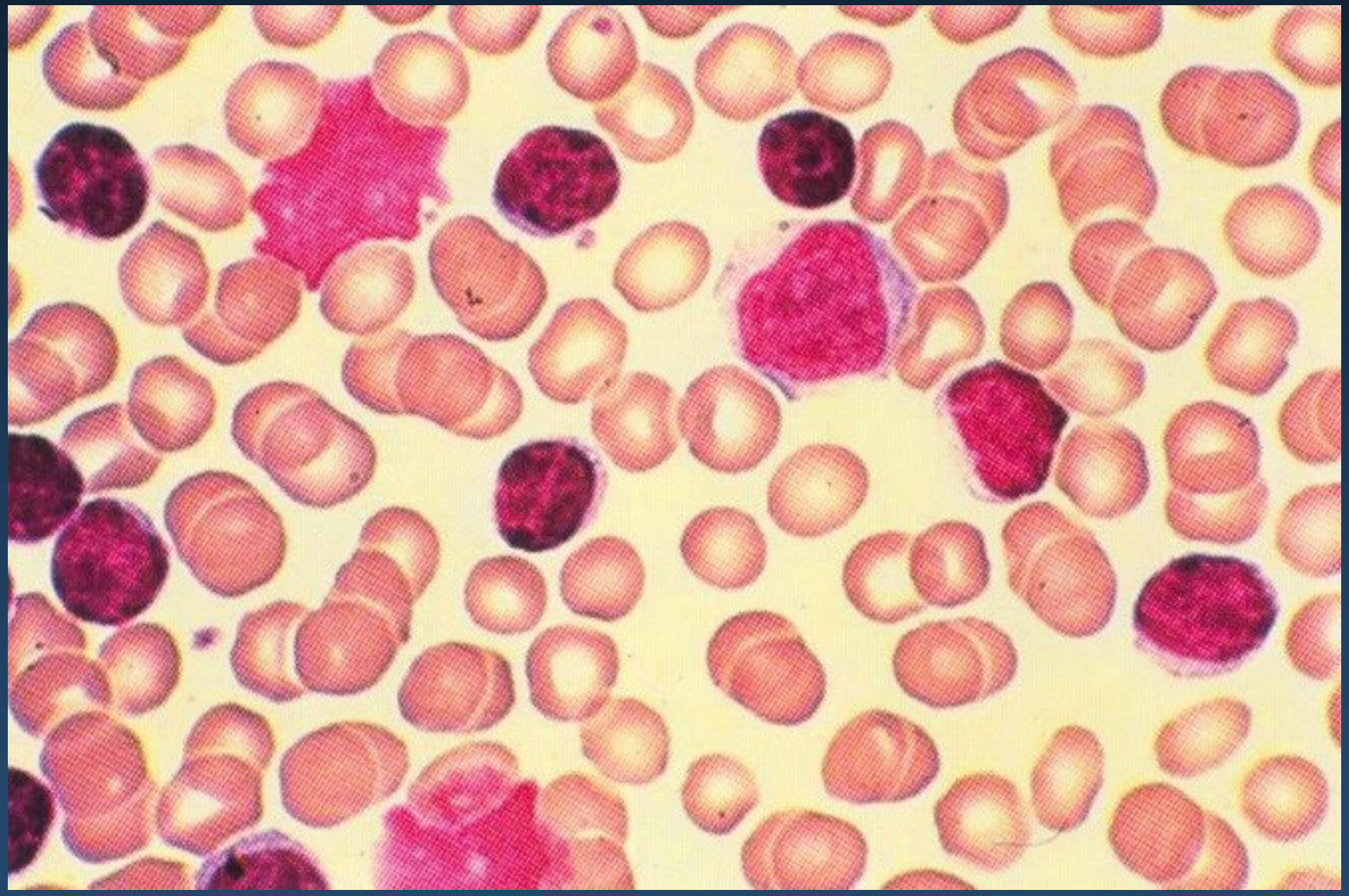
CLL

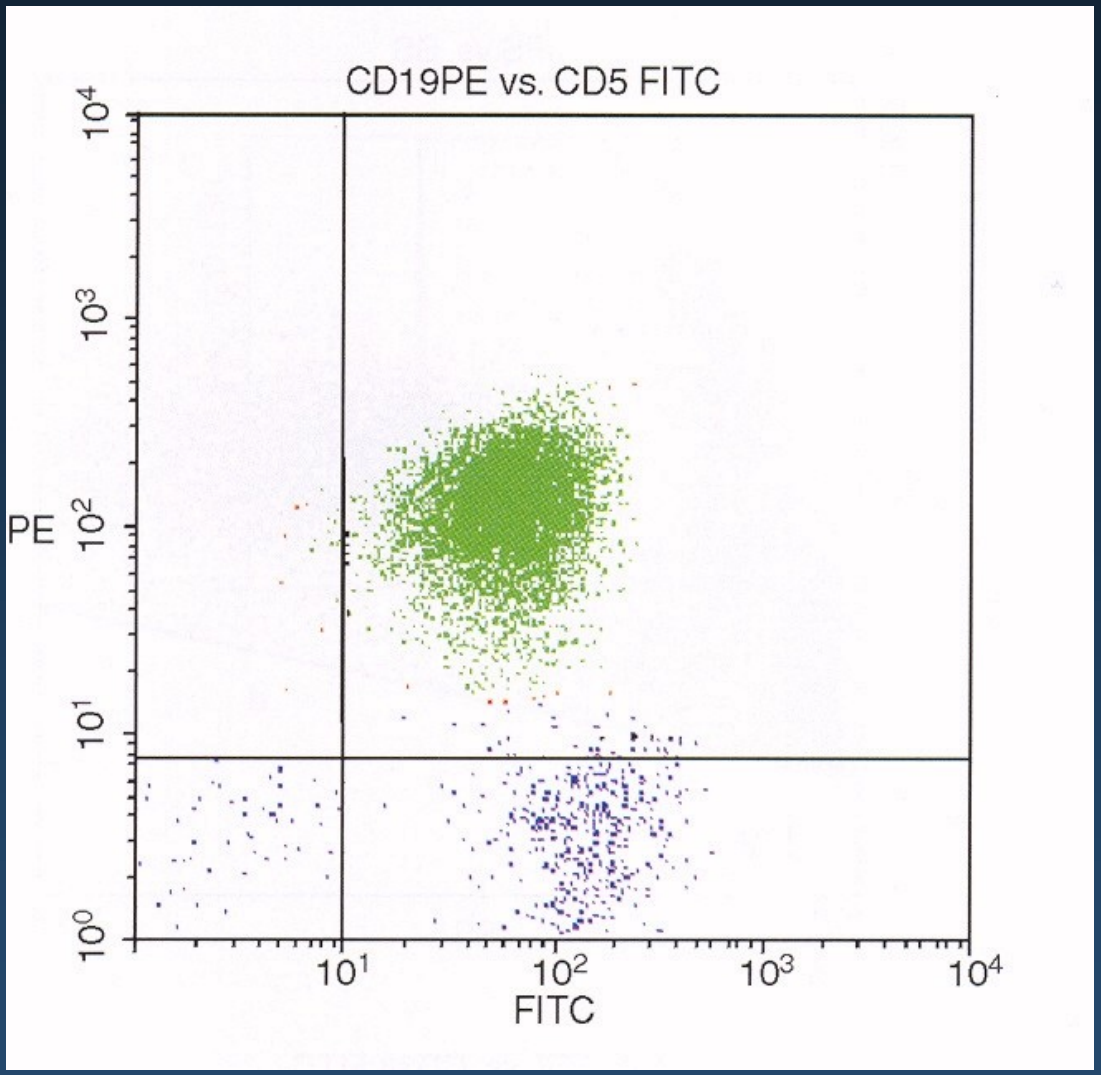
The most common leukemia of Caucasians. CLL is a disorder characterized by the accumulation of small mature-appearing lymphocytes in the blood, marrow, and lymphoid tissues.

Laboratory and clinical features:
leukocytosis (absolute lymphocytosis), lymphadenopathy, splenomegaly, hepatomegaly, anemia, thrombocytopena, often autoimune diseases (hemolysis).

Prognosis – different (better in CLL from „memory cells" (mutated genes for IgH), in CLL with del 13q14, with focal bone marrow involvment.

Median survival of CLL patients is 8 – 10 years.




CD19PE vs. CD5 FITC
PE
FITC
10^0
10^1
10^2
10^3
10^4

CLL

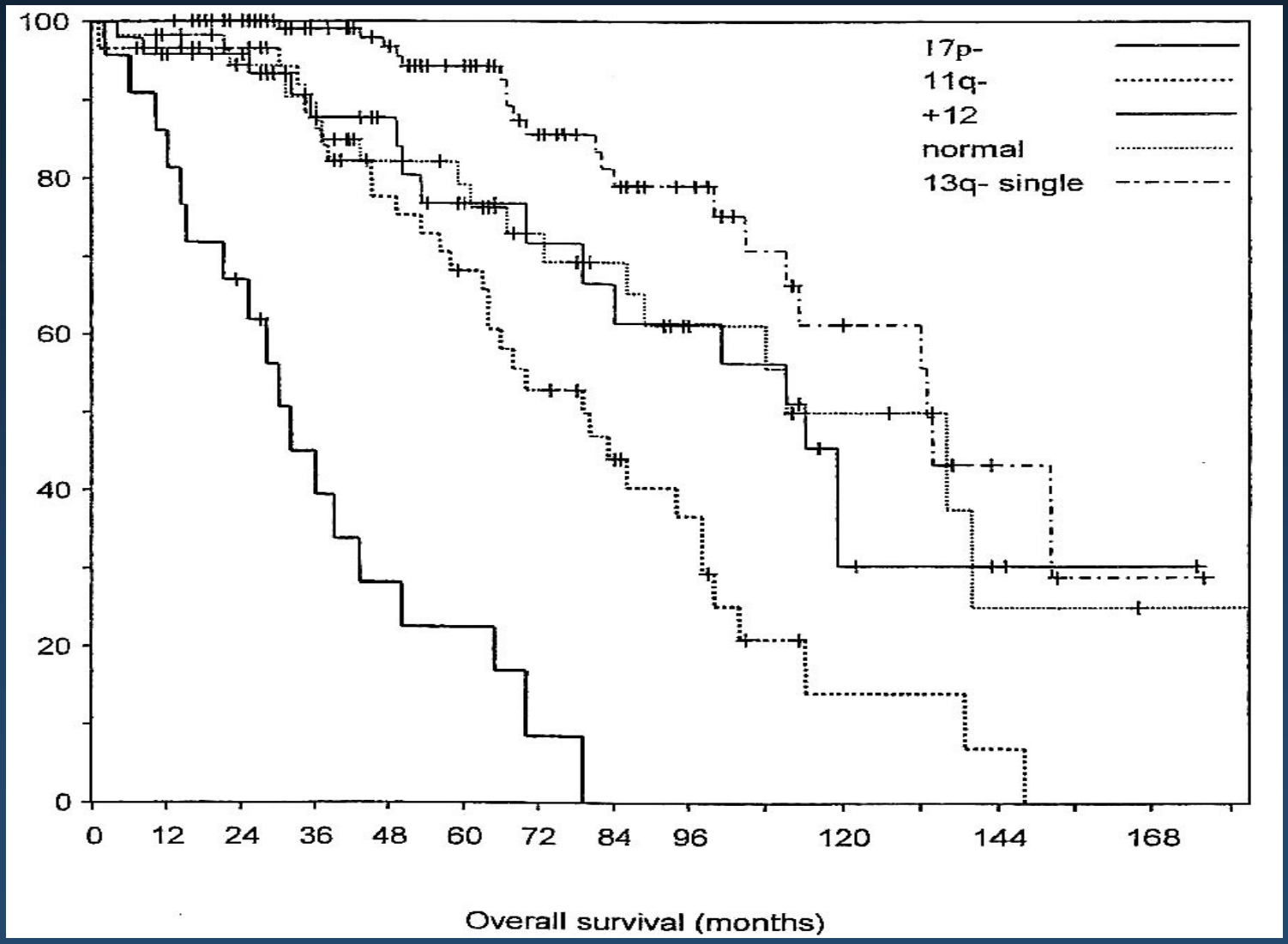
B - symptoms - fever, weight loss, sweat

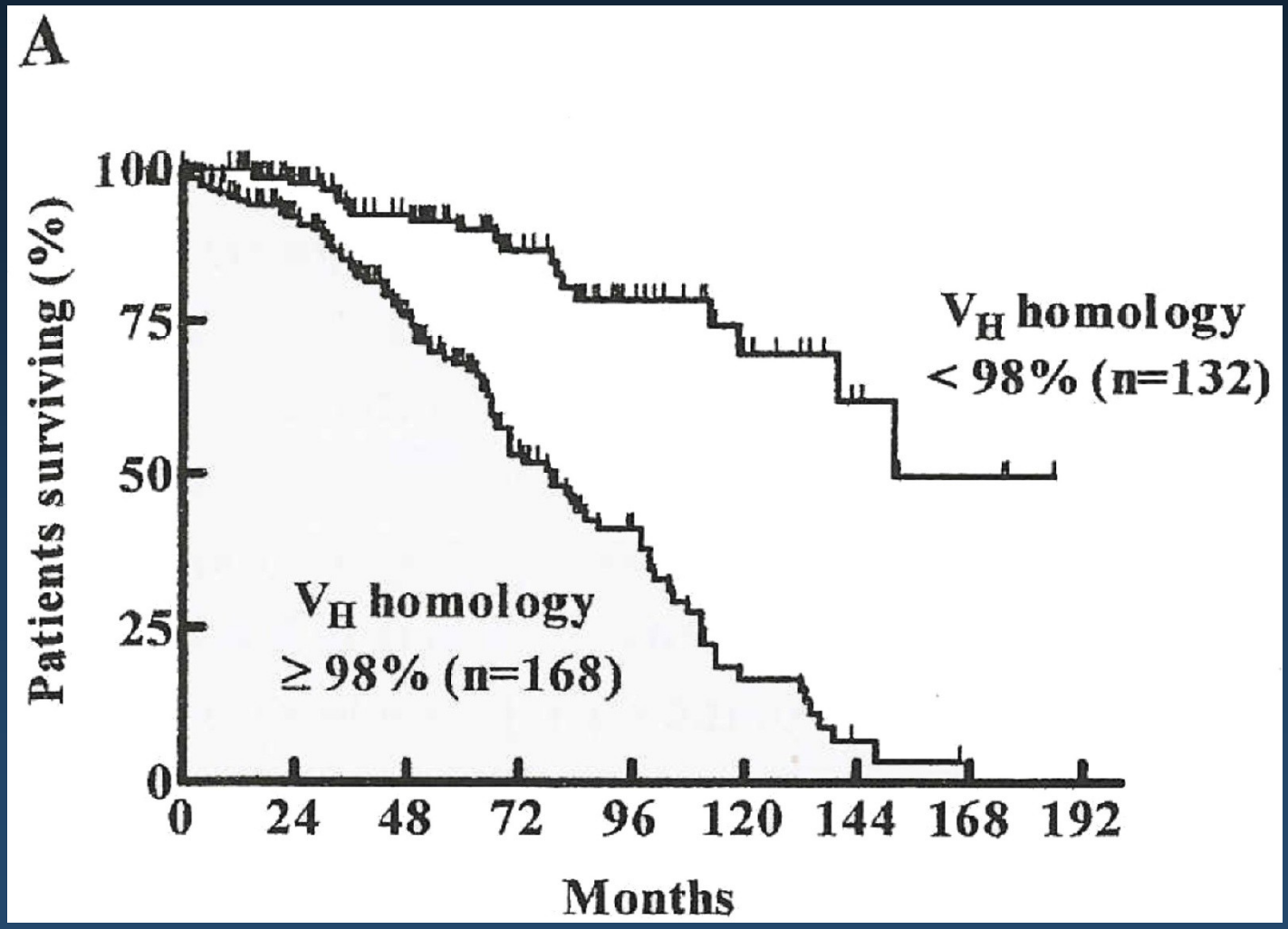
Indication for therapy:
anemia, thrombocytopenia, B-symptoms, painful spleen, doubling time of peripheral blood lymphocytes 6 months or shorter, symptomatic lymphadenopathy.

