Myeloproliferative diseases

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Definition

Malignant transformation of haematopoietic stem cell

- uncontrolled proliferation
- differentiation impairment

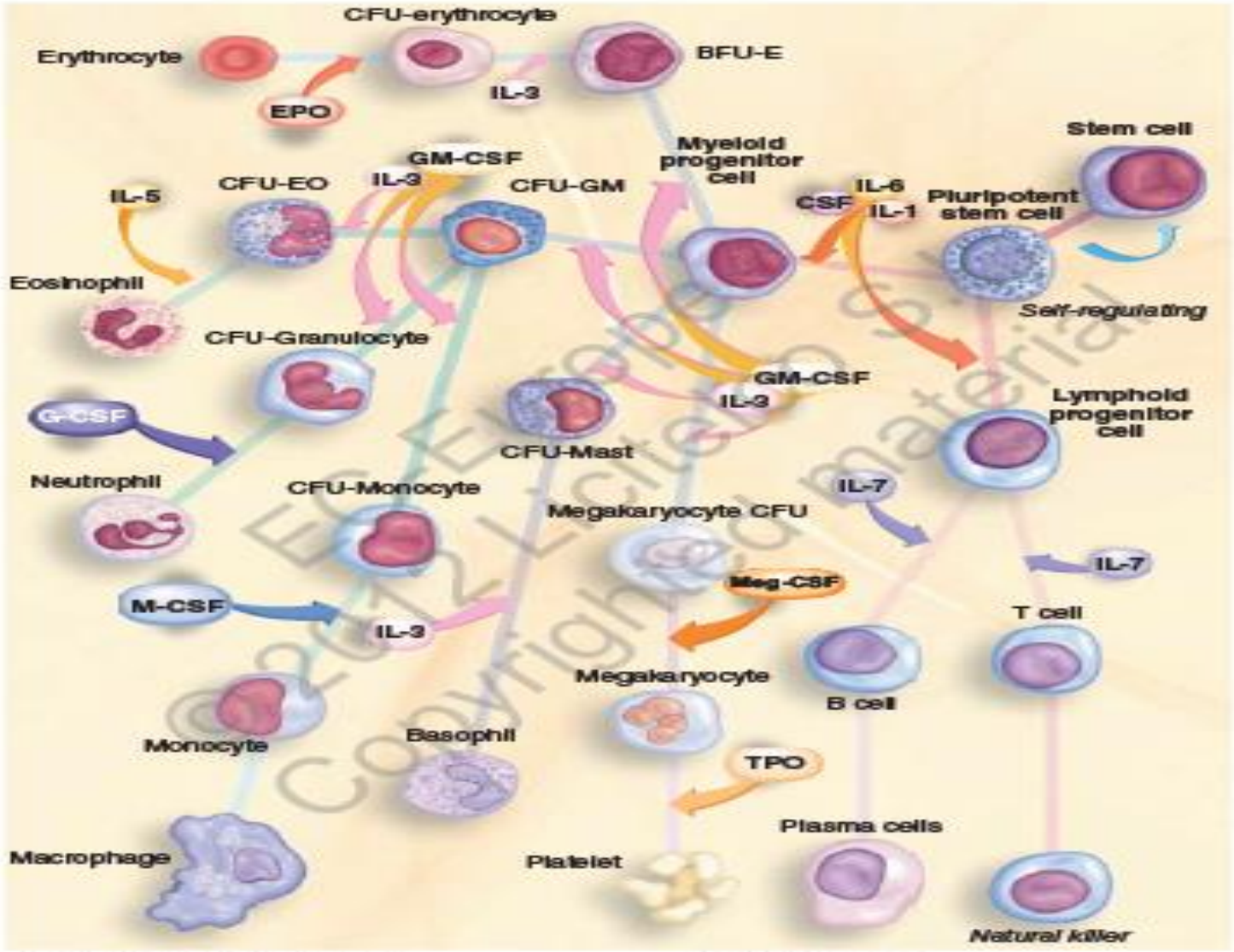
Pluripotent stem cell impairment

- abnormal proliferation of erythroid, granulopoietic and megacaryopoietic line

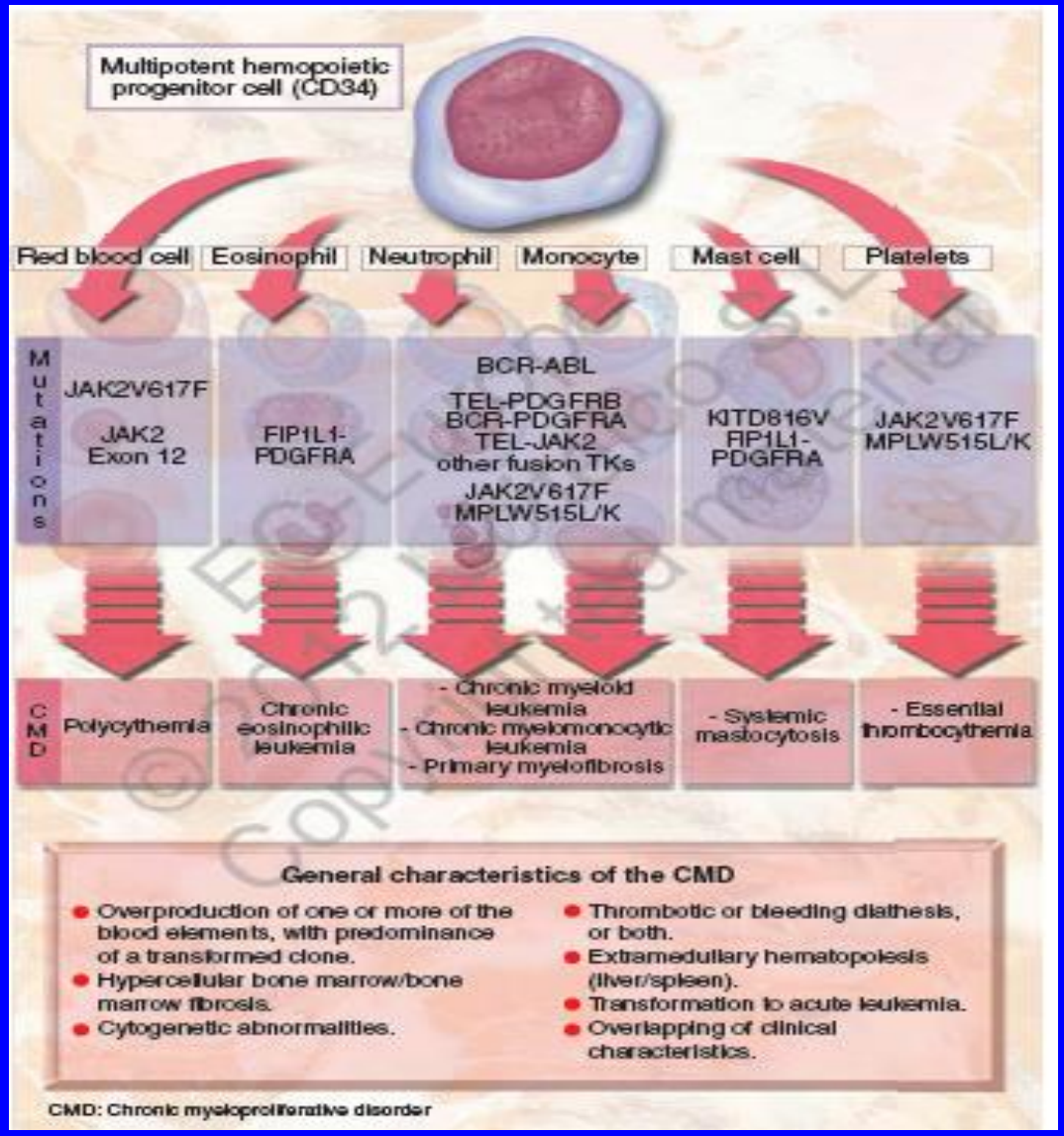
Frequently followed by:

- bone marrow fibrotisation
- extramedullary haemopoiesis in spleen and liver

Usually more than one line proliferate


CFU-erythrocyte
Erythrocyte
BFU-E
EPO
IL-3
Stem cell
Myeloid progenitor cell
GM-CSF
IL-3
CFU-EO
CFU-GM
IL-6
CSF
IL-1
Pluripotent stem cell
IL-5
Eosinophil
Self-regulating
CFU-Granulocyte
GM-CSF
IL-3
Lymphoid progenitor cell
G-CSF
CFU-Mast
Neutrophil
CFU-Monocyte
IL-7
Megakaryocyte CFU
IL-7
Meg-CSF
M-CSF
IL-3
T cell
Megakaryocyte
B cell
Monocyte
Basophil
TPO
Plasma cells
Macrophage
Platelet
Natural killer
G-CSF: Granulocyte colony-stimulating factor
Meg-CSF: Megakaryocyte colony-stimulating factor
M-CSF: Monocyte colony-stimulating factor
GM-CSF: Granulocyte macrophage colony-stimulating factor
CFU: Colony-forming unit
BFU-E: Burst-forming unit-erythroid
IL: Interleukin
TPO: Thrombopoietin

Classification of myeloproliferative disorders



Molecular pathogenesis of the MPD

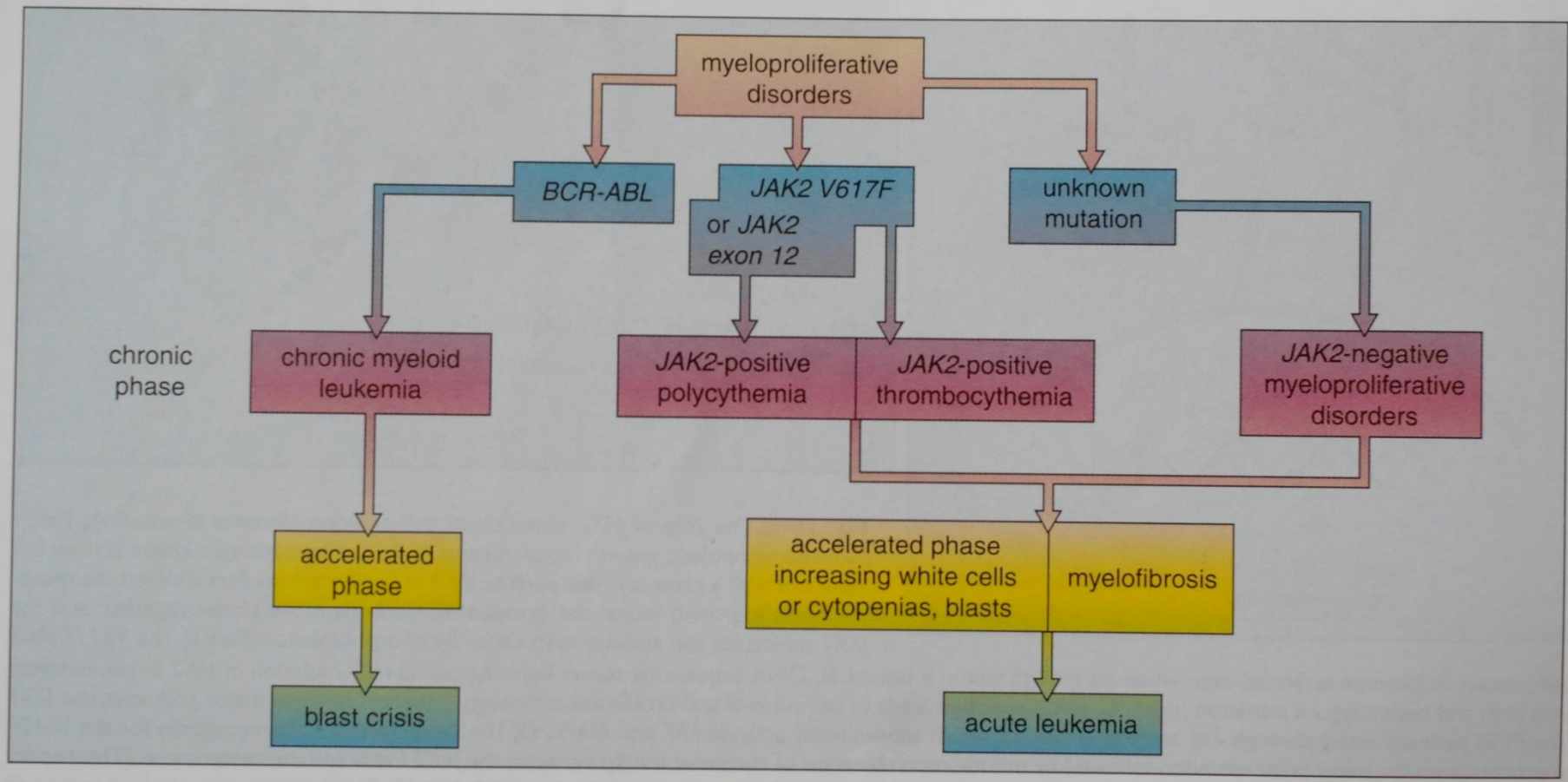


Fig. 15-2. Molecular pathogenesis of the myeloproliferative disorders.

WHO classification of myeloproliferative diseases

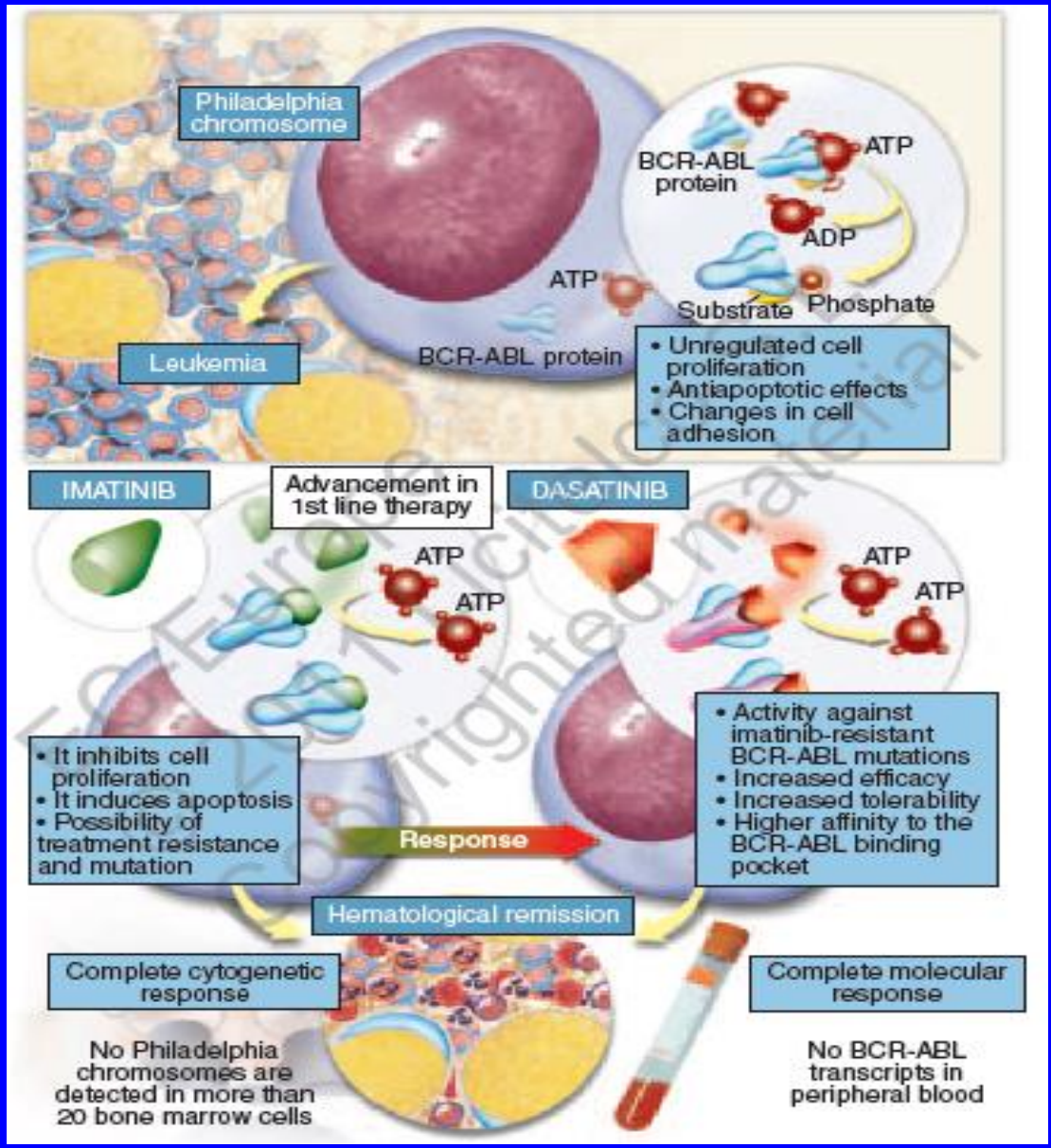
- Chronic myeloid leukaemia
- Chronic neutrophilic leukaemia
- Chronic eosinophilic leukaemia and hypereosinofilic syndrome
- Polycythaemia vera
- Chronic idiopathic myelofibrosis
- Essential trombocythaemia
- Chronic myeloproliferative disease unclassifiable