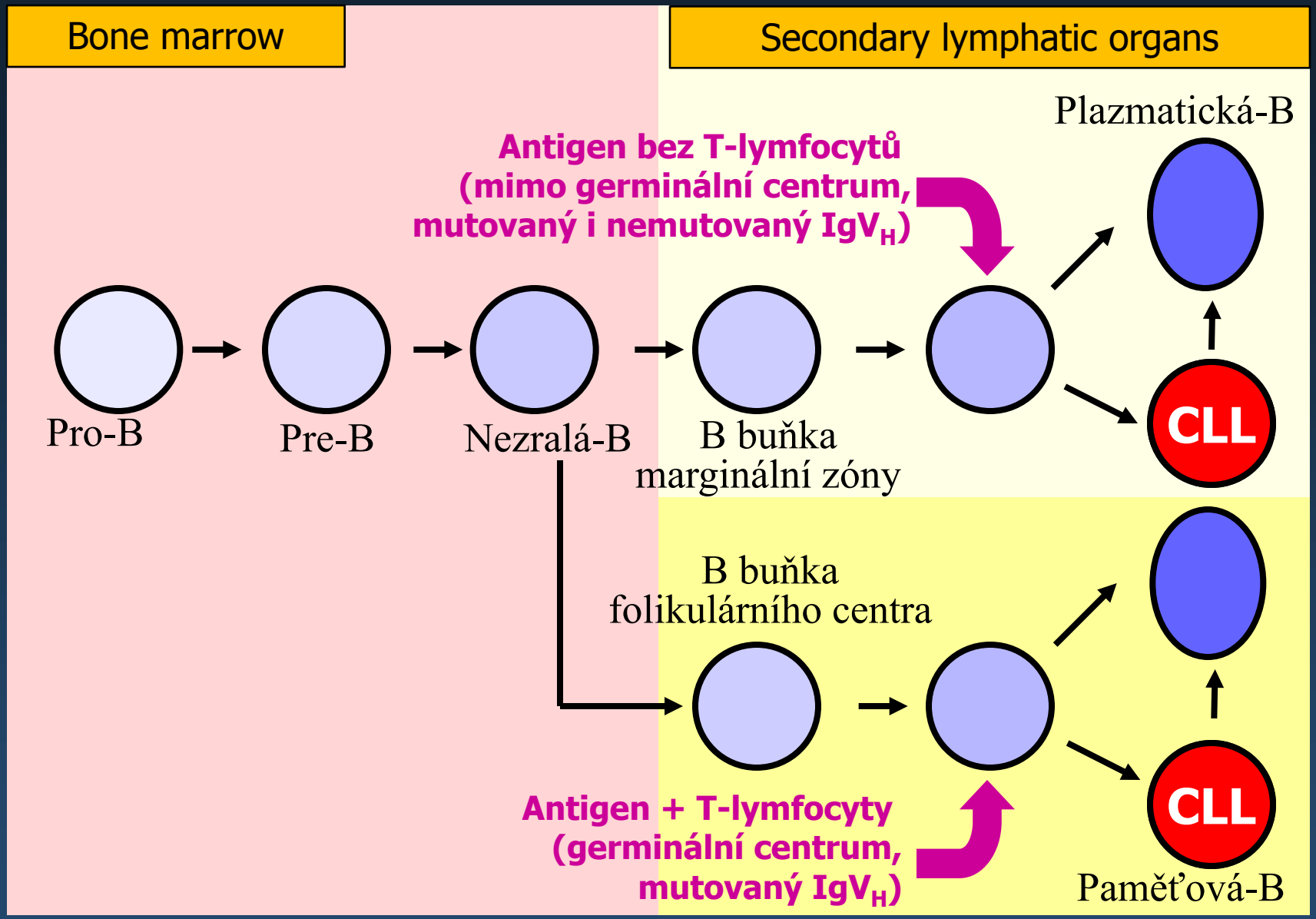
Therapy:
chlorambucil, fludarabin, cyklofosfamid, anthracyklins, anti CD52 antibody (alemtuzumab), anti CD20 antibody (rituximab)

Clinical stage (Rai)	Risk	Median survival
0 (lymphocytosis)	Low	>150 months
I (lymphocytosis + lymphadenopathy)	Intermediate	101
II (lymphocytosis + splenomegaly)	Intermediate	71
III (lymphocytosis + anemia Hb < 110 g/l)	High	19
IV (lymphocytosis + thrombocytopenia < $100x10^9$/L)	High	19
Clinical stage (Binet)		
A (involvement <3 regions)	Low	Not reached
B (involvement ≥ 3 regions)	Intermediate	84
C (anemia and thrombocytopenia)	High	24

Prognosis of CLL according cytogenetic features



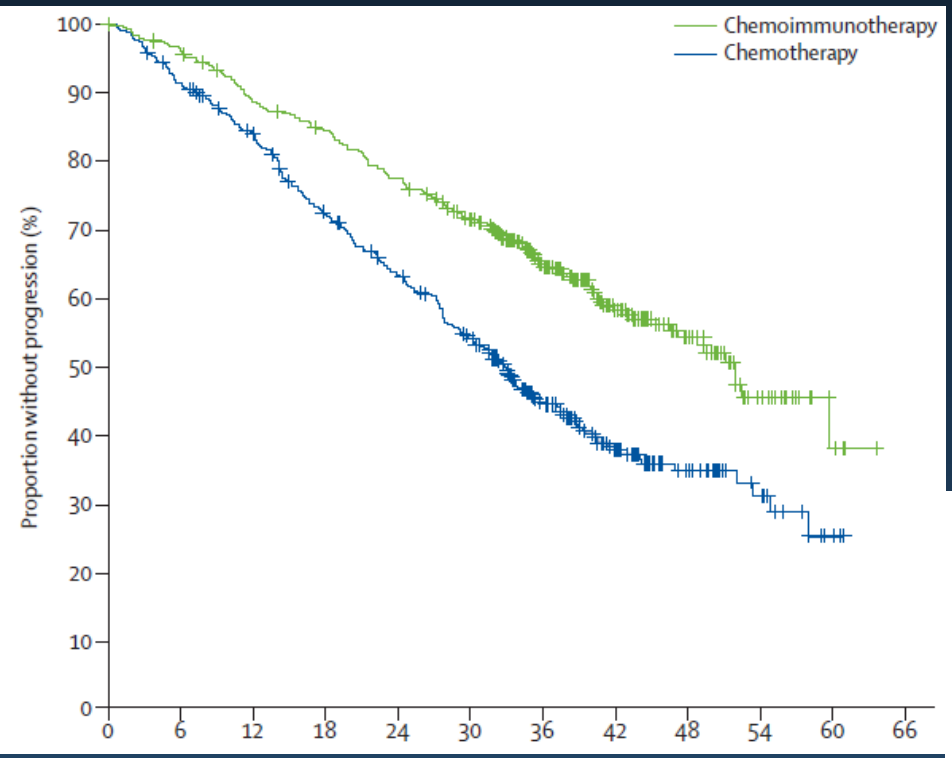

A
Patients surviving (%)
100
75
50
25
0
0
24
48
72
96
120
144
168
192
Months
V_H homology
< 98% (n=132)
V_H homology
≥ 98% (n=168)



B lymphocytes maturation

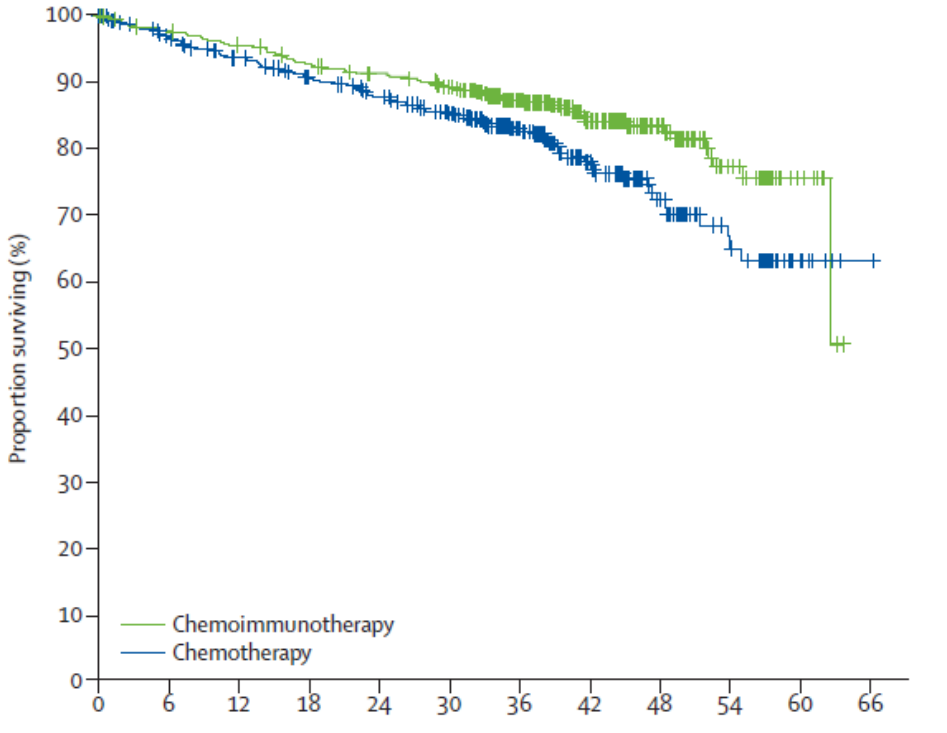
(Freda a kol., Adv. Cancer Res., 2001; Chiorazzi a kol., N. Engl. J. Med., 2005)

CLL – FCR regimen treatment



PFS at 3 years
45% vs. 65%
p < 0,0001

OS at 3 years
83% vs. 87%
p = 0,012

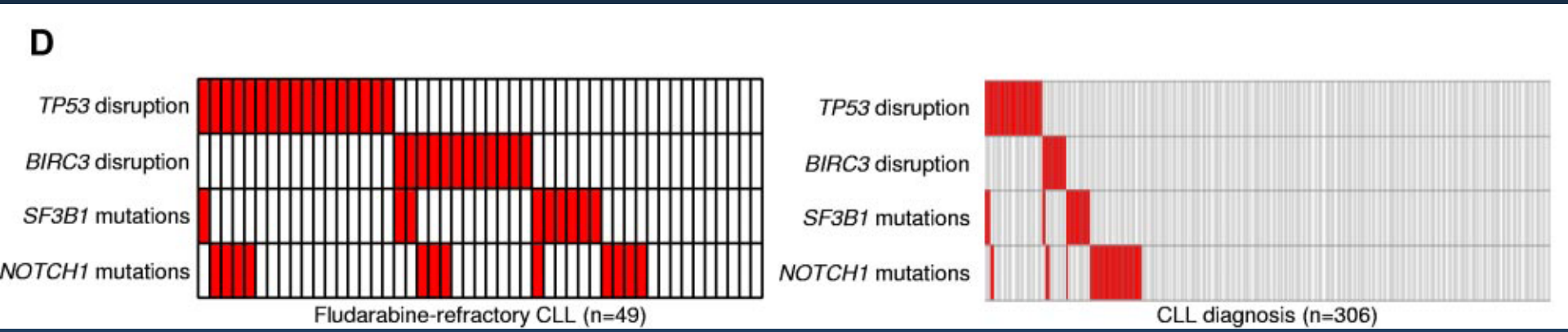


Clonal evolution in CLL – TP53

Before treatment

patient #	gender	age at diagnosis	mutation	sample	FASAY		Deep sequencing by GS Junior			
					result	[%]	result	[%]	coverage	p value
1	male	49	none	before therapy	neg.	5.7	neg.	< 0.2	> 5000	not tested
				follow-up I	neg.	4.3	neg.	< 0.2	> 5000	not tested
2	male	57	H179R	before therapy	neg.	4.0	pos	0.45	11409	< 0.001
				follow-up I	pos	75.1	pos	86.17	8307	< 0.001
3	female	44	R175H	before therapy	neg.	6.0	pos	13.03	7803	< 0.001
				follow-up I	pos	96.0	pos	94.10	12516	< 0.001
4	male	48	M246V	diagnosis	neg.	7.5	pos	1.70	5220	< 0.001
				follow-up I	pos	55.7	pos	50.87	5318	< 0.001
5	male	54	W146X	diagnosis	neg.	2.4	pos	0.38	5212	< 0.001
				follow-up I	pos	17.3	pos	69.99	9941	< 0.001
6	male	57	T211I	diagnosis	neg.	4.9	pos	0.53	6193	< 0.001
				follow-up I	pos	59.0	pos	51.73	8226	< 0.001
7	male	66	R273C	diagnosis	neg.	5.1	pos	0.24	16427	< 0.001
				follow-up I	pos	63.0	pos	74.22	6238	< 0.001
8	male	54	R249del	diagnosis	neg.	6.7	pos	2.80	7509	< 0.001
				follow-up I	pos	28.2	pos	46.04	6291	< 0.001
9	male	48	V272M	diagnosis	neg.	9.1	neg.	0.04	7064	0.5195
				follow-up I	neg.	2.6	pos	0.65	7128	< 0.001
				follow-up II	pos	52.0	pos	23.14	7369	< 0.001
10	female	59	I195T	diagnosis	neg.	8.7	pos	2.64	6250	< 0.001
			R248W		neg.		neg.	0.03	6095	0.7023
			I195T	follow-up I	pos	31.0	pos	28.05	6552	< 0.001
			R248W		neg.		pos	3.55	7343	< 0.001
			I195T	follow-up II	neg.	94.9	neg.	0.00	6979	1.0000
			R248W		pos		pos	97.80	7203	< 0.001

SFB3, NOTCH1, BIRC3, TP53 mutations

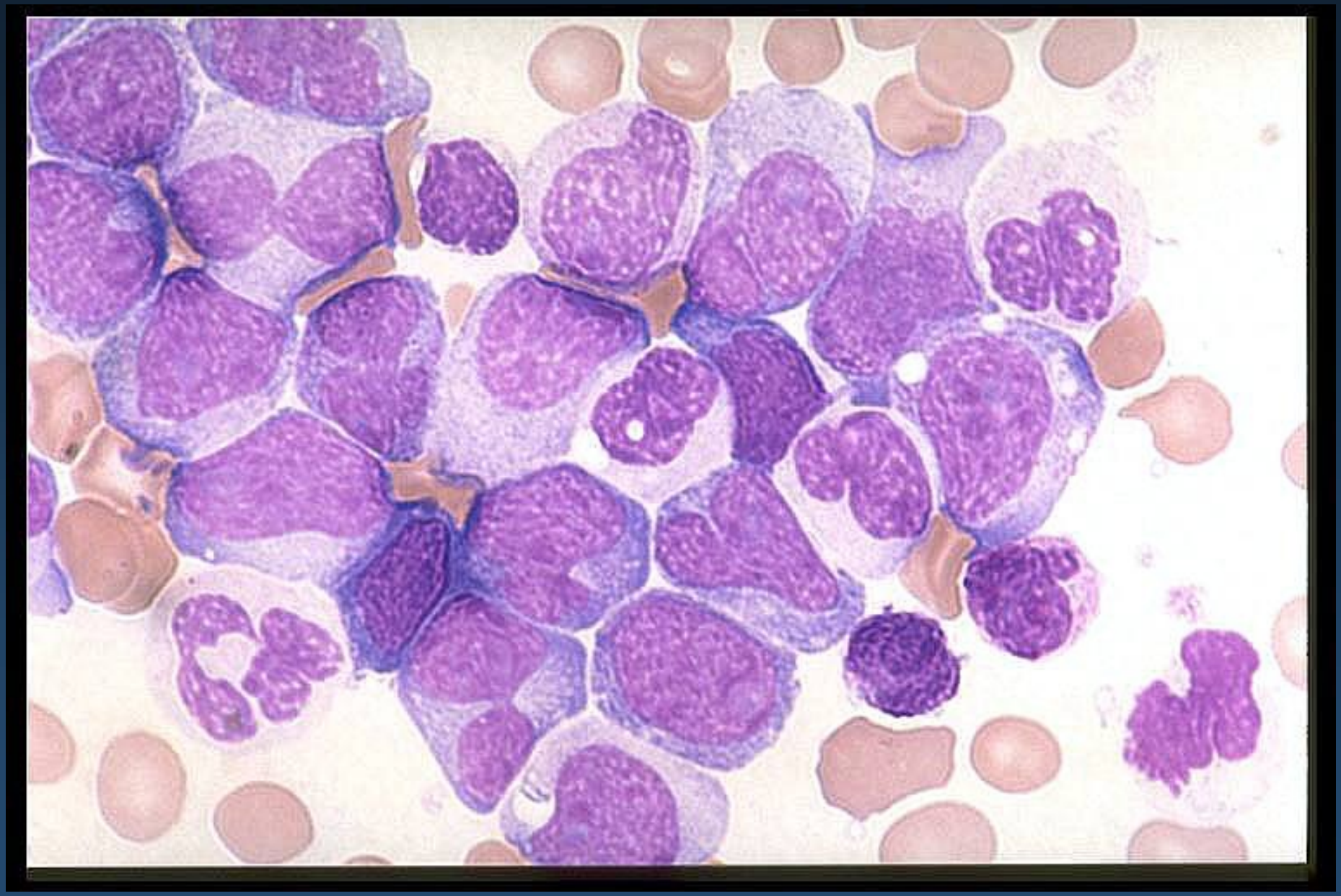


CHRONIC MYELOID LEUKEMIA

CML is a pluripotent stem cell disease that is characterized by extreme blood granulocytosis, basophilia, often thrombocytosis, anemia, and splenomegaly.

Stages of untreated CML:
chronic phase, accelerated phase (rapid increase of WBC, worsening of thrombocytopenia, new cytogenetic features, resistence to treatment), blast crisis (resembles to acute leukemia)

Etiologic role of chromosome discovered in Philadelphia - Ph chromosome!



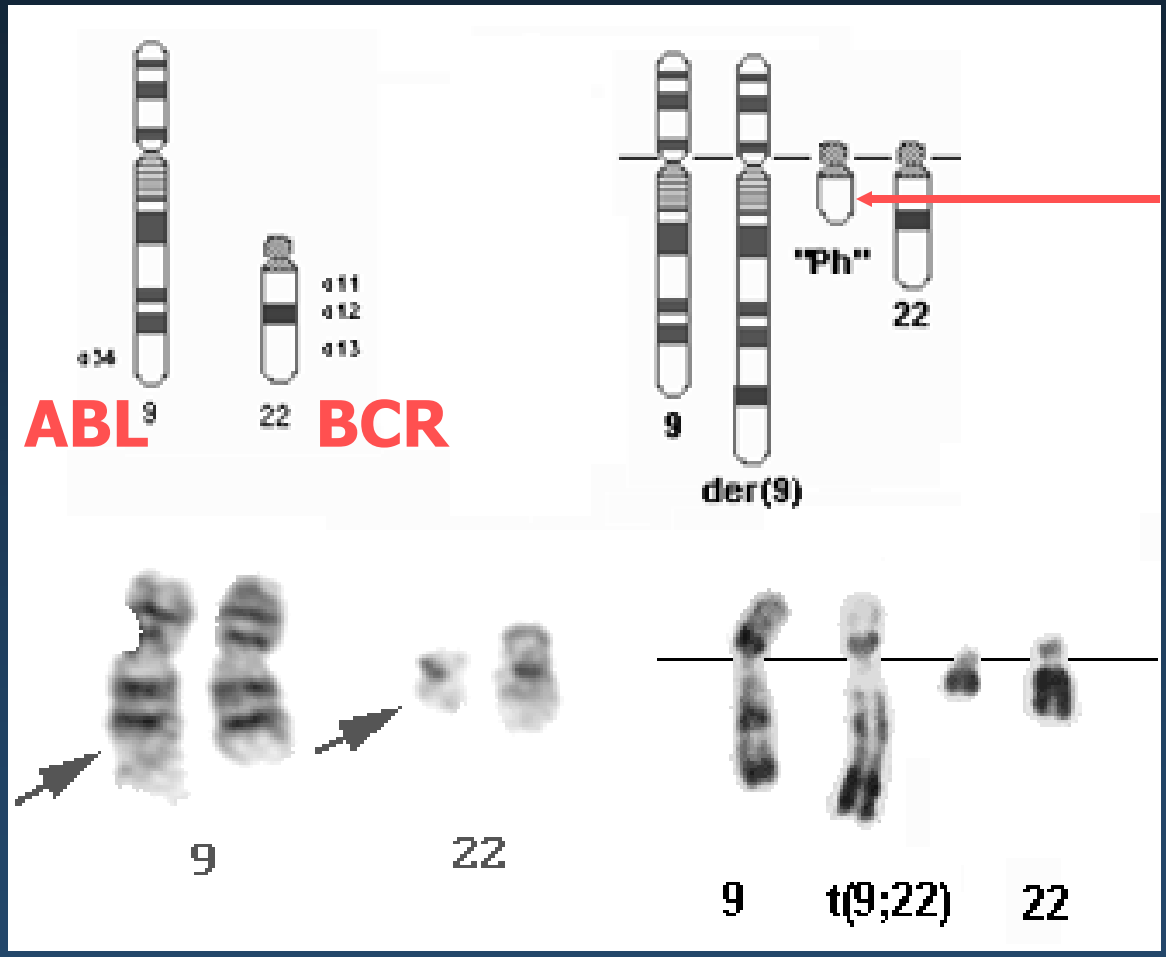
- Ph chromosome arises from t(9;22)

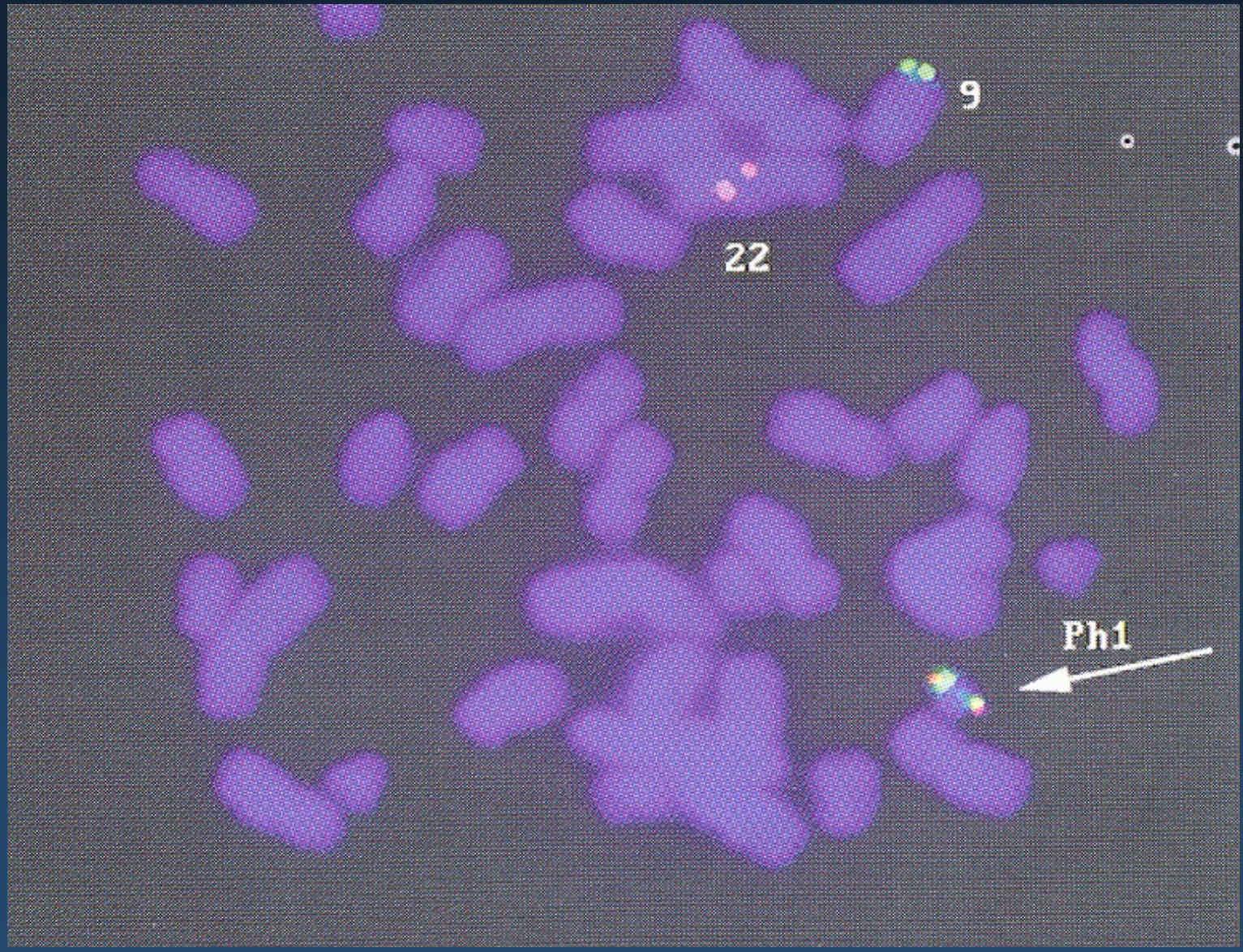
- chimeric gene BCR-ABL arises from Ph chromosome

- BCR-ABL gene produces BCR-ABL tyrosinkinase

- BCR-ABL tyrosinkinase induces defect of apoptosis

There is no BCR-ABL negative CML!


q34
q11
q12
q13
ABL
9
22
BCR
"Ph"
22
9
der(9)
BCR-ABL
9
22
9
t(9;22)
22


9
22
Ph1

Minimal residual disease during treatment

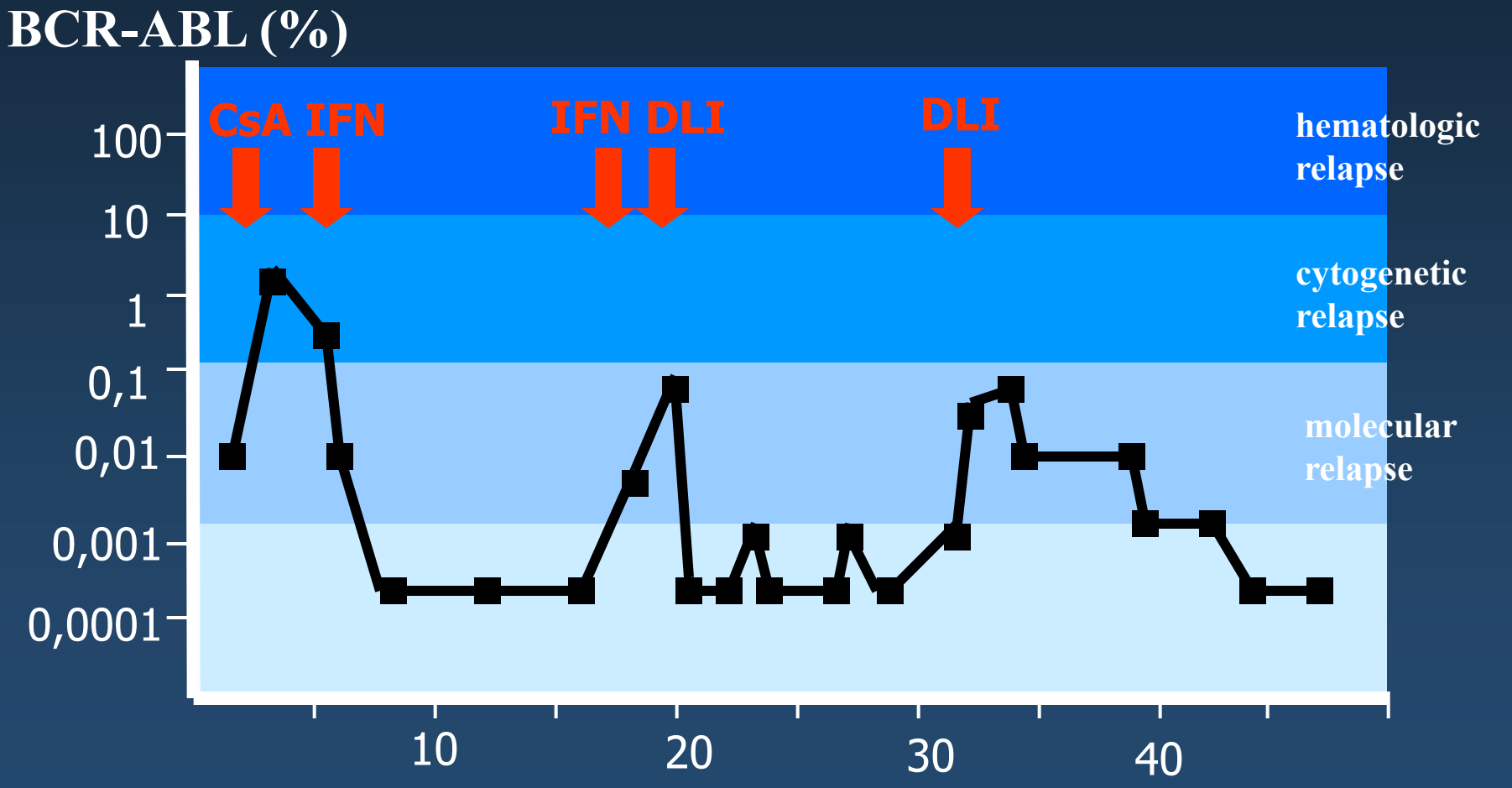
- **Hematologic monitoring**

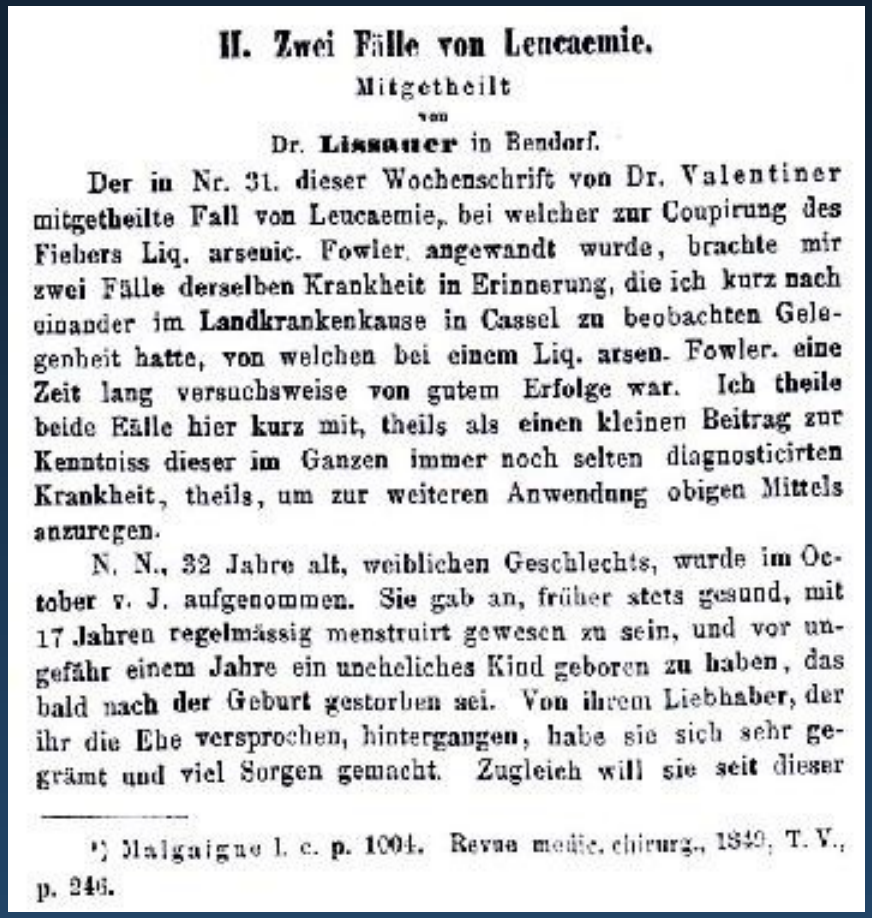
- **Cytogenetic monitoring**
  - reveal 1 pathologic cell from 100

- **Molecular genetic monitoring**
  - reveal 1 pathologic cell from 100 000

Minimal residual disease after treatment or BM/PBSC transplantation

Molecular relapse is manageable compared with cytogenetic or hematologic relapse





II. Zwei Fälle von Leucaemie.

Mitgetheilt

von

Dr. **Lissauer** in Bendorf.

Der in Nr. 31. dieser Wochenschrift von Dr. Valentiner mitgetheilte Fall von Leucaemie, bei welcher zur Coupirung des Fiebers Liq. arsenic. Fowler. angewandt wurde, brachte mir zwei Fälle derselben Krankheit in Erinnerung, die ich kurz nach einander im Landkrankenkause in Cassel zu beobachten Gelegenheit hatte, von welchen bei einem Liq. arsen. Fowler. eine Zeit lang versuchsweise von gutem Erfolge war. Ich theile beide Fälle hier kurz mit, theils als einen kleinen Beitrag zur Kenntniss dieser im Ganzen immer noch selten diagnosticirten Krankheit, theils, um zur weiteren Anwendung obigen Mittels anzuregen.

N. N., 32 Jahre alt, weiblichen Geschlechts, wurde im October v. J. aufgenommen. Sie gab an, früher stets gesund, mit 17 Jahren regelmässig menstruirt gewesen zu sein, und vor ungefähr einem Jahre ein uneheliches Kind geboren zu haben, das bald nach der Geburt gestorben sei. Von ihrem Liebhaber, der ihr die Ehe versprochen, hintergangen, habe sie sich sehr gegrämt und viel Sorgen gemacht. Zugleich will sie seit dieser

*) Malgaigne l. c. p. 1004. Revue médic. chirurg., 1849, T. V., p. 246.