Polycytaemia vera

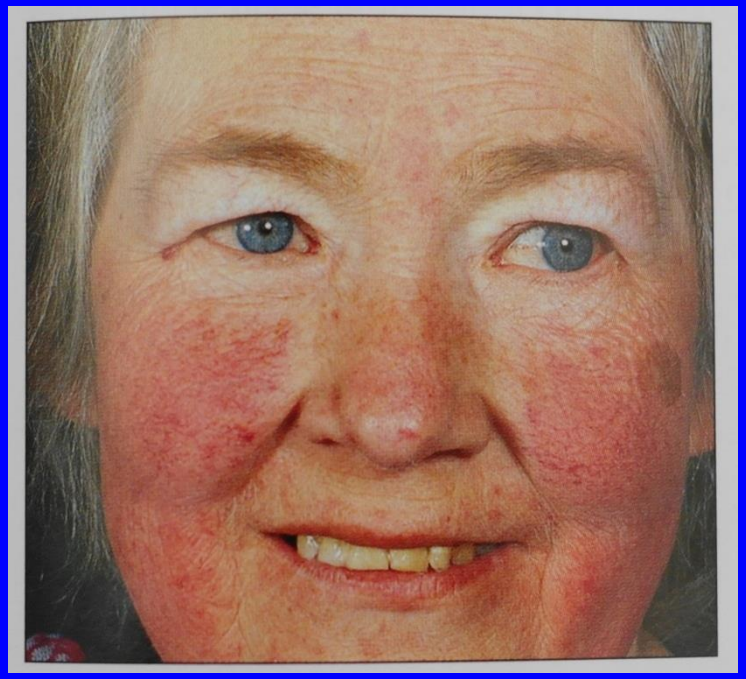
- primary polycythaemia

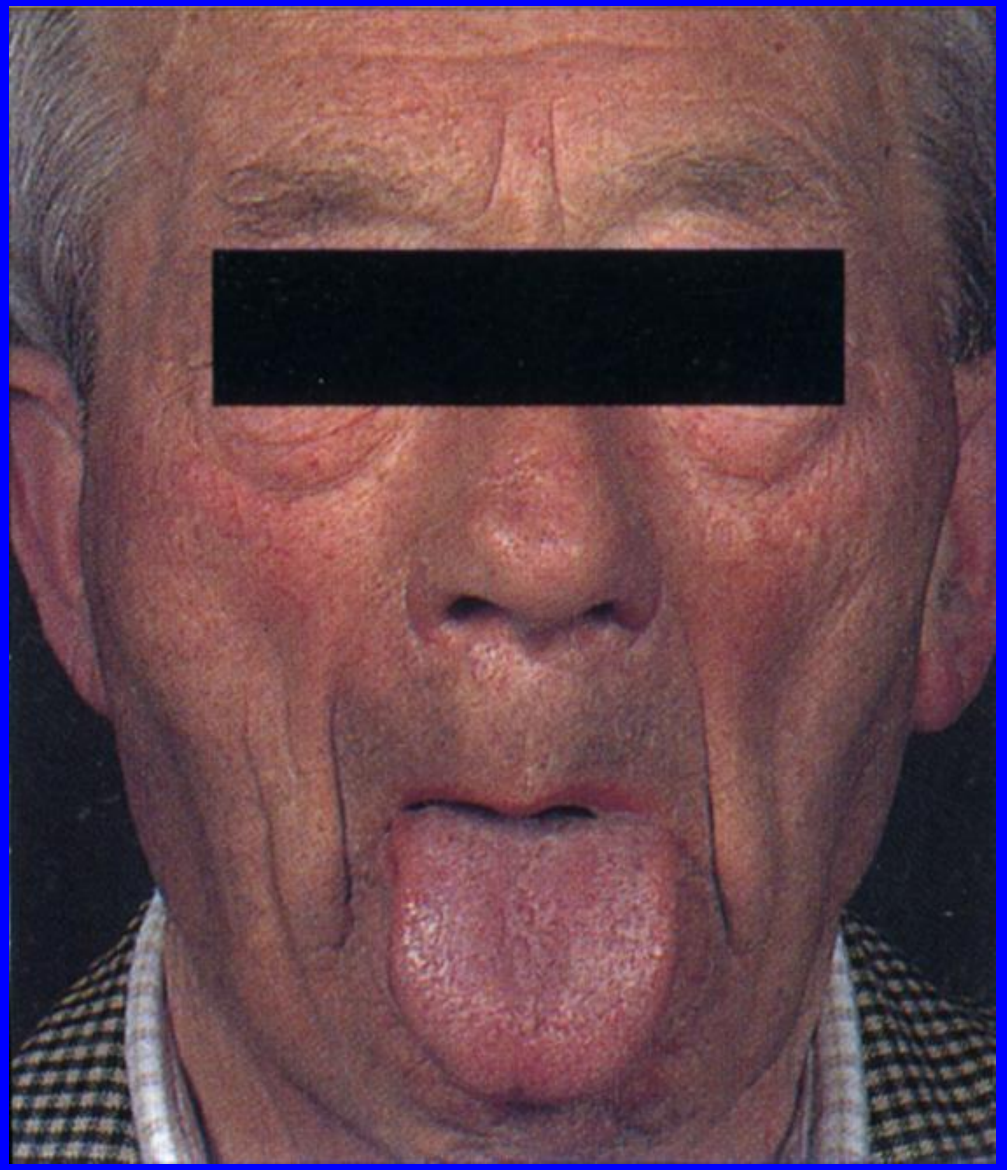
- Clonal disease , 95% nucleotid mutation JAK2 V617F
- Enhanced proliferative activity
- Differentiation mostly to erythroid line
- Increases circulating blood volume
- Absolute increase of erytrocytes more than 25% above limit
- Hb 170 g/l, Ery $6x10^{12}$/l, hc 0,55
- all lines impaired
- later marrow fibrosis or acute leukaemia transformation

Management of patients with CML



Facial appearance





Further tests

- Abdominal USG: splenomagaly, no kidney abnormality (x erythropoietin secreting tumor)
- No congenital heart disease (x plasma volume reduction, diuretic therapy)
- Normal blood gases, normal pulmonary function tests (x chronic hypoxia)