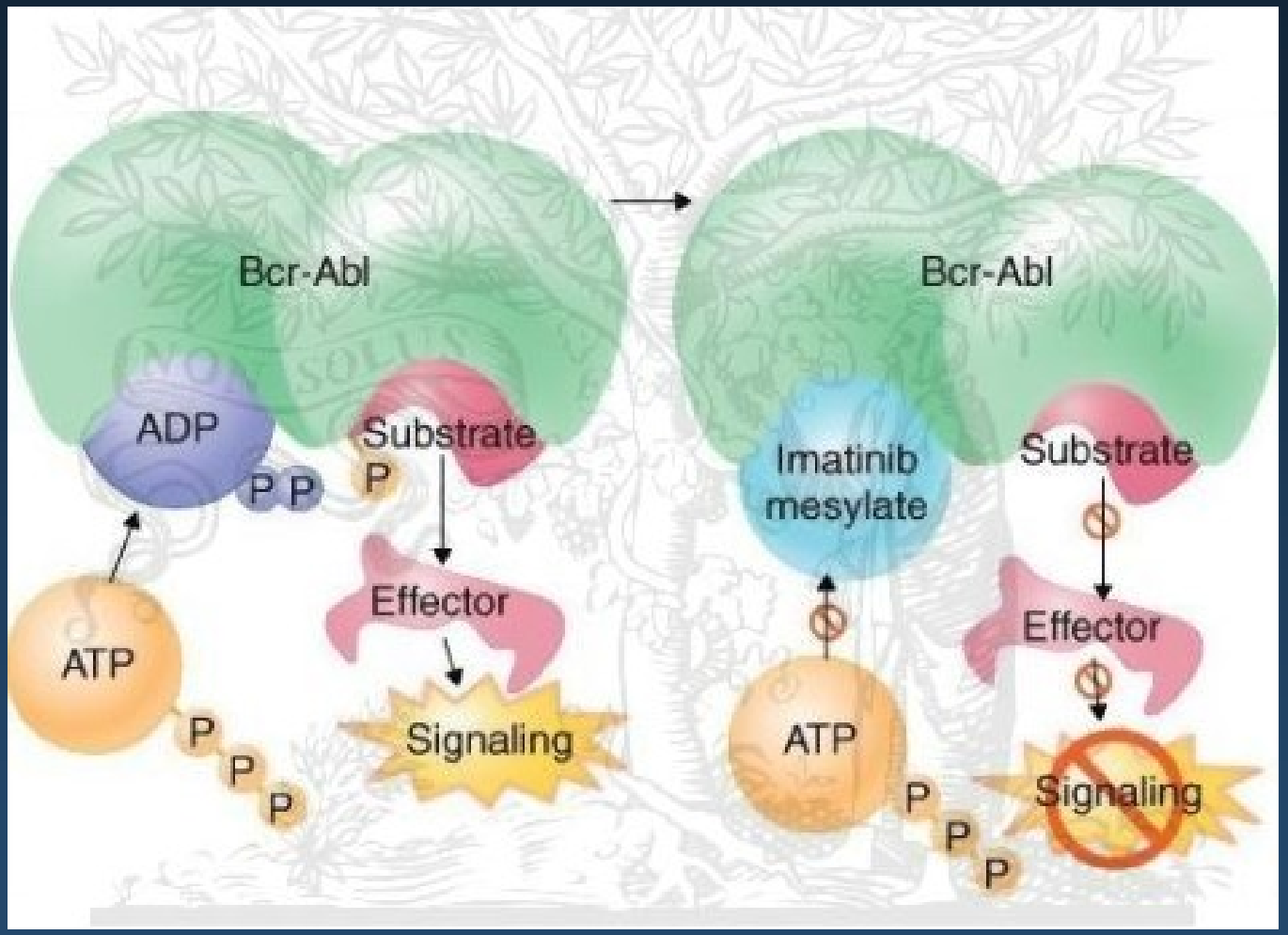
Arsenik – As_2O_3

Lissauer: Zwei Fälle von Leucaemie.

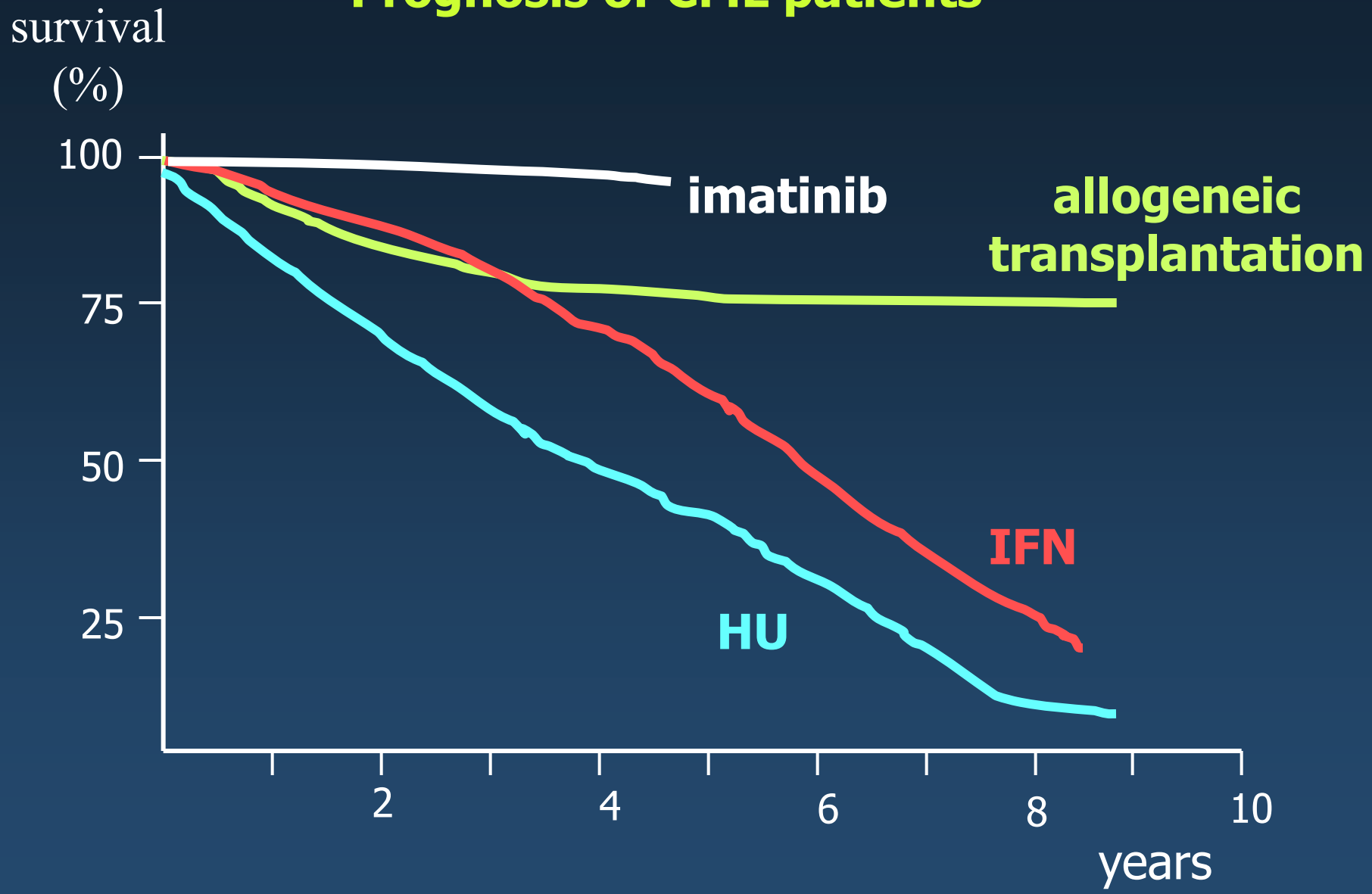
Berlin. Klin. Wochenschrift, 2, 1865, s. 403 - 404

CML management

CP-CML	Léčebná strategie
1. linie:	▪Imatinib 400 mg
2. linie:	
IM-intolerance	▪DASATINIB nebo NILOTINIB
IM-selhání	▪DASATINIB nebo NILOTINIB ▪aloTKB (progrese do AP/BC, T315I)
IM-suboptimální odpověď	▪IM stejná dávka ▪IM navýšení dávky ▪DASATINIB nebo NILOTINIB


Bcr-Abl
ADP
P P
Substrate
P
Effector
ATP
P P P
Signaling
Bcr-Abl
Imatinib
mesylate
Substrate
Effector
ATP
P P P
Signaling

Prognosis of CML patients

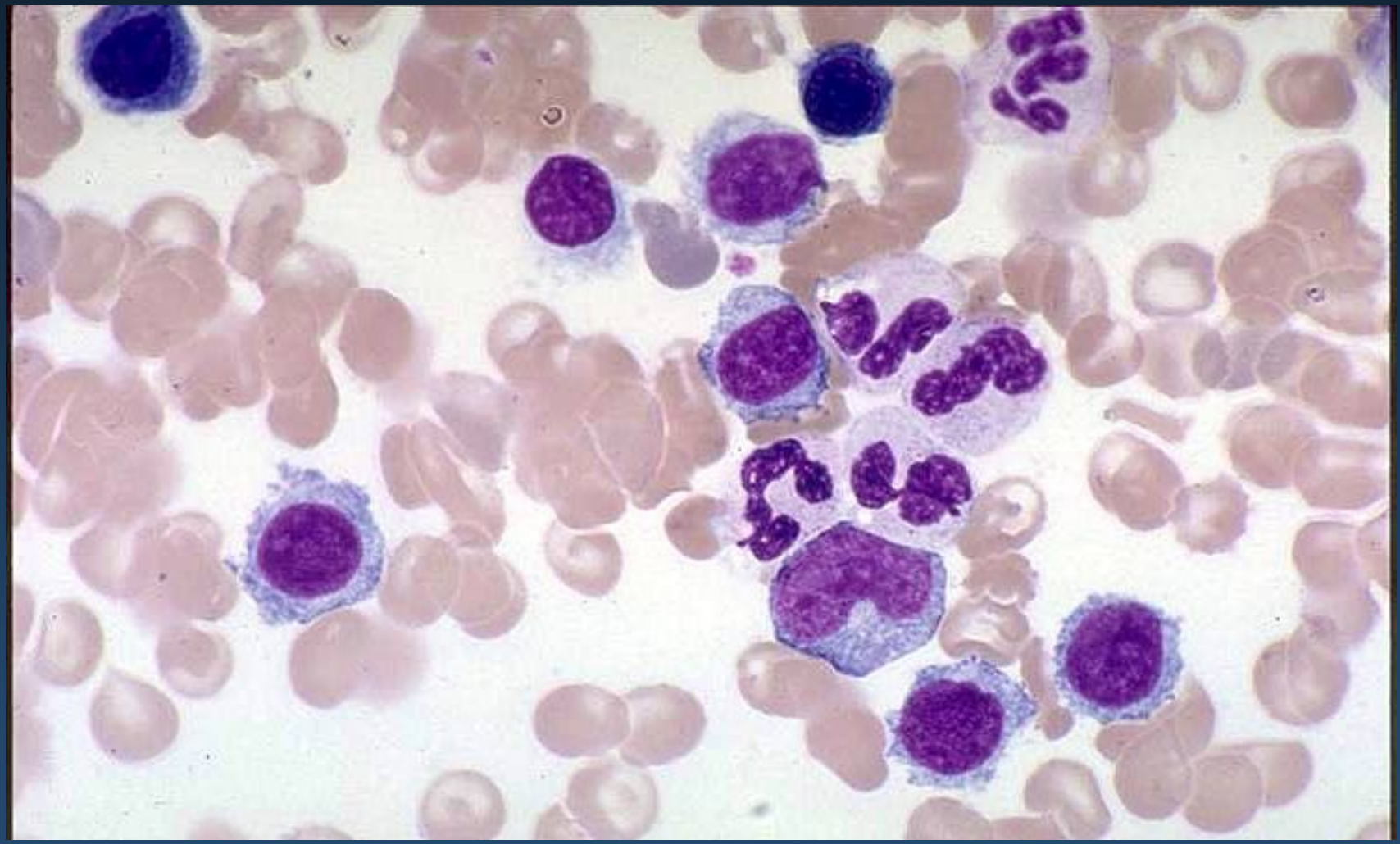


CLASSICAL HAIRY CELL LEUKEMIA

HCL is characterized by leukopenia and splenomegaly

Leukemia with excellent prognosis

Treatment of choice - cladribine for 7 days
(treatment is recommended only for symptomatic, neutropenic, thrombocytopenic or anemic patients)



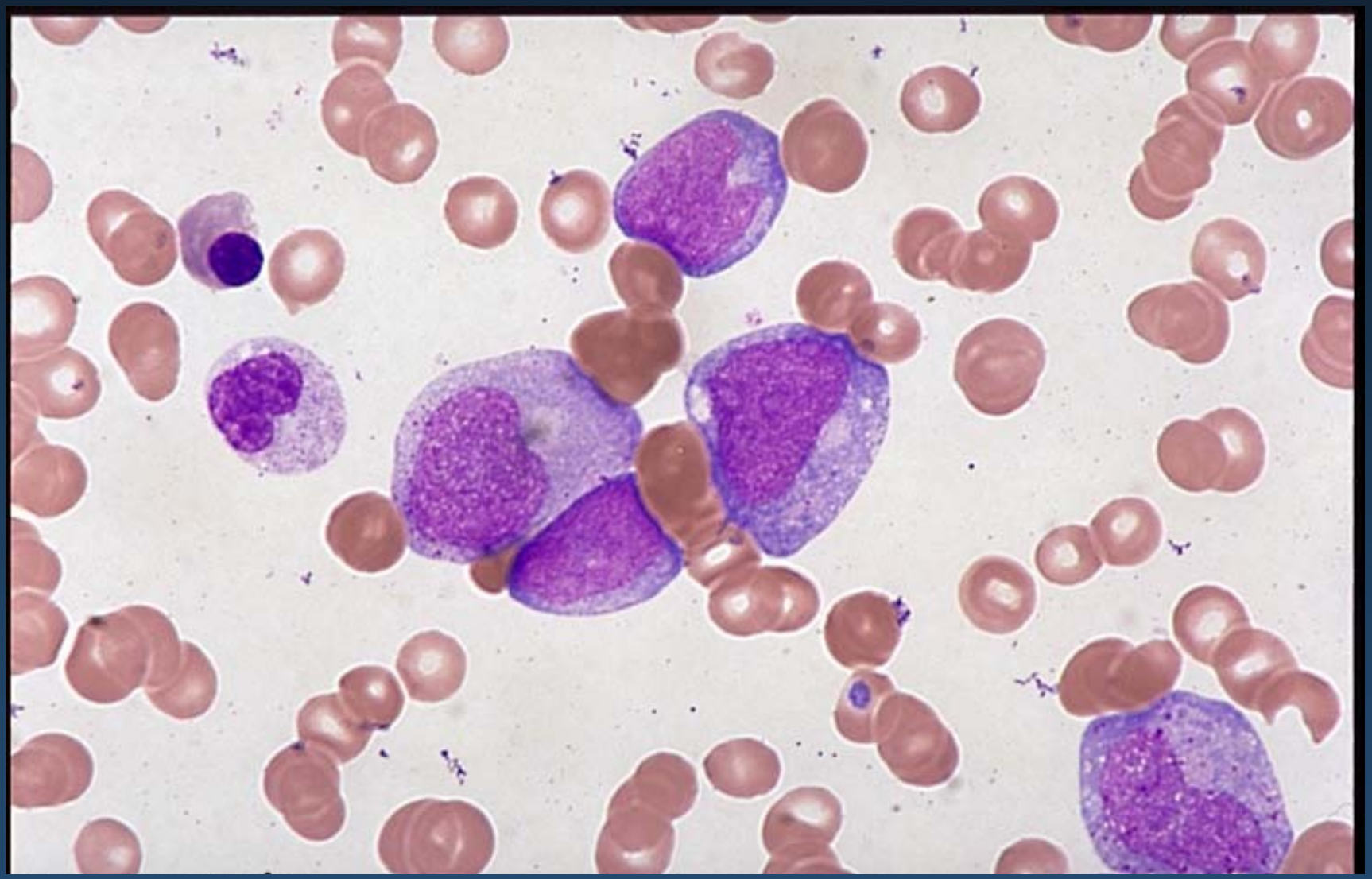
ACUTE MYELOBLASTIC LEUKEMIA

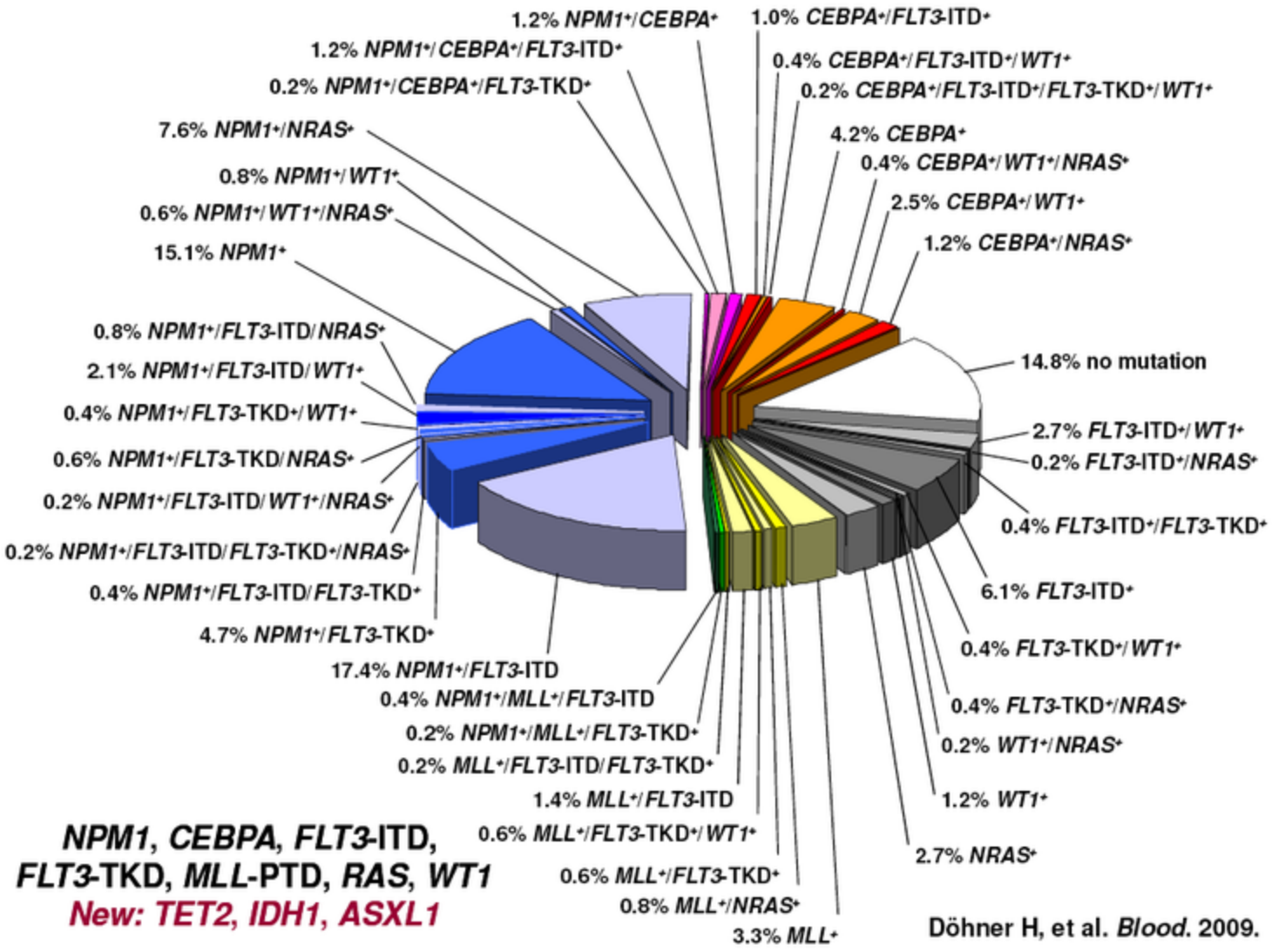
AML is clonal malignant disease that is characterized by the proliferation of abnormal (leukemic) blasts, principially in the marrow, and impaired production of normal blood cells.

Signs and symptoms of AML include pallor, fatigue, weakness, palpitations, bleeding, fever, and dyspnena.

In bone marrow, there is more than 20% of blast cells. (less than 20% - myelodysplastic syndrome)

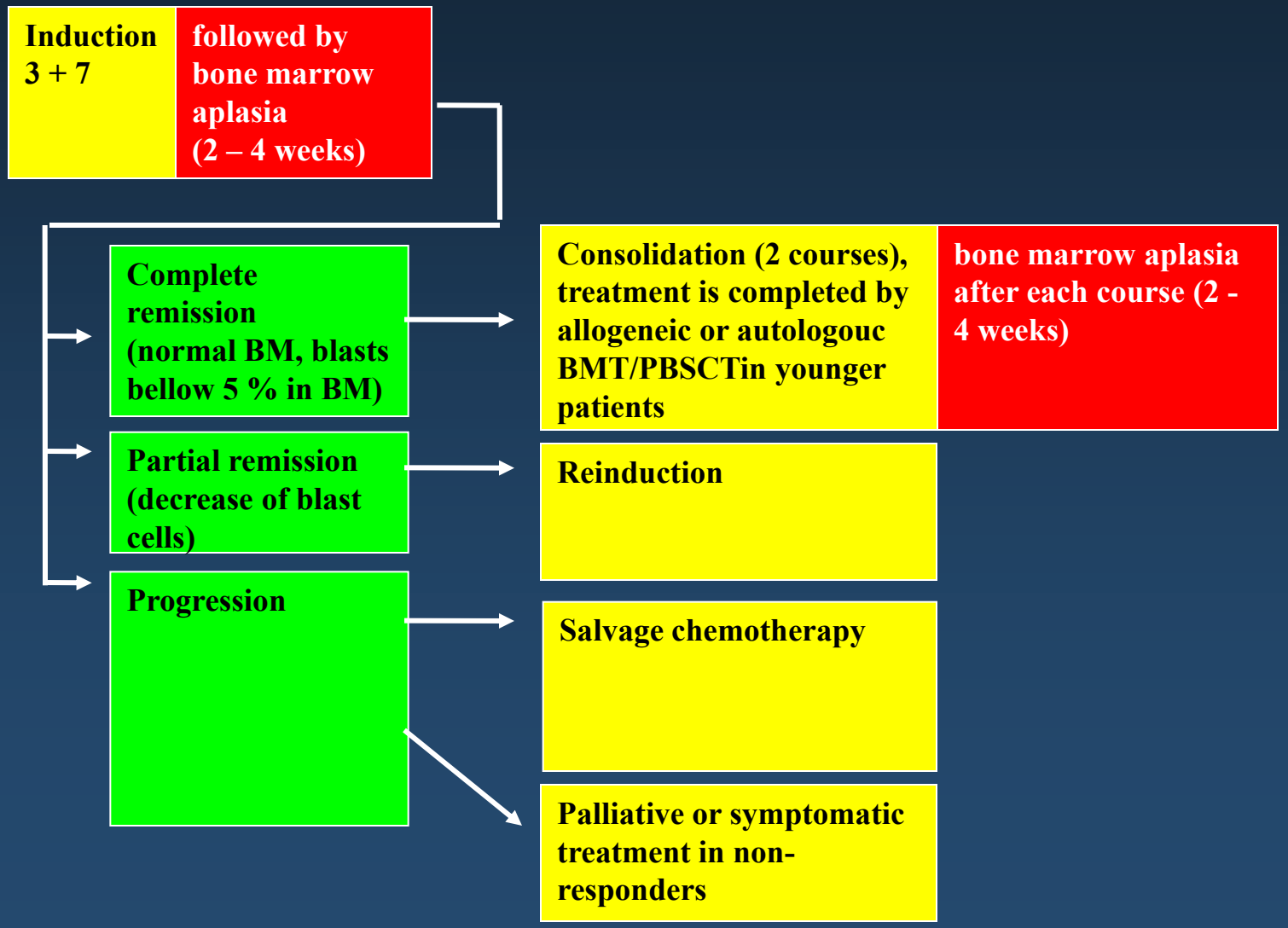
Median survival of untreated patients is 6 weeks.




1.2% NPM1+/CEBPA+
1.0% CEBPA+/FLT3-ITD+
1.2% NPM1+/CEBPA+/FLT3-ITD+
0.4% CEBPA+/FLT3-ITD+/WT1+
0.2% NPM1+/CEBPA+/FLT3-TKD+
0.2% CEBPA+/FLT3-ITD+/FLT3-TKD+/WT1+
7.6% NPM1+/NRAS+
4.2% CEBPA+
0.8% NPM1+/WT1+
0.4% CEBPA+/WT1+/NRAS+
0.6% NPM1+/WT1+/NRAS+
2.5% CEBPA+/WT1+
15.1% NPM1+
1.2% CEBPA+/NRAS+
0.8% NPM1+/FLT3-ITD/NRAS+
14.8% no mutation
2.1% NPM1+/FLT3-ITD/WT1+
2.7% FLT3-ITD+/WT1+
0.4% NPM1+/FLT3-TKD+/WT1+
0.2% FLT3-ITD+/NRAS+
0.6% NPM1+/FLT3-TKD/NRAS+
0.4% FLT3-ITD+/FLT3-TKD+
0.2% NPM1+/FLT3-ITD/WT1+/NRAS+
6.1% FLT3-ITD+
0.2% NPM1+/FLT3-ITD/FLT3-TKD+/NRAS+
0.4% NPM1+/FLT3-ITD/FLT3-TKD+
0.4% FLT3-TKD+/WT1+
4.7% NPM1+/FLT3-TKD+
17.4% NPM1+/FLT3-ITD
0.4% FLT3-TKD+/NRAS+
0.4% NPM1+/MLL+/FLT3-ITD
0.2% NPM1+/MLL+/FLT3-TKD+
0.2% WT1+/NRAS+
0.2% MLL+/FLT3-ITD/FLT3-TKD+
1.2% WT1+
1.4% MLL+/FLT3-ITD
0.6% MLL+/FLT3-TKD+/WT1+
2.7% NRAS+
0.6% MLL+/FLT3-TKD+
0.8% MLL+/NRAS+
3.3% MLL+
NPM1, CEBPA, FLT3-ITD,
FLT3-TKD, MLL-PTD, RAS, WT1
New: TET2, IDH1, ASXL1
Döhner H, et al. Blood. 2009.

Treatment of AML

Treatment of choice of AML are courses of chemotherapy, the most potent drugs are cytosinarabinoside and anthracyclines.



Acute promyelocytic leukemia, AML M3

APL is variant of AML (constitutes about 5-10% of AML in central Europe, about 25% of AML southern Europe, and 50 % of AML in eastern Asia).

There are prominent hemorrhagic complications (DIC, melena, hematuria, pulmonary bleeding, CNS bleeding)

Prognosis of APL was very poor 25 years ago (almost all patients died).

Nowadays, DFS is 80%.

Acute promyelocytic leukemia, AML M3

Promyelocytes are granular cells. In granula are coagulopathy-inducing factors (tissue factor…).

Majority of APL is characterized by t(15,17).
A translocation between chromosome 17 and 15 results in chimeric fusion gene PML-RARα.

PML-RARα gene produces PML-RARα abnormal receprior for retinoids. (Retinoids are necessary for normal bone marrow cells differentiation). In cells with t(15,17) normal differentiation is stopped.

We can restore differentiation by means of ATRA.

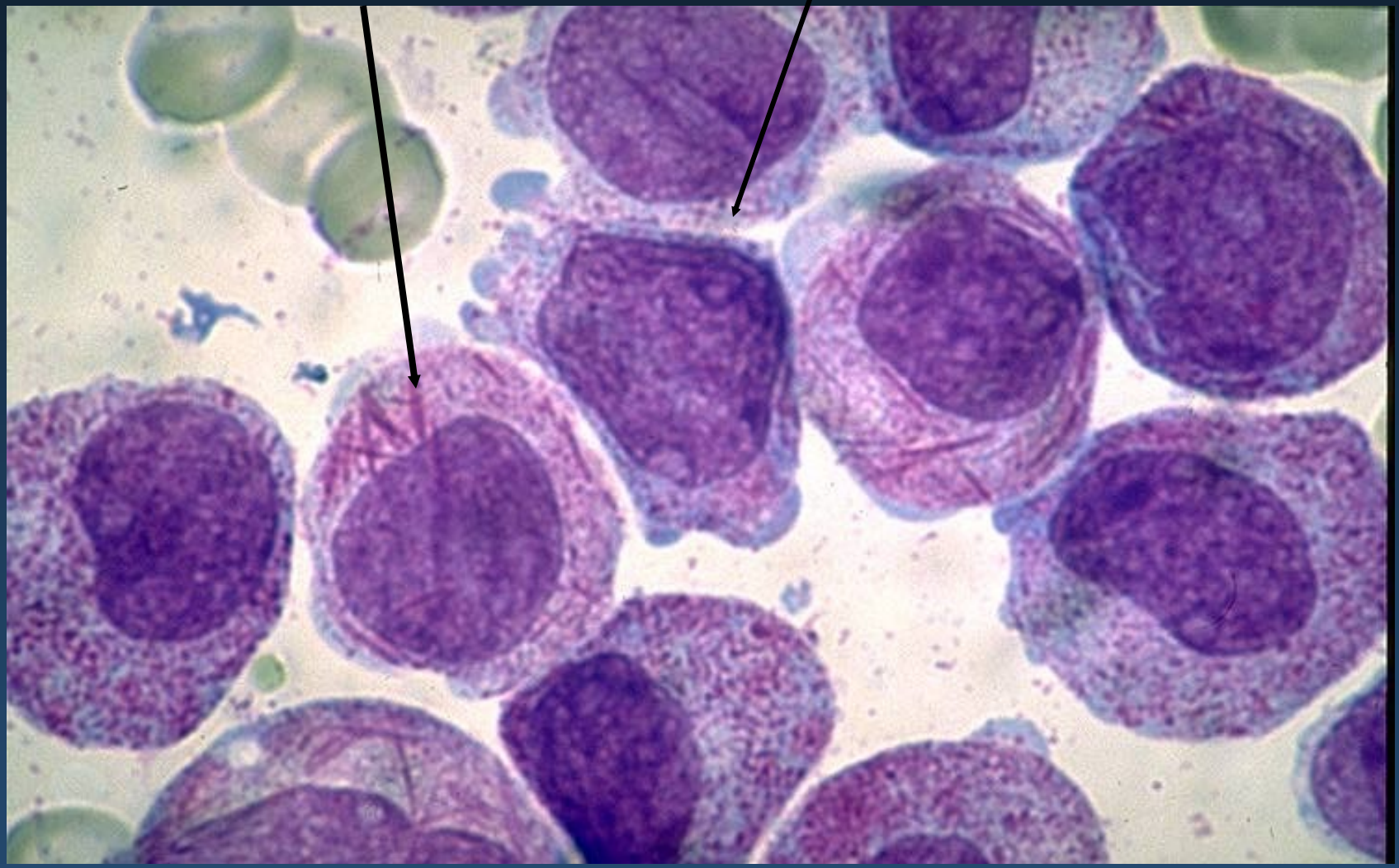
Acute promyelocytic leukemia, AML M3

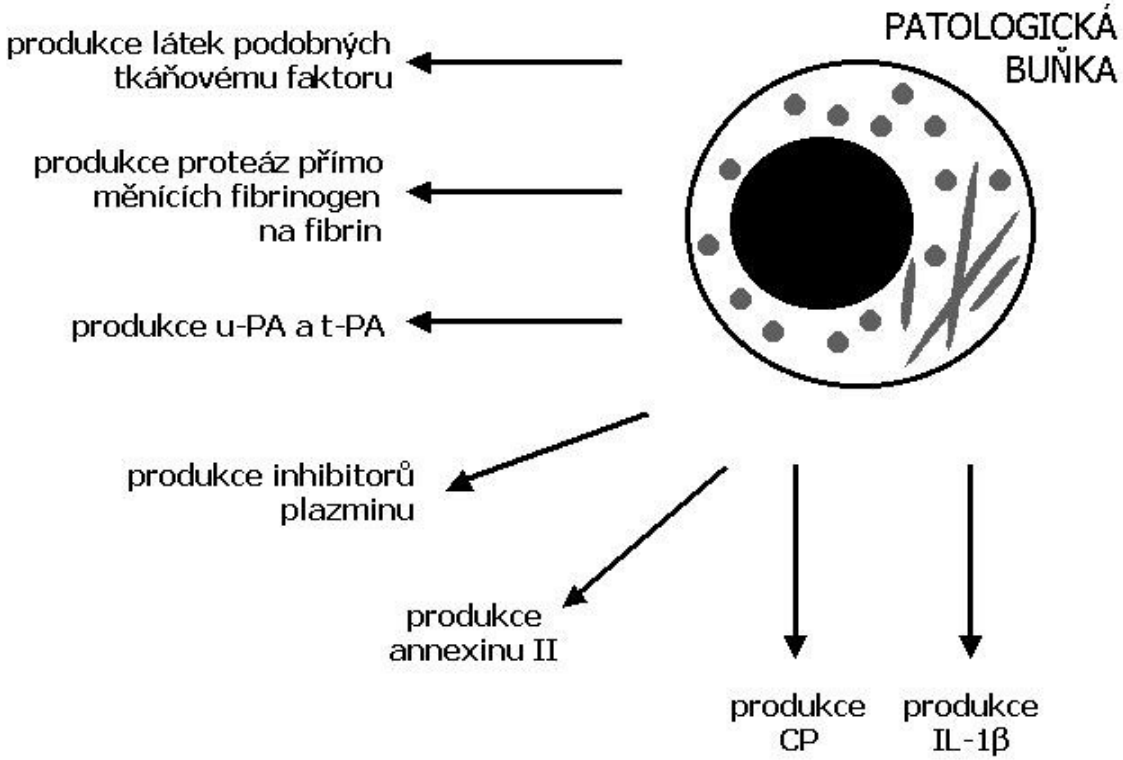
Chemotherapy + ATRA is treatment of choice for APL!