Suggested treatment

- Venesection, erytrocytopheresis
- Interferon α
- Hydroxyurea
- Selective JAK2 inhibitors, JAK2+flt3, JAK1/JAK2 TKI a pomalidomid

- Acetylsalicylic acid 75 mg/day

- No iron supplements

Essential myelofibrosis

- chronic idiopatic myelofibrosis, myelosclerosis

- Gradual replacement of haematopoiesis in bone marrow with fibrotic tissue. Platelets growth factor stimulates fibroblasts to collagen production
- Proliferation of haemotopoietic tissue with extramedulary localisation (spleen and liver with organomegaly)
- malignant transformation of stem cell
- in parallel unmatured granulocytes and erytroblasts in the circulation
- 50-60% mutation JAK2 V617F

- Prefibrotic and fibrotic stadium
- Acute leukaemia transformation

Examination of abdomen

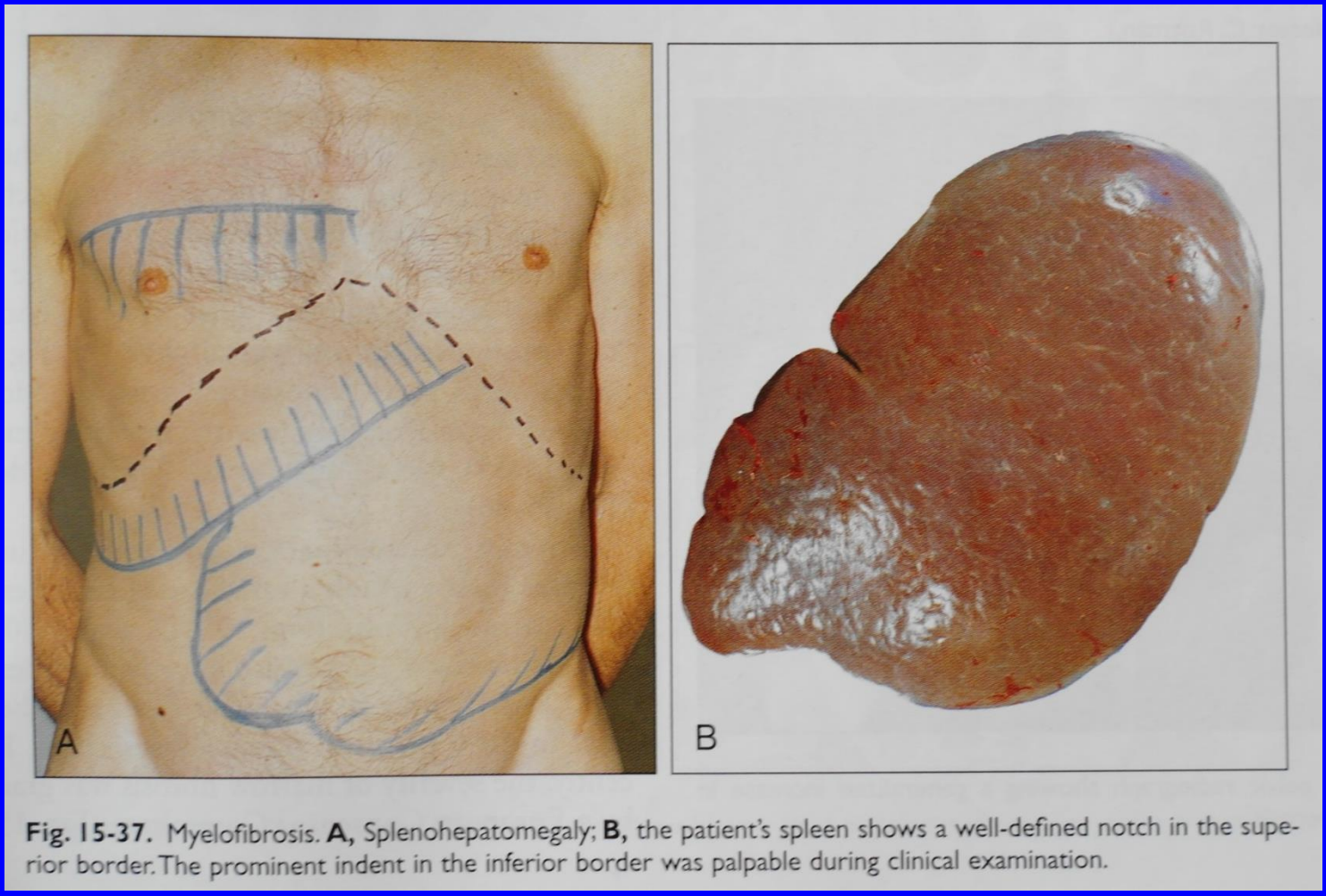
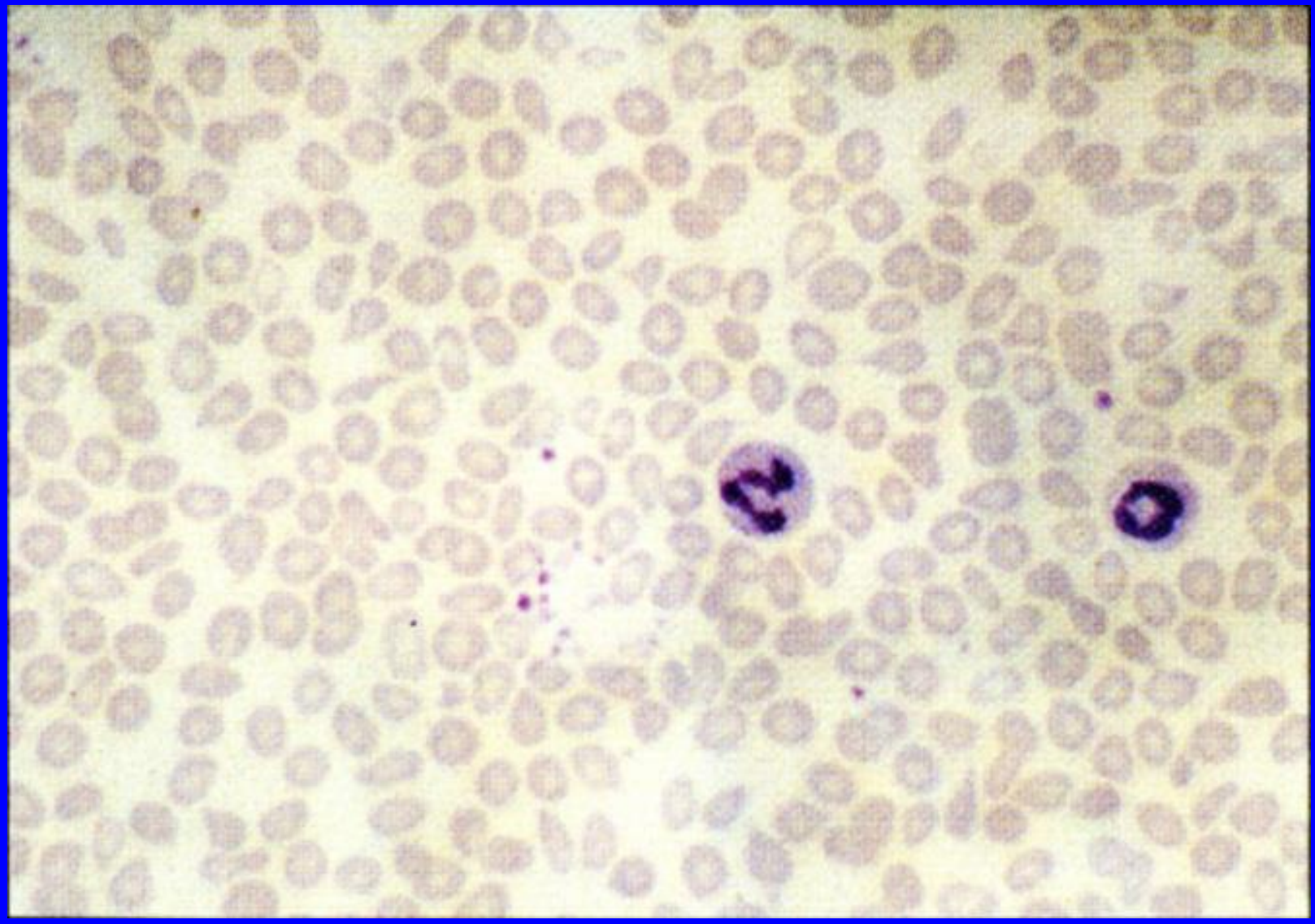
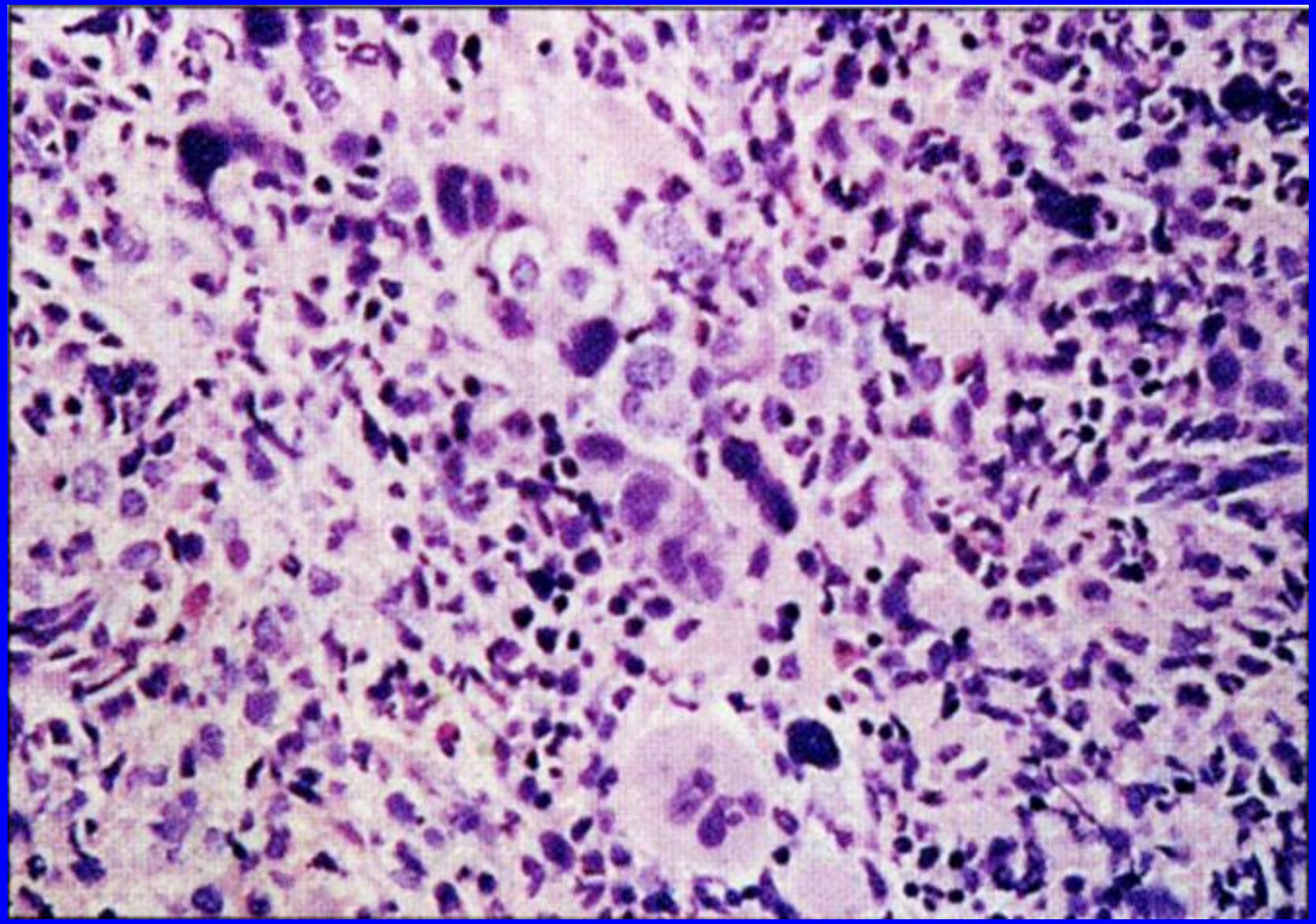


Fig. 15-37. Myelofibrosis. **A,** Splenohepatomegaly; **B,** the patient's spleen shows a well-defined notch in the superior border. The prominent indent in the inferior border was palpable during clinical examination.

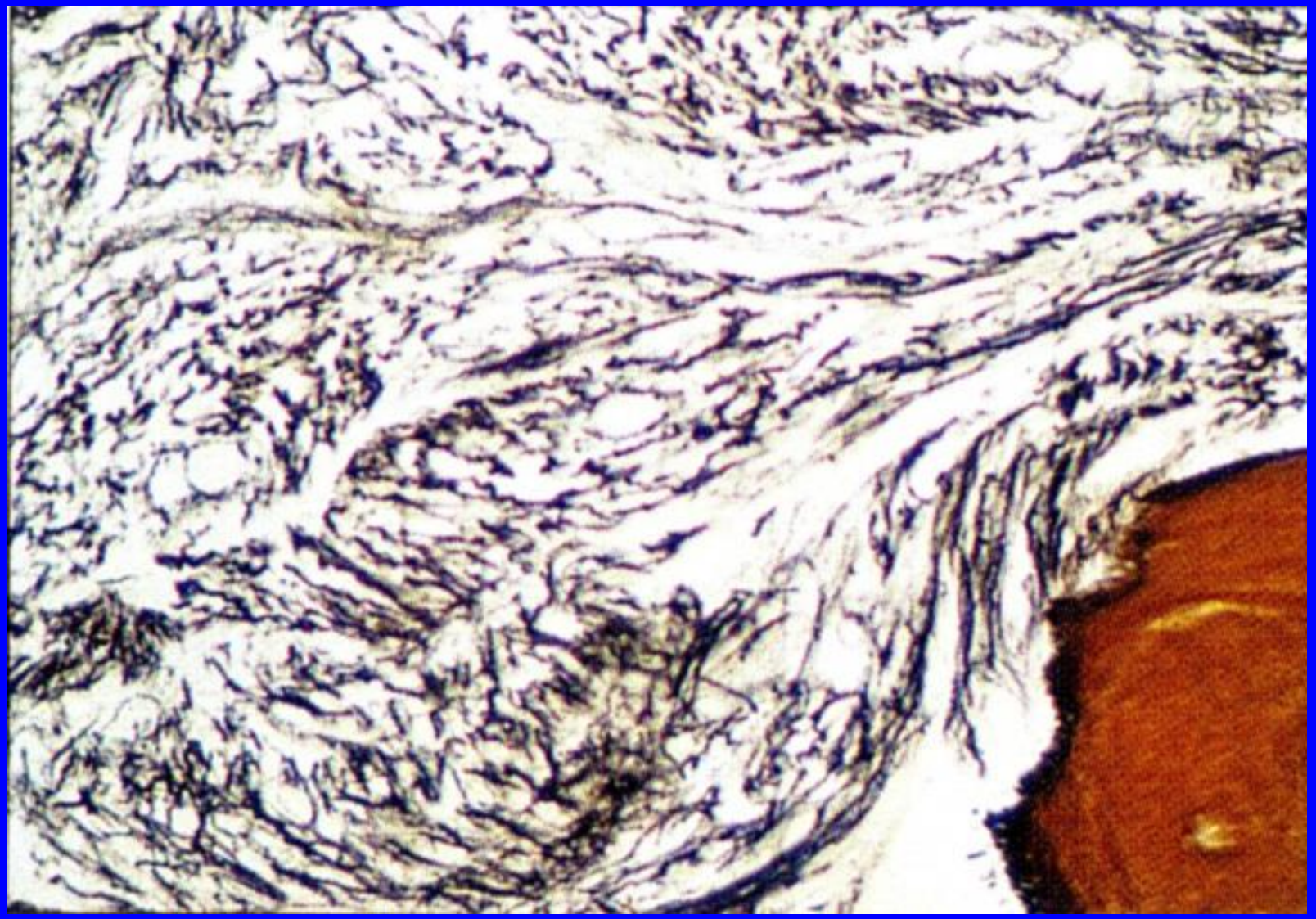
Blood film



Trephine biopsy



Trephine biopsy



Treatment approach

- No splenectomy if not needed (haemolysis, high abdominal tenderness)
- Supportive care (transfusions with chelation, antiinfective treatment if necessary)
- Hydroxyurea, interferon α (reducing spleen size and secondary symptoms)
- Selective JAK2 inhibitors -JAK1/JAK2 ruxolitinib
- Experimentaly: Thalidomide a Lenalidomide, Pomalidomide – immunomodulatory drugs

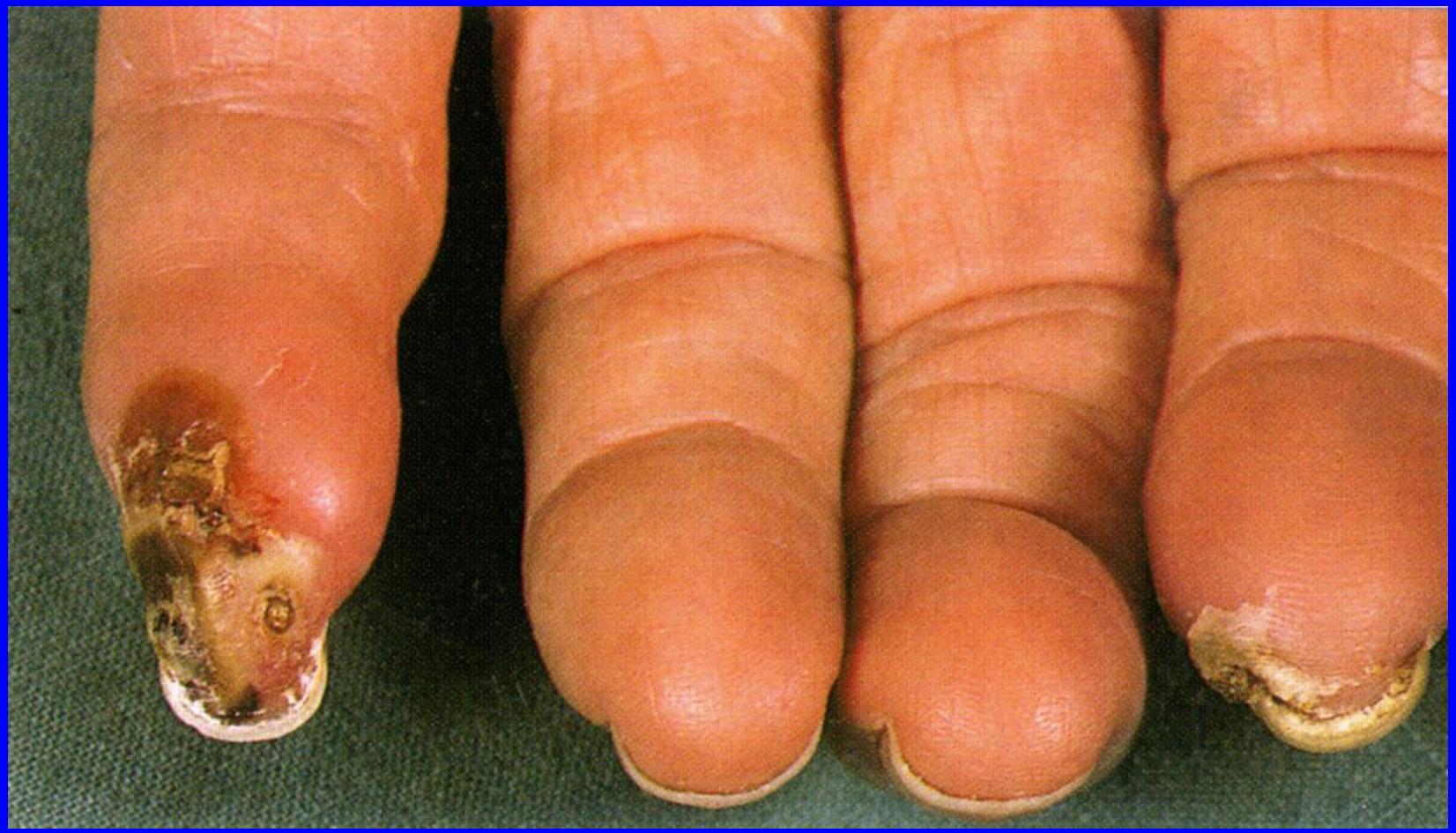
- Allogeneic HSC transplantation

Essential trombocytaemia

- Hyperplasia of megakaryocytic line with platelets elevation (over 1000x 10e9/l, i 3000)
- Platelets are functionally impaired, together with coagulation factors consumption, →
- in parallel bleeding and thrombotic complications

Ethiology:

- enhanced production of thrombopoetin
- defect of TPO receptor



Diferential diagnosis of thrombocythaemia?

- Infection
- Bleeding
- Iron deficiency
- Malignancy
- MDS- 5q-

- Chronic myeloid leukemia
- Polycythaemia vera
- Prefibrotic stage of idiopatic myelofibrosis

Treatment approach

- Acetylsalicylic acid if not bleeding
- Keeping platelets below 1000 x 10e9/l

- Anagrelide
- Interferon
- Hydroxyurea

- Thrombocytopheresis

TABLE I. The 2008 World Health Organization Diagnostic Criteria for PV, ET, and PMF [2]

	PV[a]	ET[a]	PMF[a]
Major criteria	(1) Hgb > 18.5 g/dL (men) > 16.5 g/dL (women) or Hgb > 17 g/dL (men), or > 15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that can not be attributed to correction of iron deficiency or[c]	(1) Platelet count ≥450 × 10^9/L	(1) Megakaryocyte proliferation and atypia[b] accompanied by either reticulin and/or collagen fibrosis, or in the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF)
	(2) Presence of JAK2V617F or similar mutation	(2) Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid proliferation	(2) Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
		(3) Not meeting WHO criteria for CML, PV, PMF, MDS, or other myeloid neoplasm	(3) Demonstration of JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis
		(4) Demonstration of JAK2V617F or other clonal marker or no evidence of reactive thrombocytosis	
Minor criteria	(1) BM trilineage myeloproliferation (2) Subnormal serum Epo level (3) EEC growth		(1) Leukoerythroblastosis (2) Increased serum LDH (3) Anemia (4) Palpable splenomegaly

Hgb, hemoglobin; Hct, hematocrit; Epo, erythropoietin; EEC, endogenous erythroid colony; WHO, World Health Organization; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; LDH, lactate dehydrogenase.

[a]Diagnosis of PV requires meeting either both major criteria and one minor criterion or the first major criterion and two minor criteria; diagnosis of ET requires meeting all four major criteria; diagnosis of PMF requires meeting all three major criteria and two minor criteria.