Or aresink trioxide

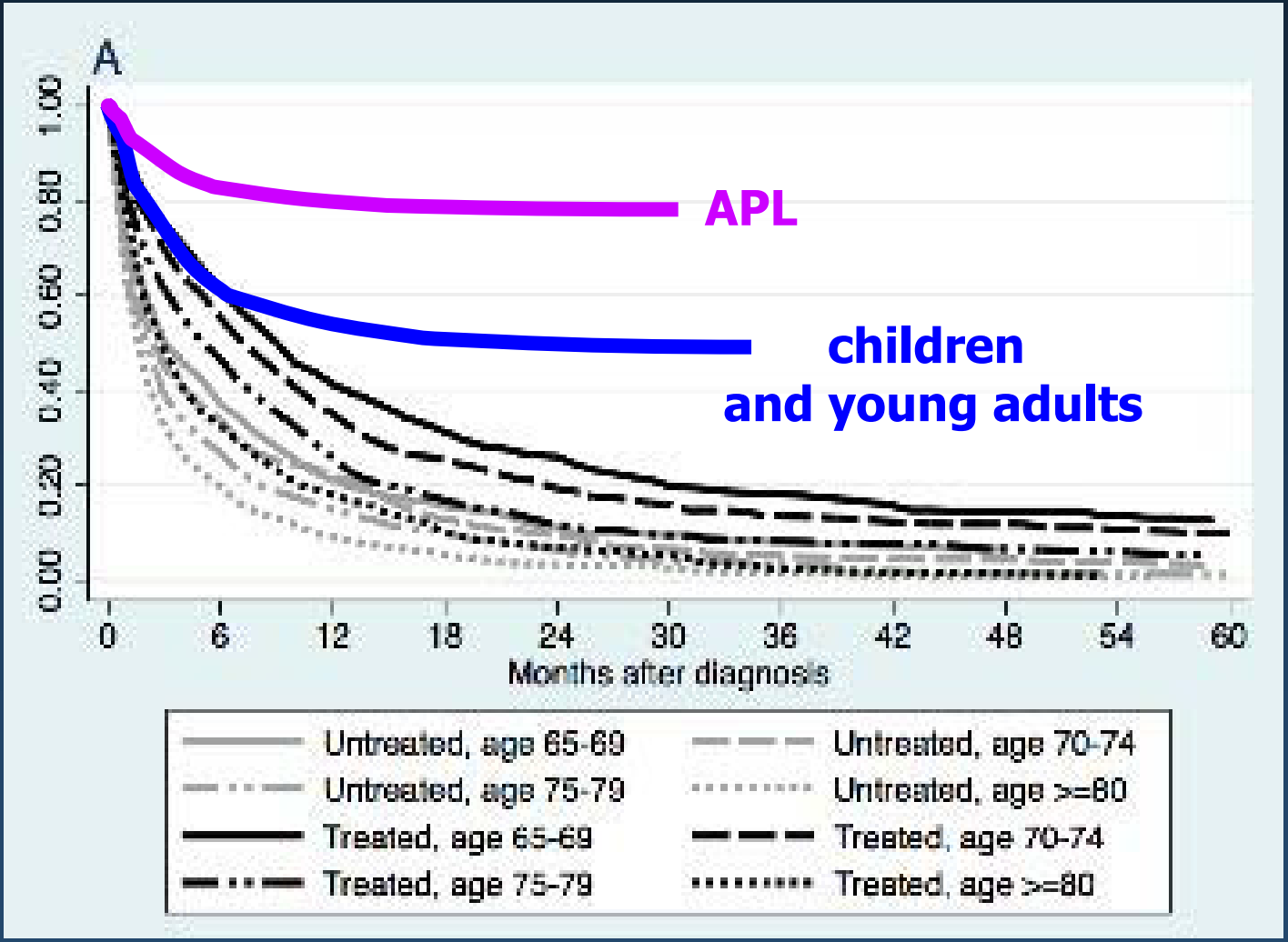
Auer rods, „faggots“

granular plasma

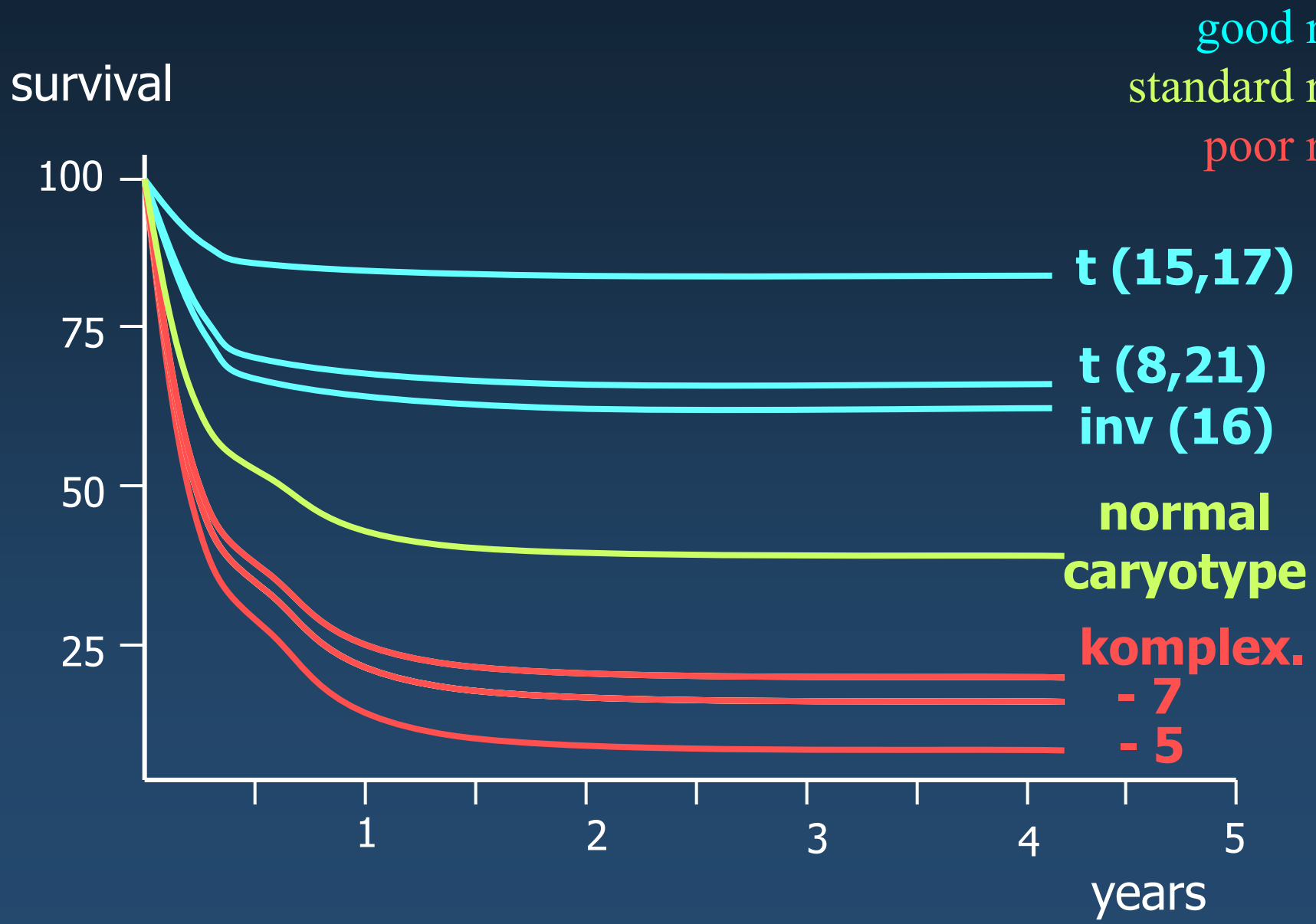



PATOLOGICKÁ BUŇKA
produkce látek podobných tkáňovému faktoru
produkce proteáz přímo měnících fibrinogen na fibrin
produkce u-PA a t-PA
produkce inhibitorů plazminu
produkce annexinu II
produkce CP
produkce IL-1β

Survival of AML patients



Prognosis of AML according to cytogenetic features



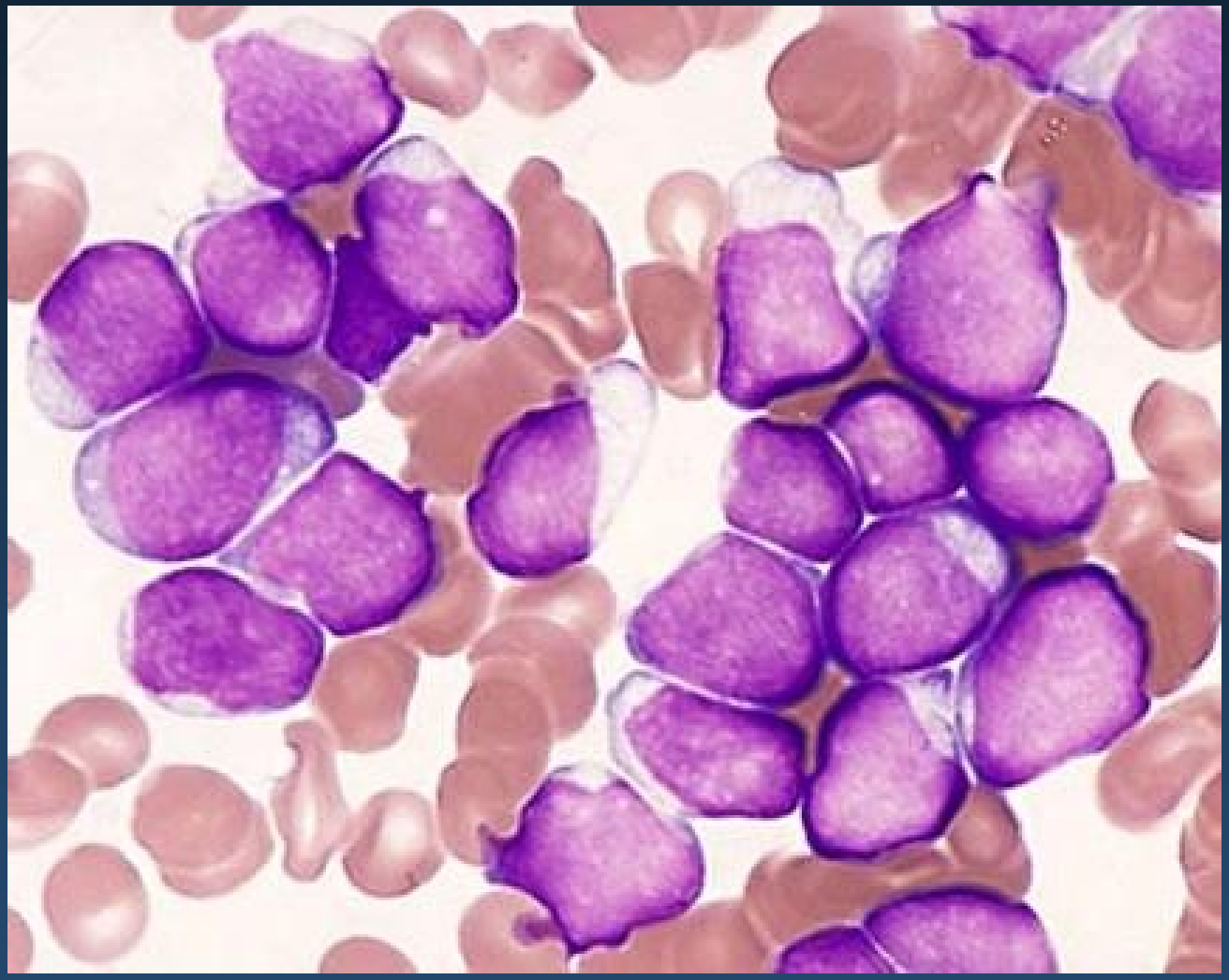
AKCUTE LYMPHOBLASTIC LEUKEMIA

The most common leukemia in childhood.

In children - very good prognosis.
In adults - very poor prognosis.

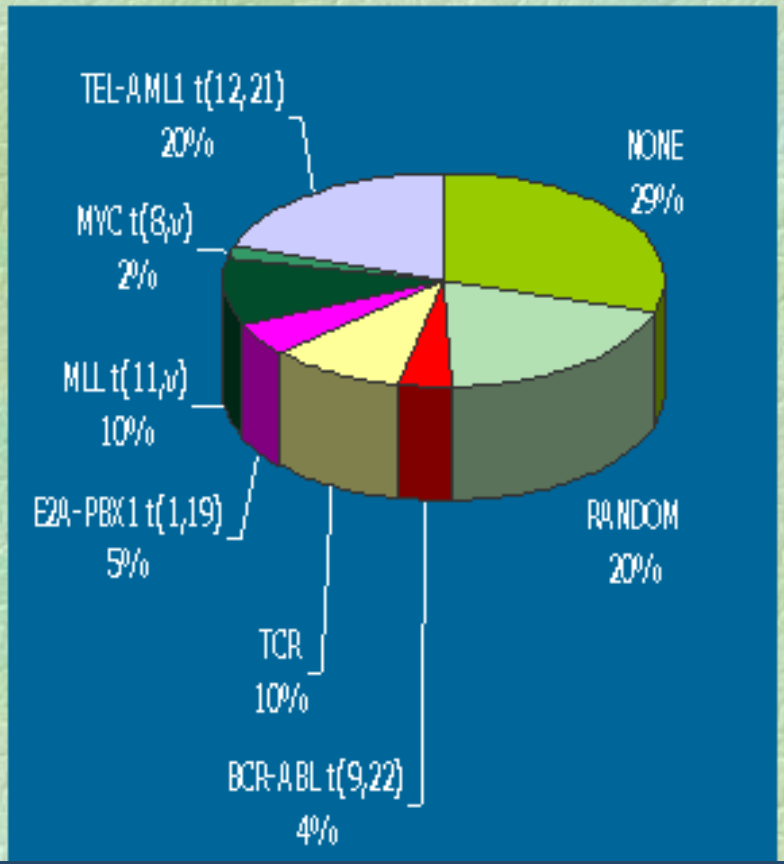
ALL is a neoplastic disease resulting from somatic mutation in a single lymphoid progenitor cell.

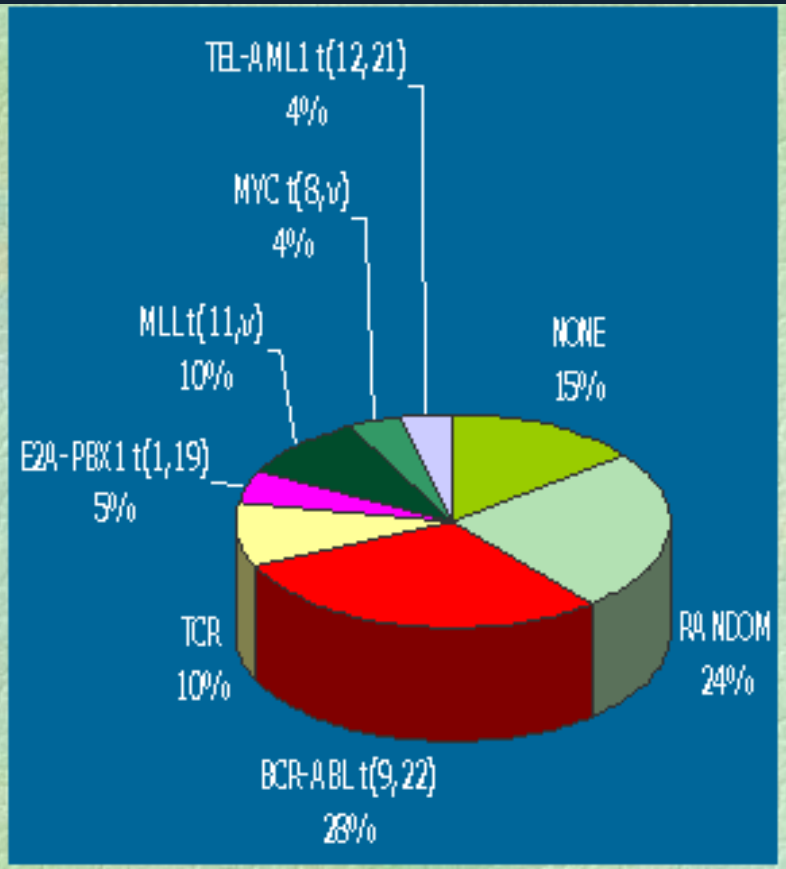
BM - more than 20% of lymphoblasts (usually 80 - 100%).



Chromosomal translocations in ALL

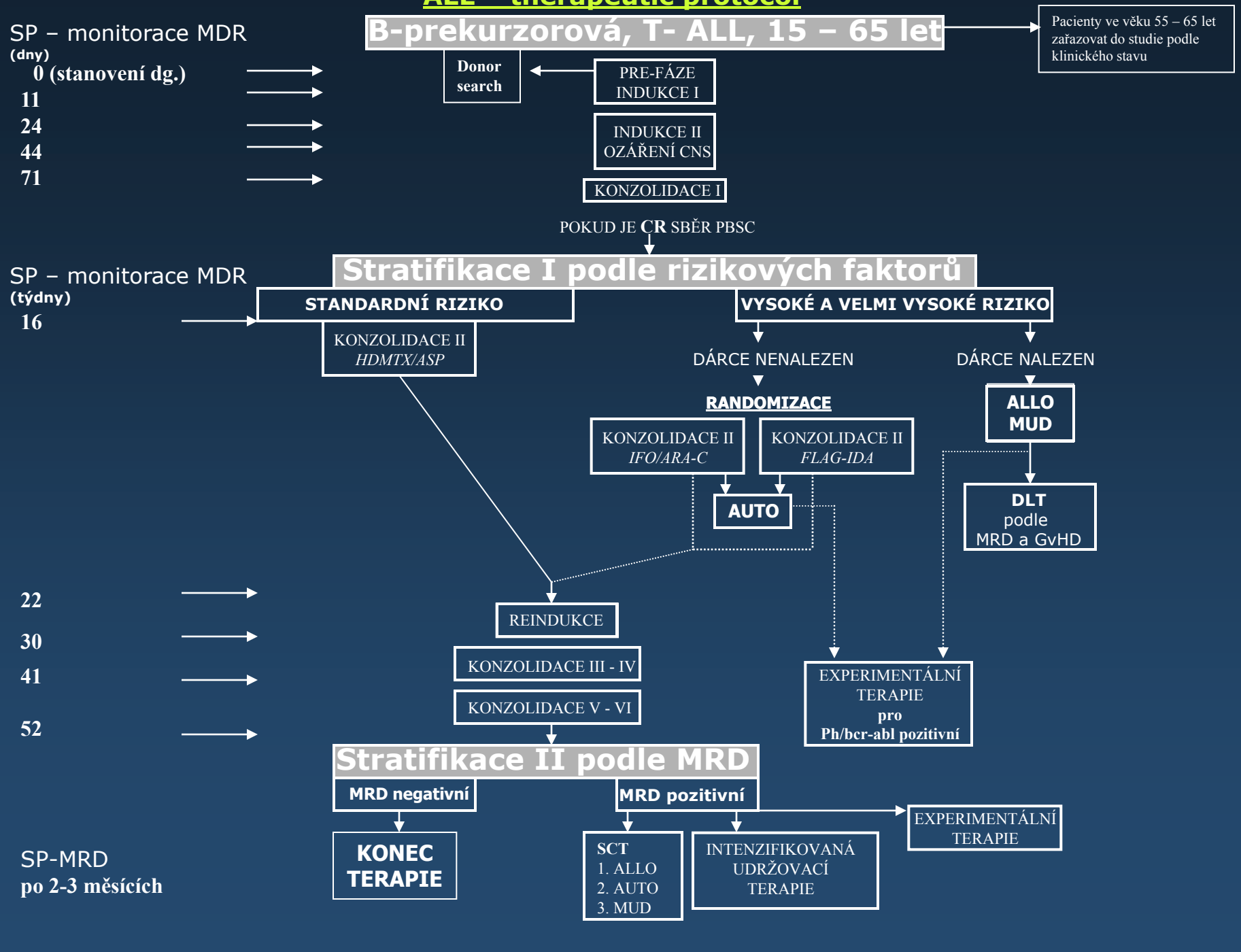
children

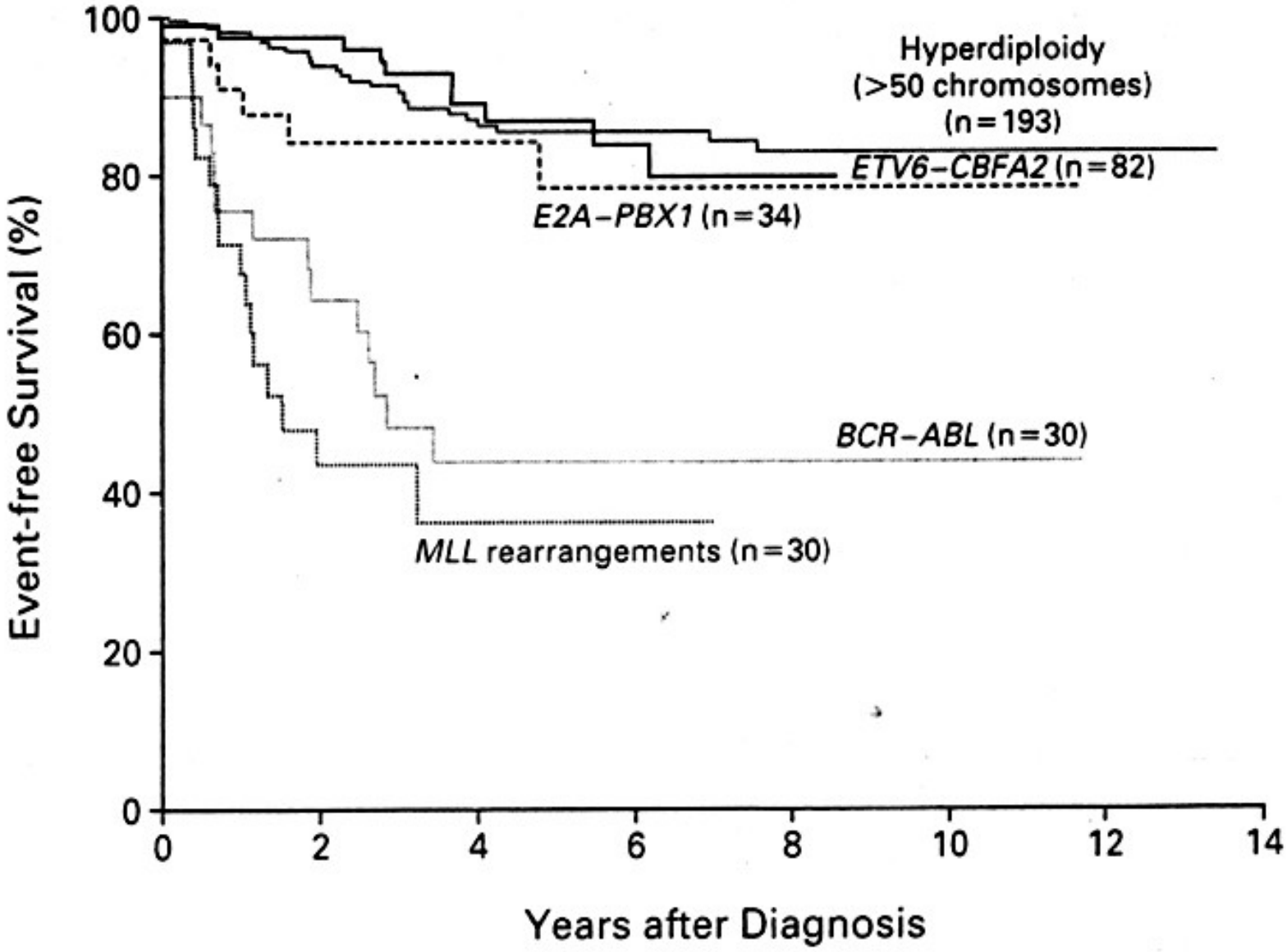




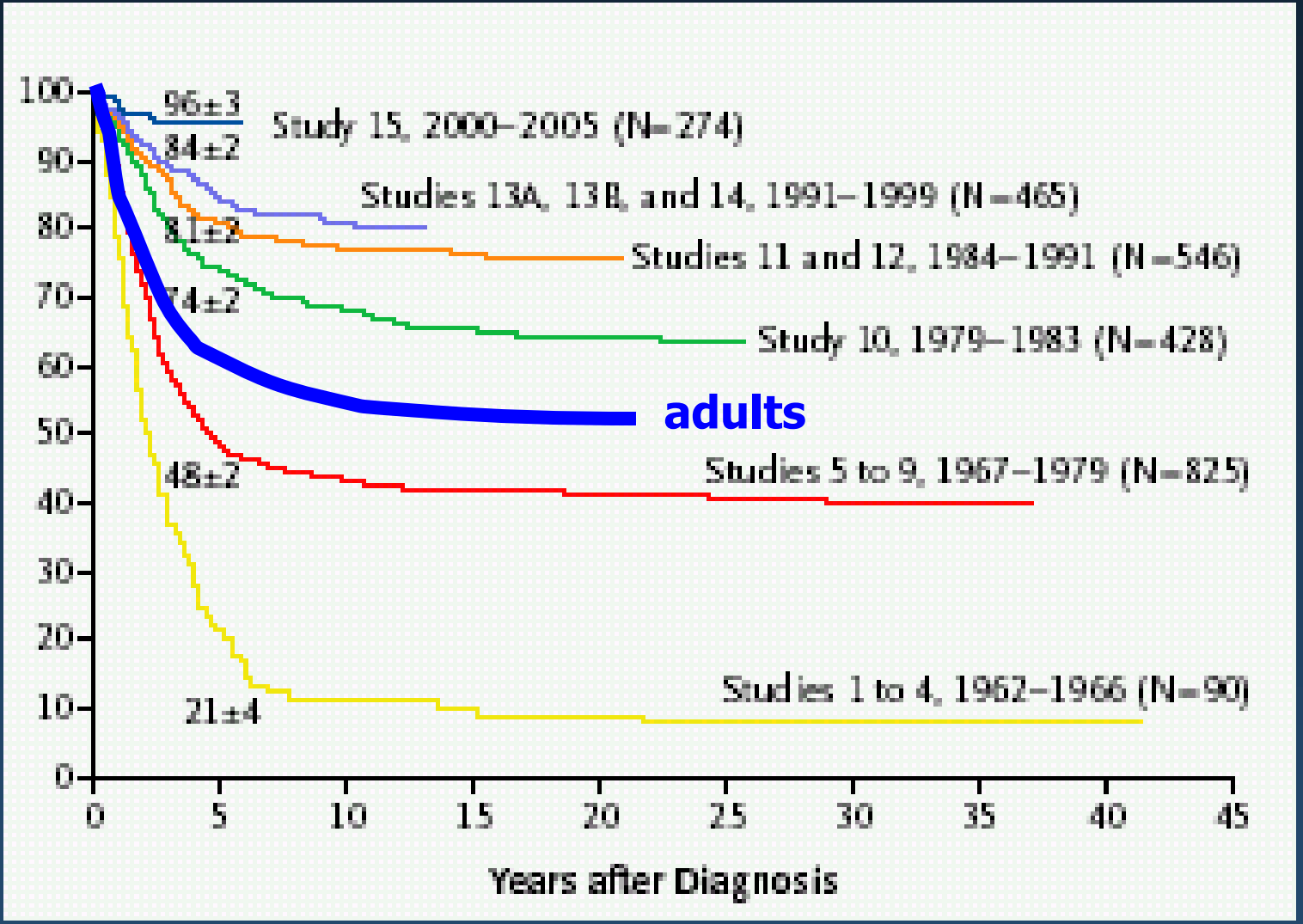
adults

ALL – therapeutic protocol




Event-free Survival (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Years after Diagnosis
Hyperdiploidy
(>50 chromosomes)
(n=193)
ETV6–CBFA2 (n=82)
E2A–PBX1 (n=34)
BCR–ABL (n=30)
MLL rearrangements (n=30)

Childhood ALL - survival



MYELODYSPLASTIC SYNDROMES

Heterogeneous group of malignant diseases with different prognosis (preleukemias).

In BM - blasts bellow 20 % and dysplastic features (hypogranular cells, cells with atypical shape of nucleus, hypergranular cells, cells with abnormal plasma)

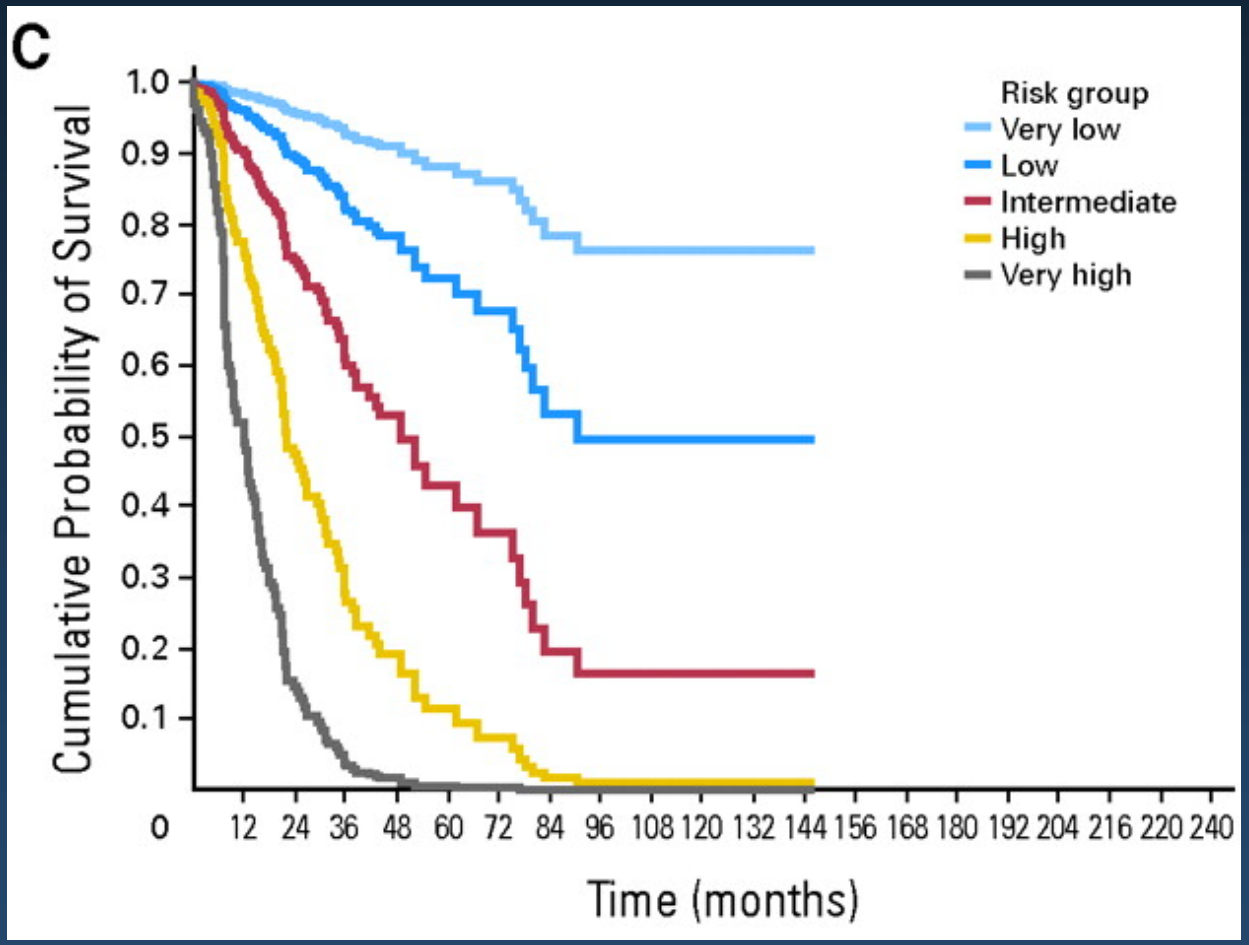
The only curative option is BMT/PBSCT in high risk patients.

Patients asyptomatic or without donor -
only symptomatic treatment
or watch and wait strategy.