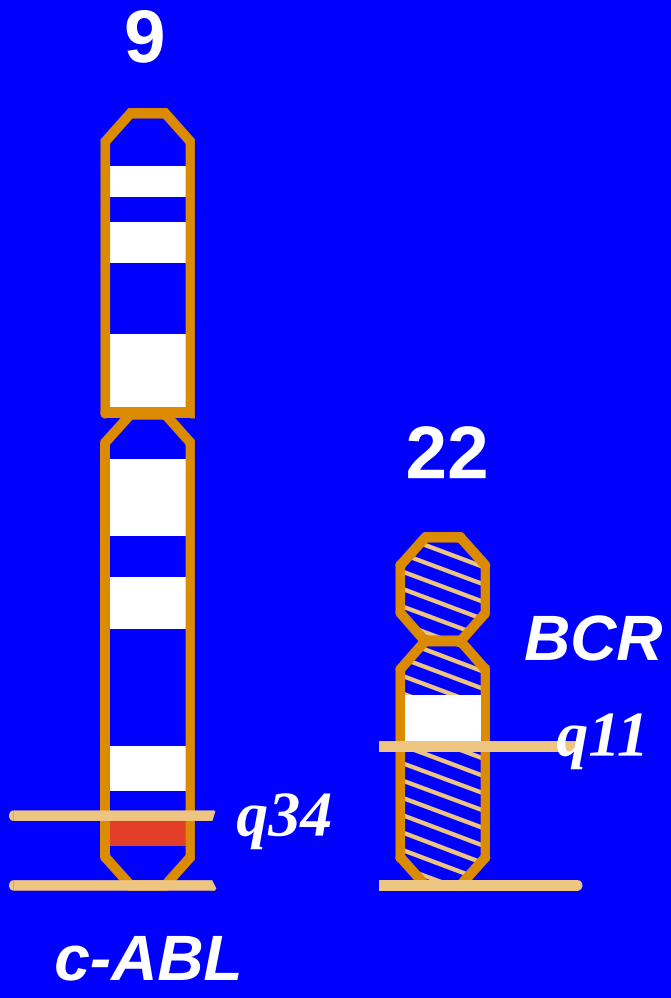
[b]Small to large megakaryocytes with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

[c]or Hgb or Hct >99th percentile of reference range for age, sex, or altitude of residence or red cell mass >25% above mean normal predicted.

Chronic myelogenous leukaemia

- clonal myelopoliferative disease rising by malignant transformation of haematopoietic stem cell with the impairment of its differentiation and proliferation
- 10-25% of leukaemia in adults
- incidence 1-2/ 100 000
  - 5,000 newly diagnosed in the USA
  - 5,000 Europe
  - 100 - 150 CZ
- increasing incidence with age, median 55 let

Function of genes ABL and BCR



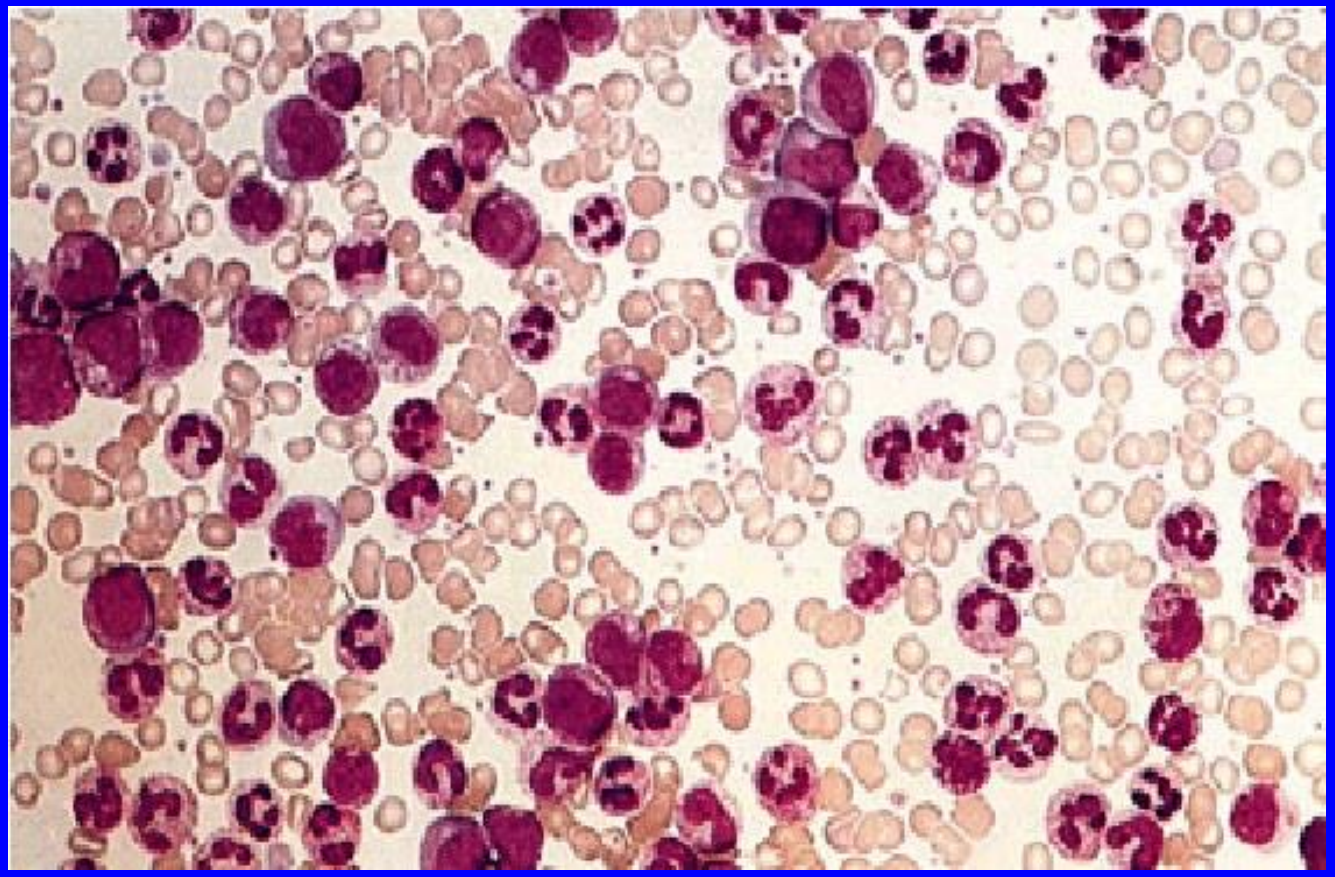
- protein $p145^{ABL}$ with tyrozinproteinkinase activity
  - negative regulator of mitotic activity by binding regulatory proteins (pRb a p53)
  - facilitates damaged DNA repair DNA
- protein $p160^{BCR}$ with serintreoninproteinkinase activity
  - important role in patogenesis of CML

Chimeric (fusion) gene BCR-ABL

BCR-ABL gene

- protein $p210^{BCR-ABL}$ has thyrosin-kinase activity of Abl
- The activity is multiplicated
- There is autophosphorylation –loosing proper regulation
- Proteins responsible to signal initiation of mitoses are activated
- Cells are transformated

Peripheral blood smear



Clinical stages of the disease

Chronic phase	Advanced phases	
	Accelerated phase	Blastic transformation
Median 6–8 years in stable stage (15-20 y. TKI)	Median of duration less than 1 year	Median of survival 6-8 months Terminal phase

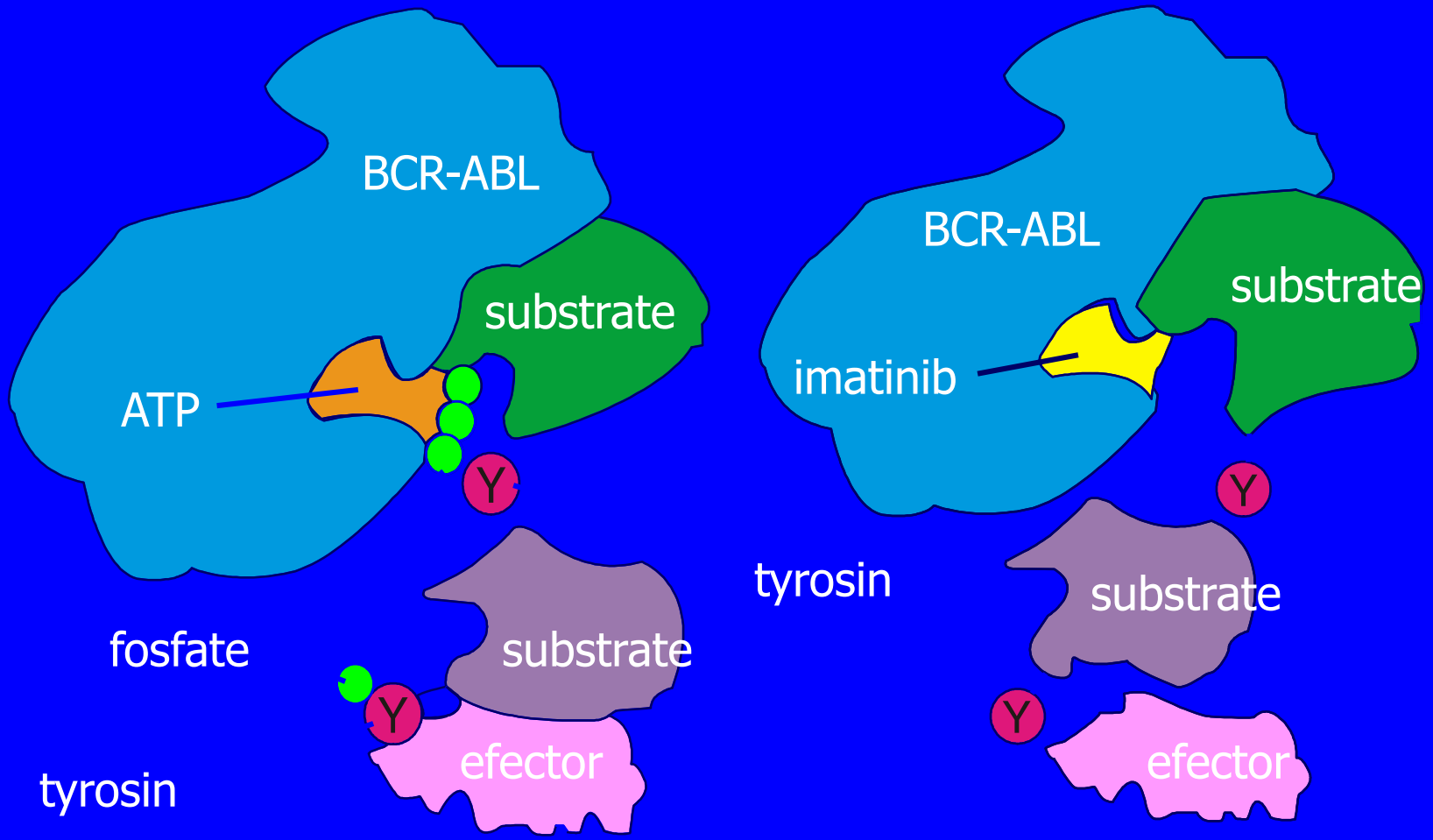
Treatment strategies in CML:

1. Inhibitors of thyrosin-kinase BCR-ABL first generation - imatinib mesylate
2. Inhibitors of thyrosin-kinase BCR-ABL second generation - dasatinib, nilotinib, bosutinib
3. TKI 3. generation – ponatinib)
4. Allogenneic transplantation
5. Interferon

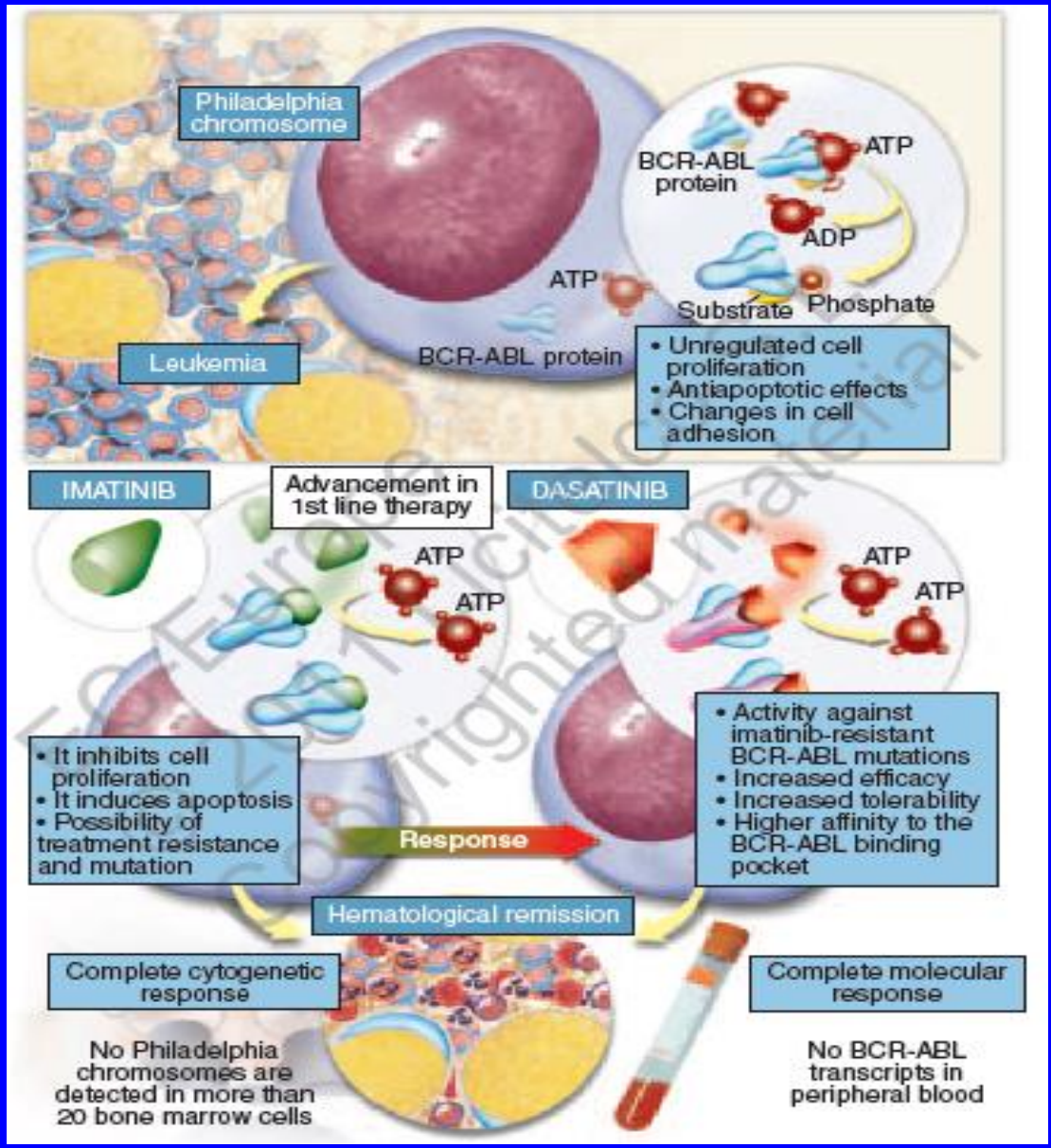
6. Experimental treatment - pegylated interferon
   - homoharringtonin
   - 5-aza-2-deoxycytidine
   - gene therapy (antisenseoligonukleotidy)
   - vaccination, enzymes, growth factors

(7. Conventional chemotherapy)

Mechanism of imatinib



Management of patients with CML



Questions on the topic

- Does myeloproliferative disease also include lymphoma ?
- By which laboratory examination can we diagnose CML ?
- By which laboratory examination can we diagnose CML ?
- Anagrelide is used in the treatment of which MPO ?
- What KO values can be expected in polycythaemia vera ?