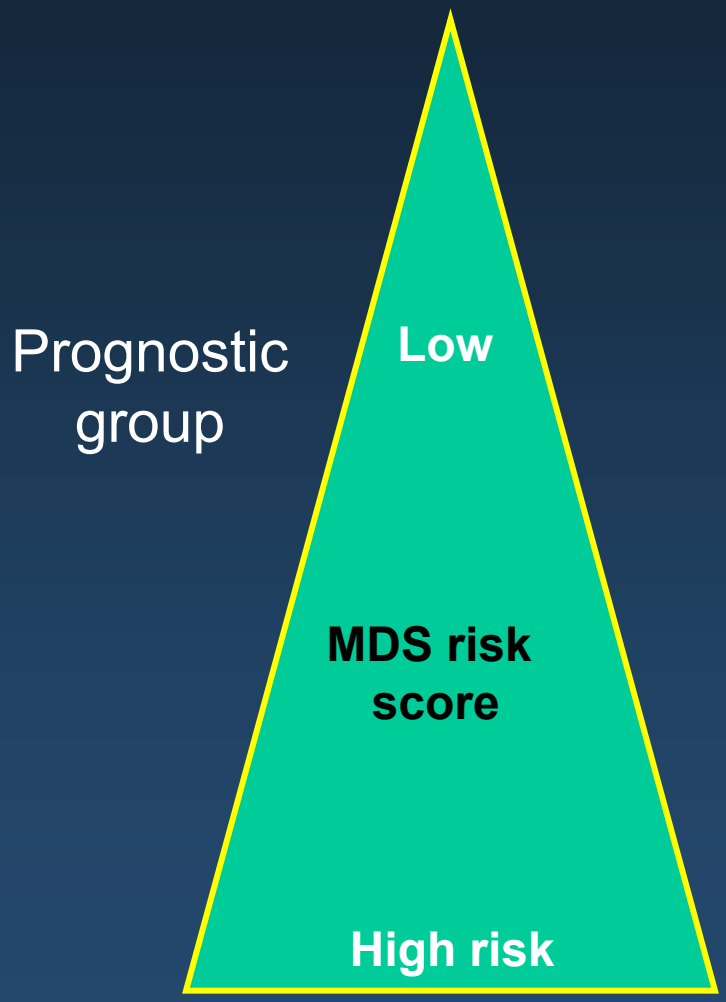
MDS - prognosis

	Score				
Prognostic marker	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts (%)	< 5	5–10		11–20	21–30
Karyotype*	Good	Intermediate	Poor		
Cytopenia	0/1	2/3			

Score	IPSS subgroup	Median survival (years)
0	Low	5.7
0.5–1.0	Int-1	3.5
1.5–2.0	Int-2	1.2
> 2.5	High	0.4

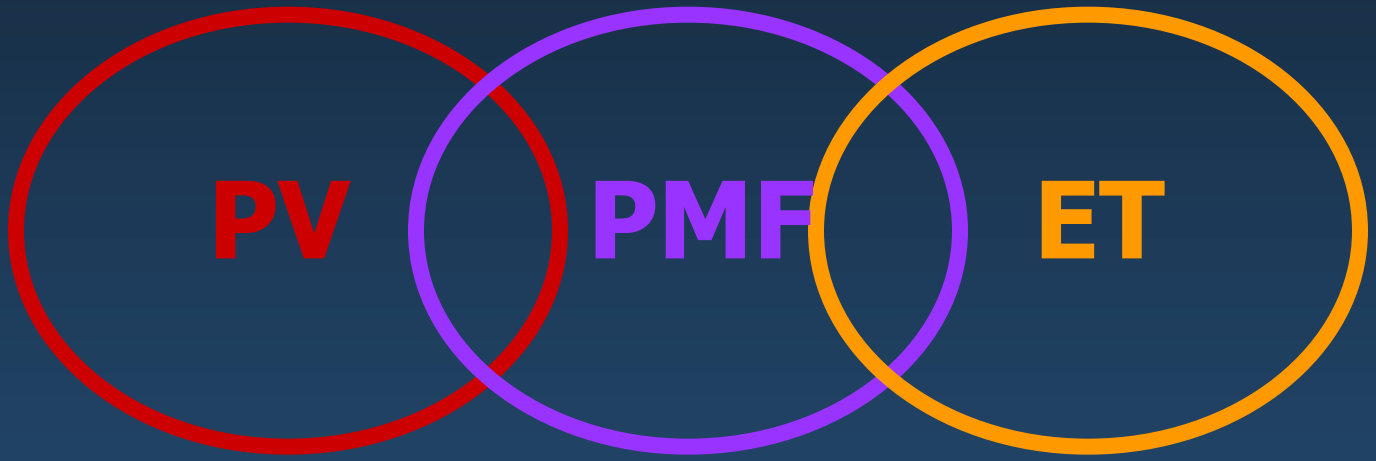

C
Cumulative Probability of Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 220 240
Time (months)
Risk group
Very low
Low
Intermediate
High
Very high

Therapeutic options in MDS



- Supportiv care, transfusions, prophylaxis of iron overload
- Immnosupressive therapy
- Arsenic trioxide
- Low dose chemotherapy
- Epigenetic therapy
- Allo-SCT, intensive chemo

MPN



POLYCYTHEMIA

Polycythemia is characterized by an increase of the total red cell volume. It exists in the primary form (PV, clonal neoplastic disorder) and in secondary forms due to appropriate or inappropriate increases in levels of EPO (hemoglobins with high affinity to oxygen, high altitudes, pulomary and heart diseases, tumours producing EPO).

PV is characterised by increases not only of the number of red cells but also of the granulocytes and platelets and splenomegaly.

POLYCYTHEMIA VERA

Diagnosis

Peripheral blood count
Histology of bone marrow
Total erythrocyte volum
Analysis of growth of erythroid precursors (BFU-E) without EPO
JAK2 V617F mutation

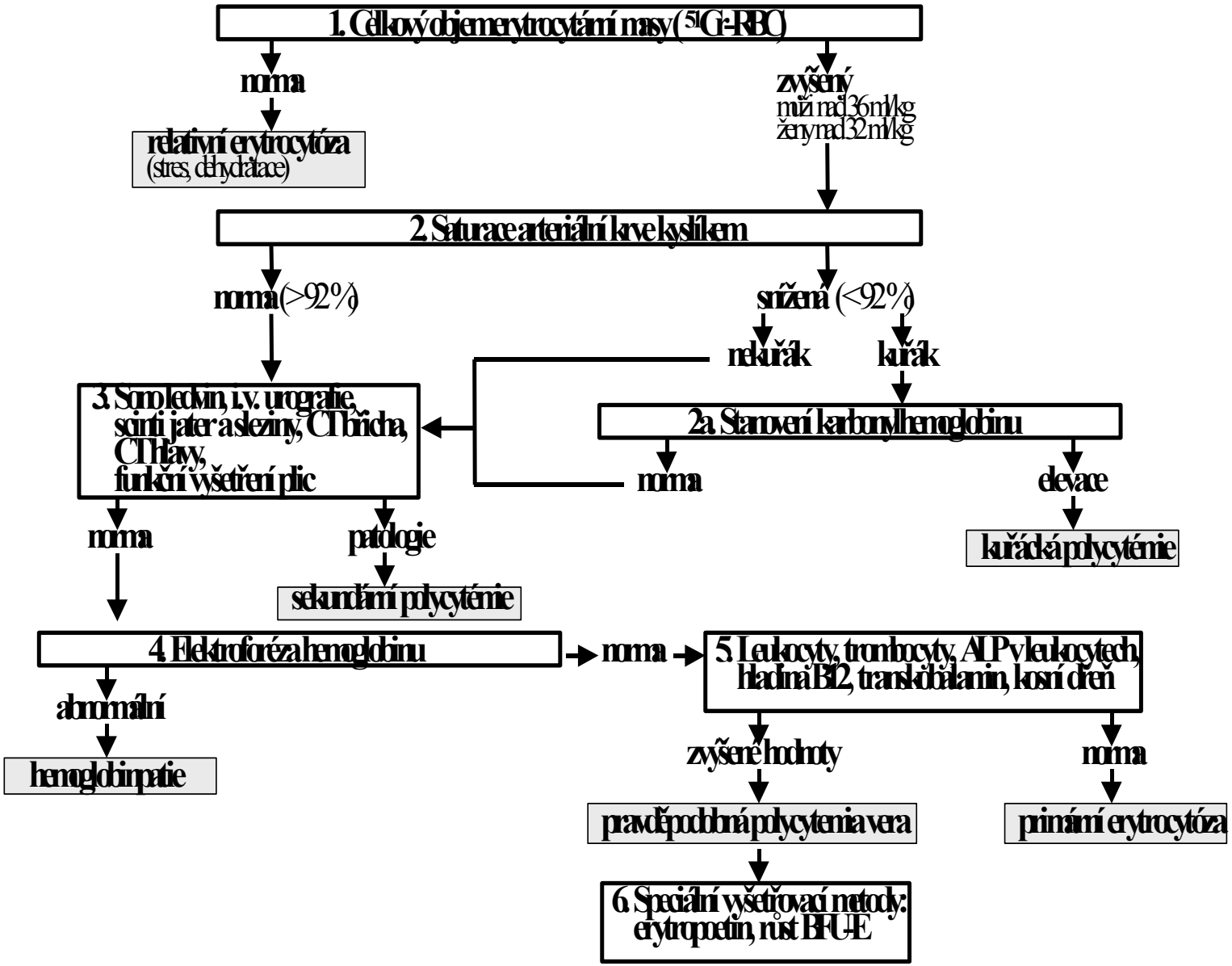
We have to exclude all secondary polycythemias. Secondary polycyhemias are more frequent than PV.

Prognosis – median survival is 15 years.

Complications - bleeding, thrombosis, leukemia

Differential diagnosis

We have to distinguish between primary and secondary polycythemias.



Treatment of polycythemia vera

1) ALL PATIENTS

phlebotomy - decrease and maintain hematocrit below 45%,
Anopyrin 50 - 100 mg/d,
or **anticoagulants**

2) BELLOW 40 YEARS

- BM donor YES → consider **TRANSPLANTATION**
- BM donor NO → **INTERFERON**

40 - 60 YEARS → **INTERFERON**

OLD PATIENTS → **HYDROXYUREA**

ESSENTIAL THROMBOCYTHEMIA

Clonal proliferation of megakaryocytes in bone marrow.
Result: incresed peripheral blood platalet count.
JAK2 mutation, calreticulin mutation

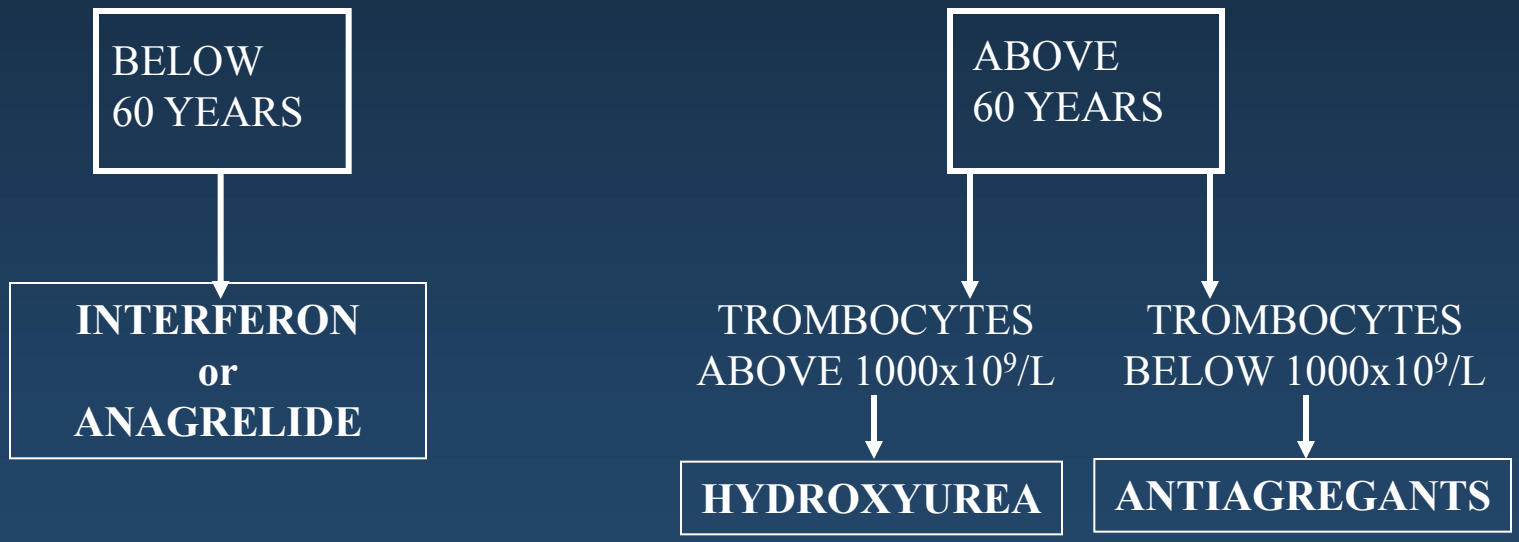
Differential diagnosis: We have to distinguish
Secondary thrombocytemias (sideropenia, chronic infection, splenectomy, malignancies, bleeding, hemolysis).
Myeloproliferative disorders, MDS

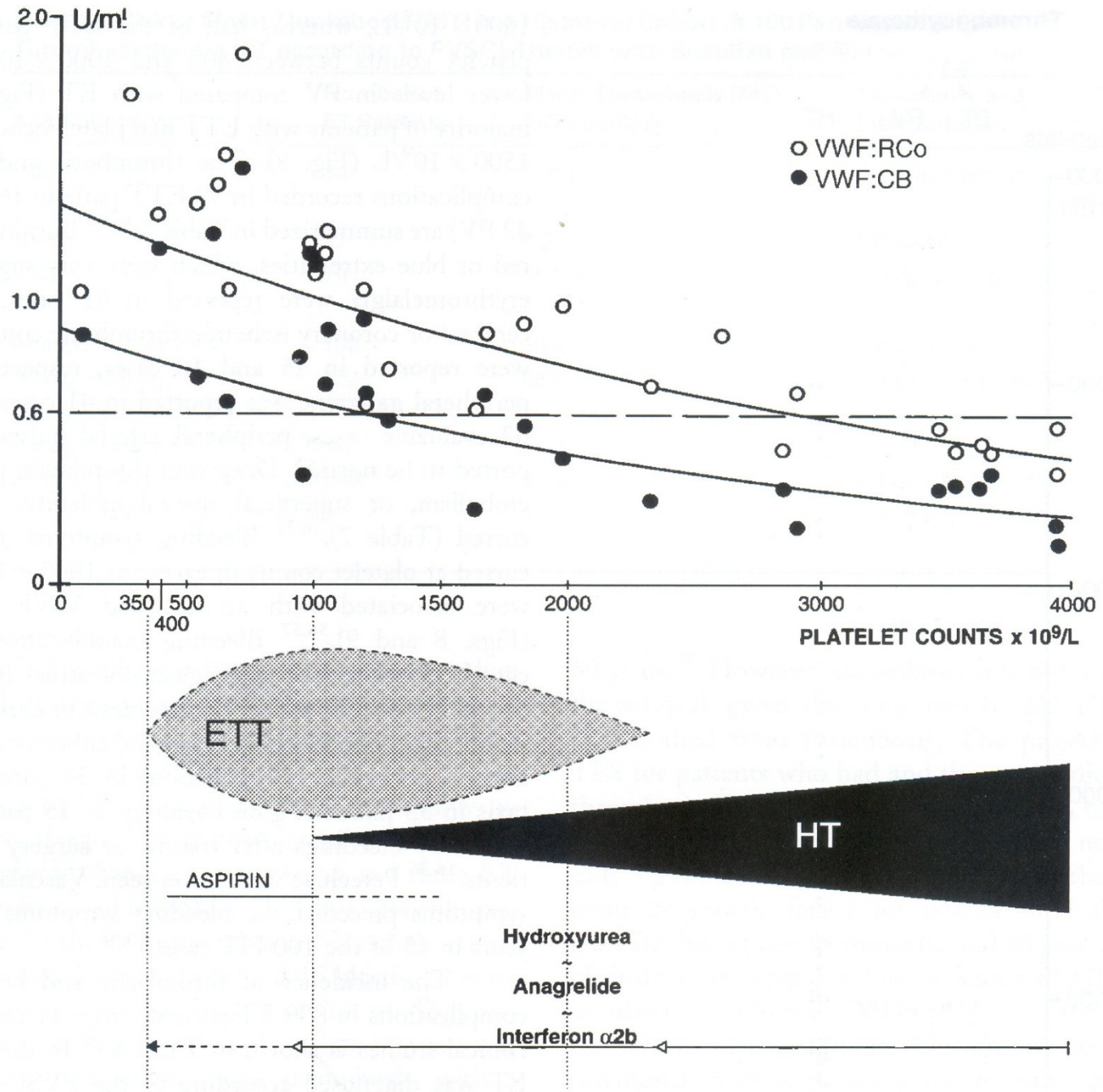
Prognosis – median survival is 12 - 15 years.

Complications - bleeding, thrombosis, leukemia

Algorythm of treatment of ET

ALL PATIENTS
Anopyrin 100 mg/d when trombocytes are below 1000.10^9/L (when above Anypyrin is not reccomended)





ETT: ERYTHROMELALGIC THROMBOTIC THROMBOCYTHEMIA
HT: HEMORRHAGIC THROMBOCYTHEMIA

PRIMARY MYELOFIBROSIS

Clonal disorder chracterized by transformation of normal bone marrow to fibrotic and non-functional bone marrow. JAK2 mutation in cca 50% of cases.

Hyperplastic stage - increased precurors of platalets in BM, increased WBC, RBC and PLT.

Late stage – fibrosis (extramedullary hematopoiesis leading to massive splenomegaly).

Prognosis – median survival only 3 - 5 years.

Treatment of choice - BMT/PBSCT
(Patients not eligible for BMT/PBSCT - symptomatic approach or watch and wait).

„Positive mutation“