Chronic myeloid leukemia

By
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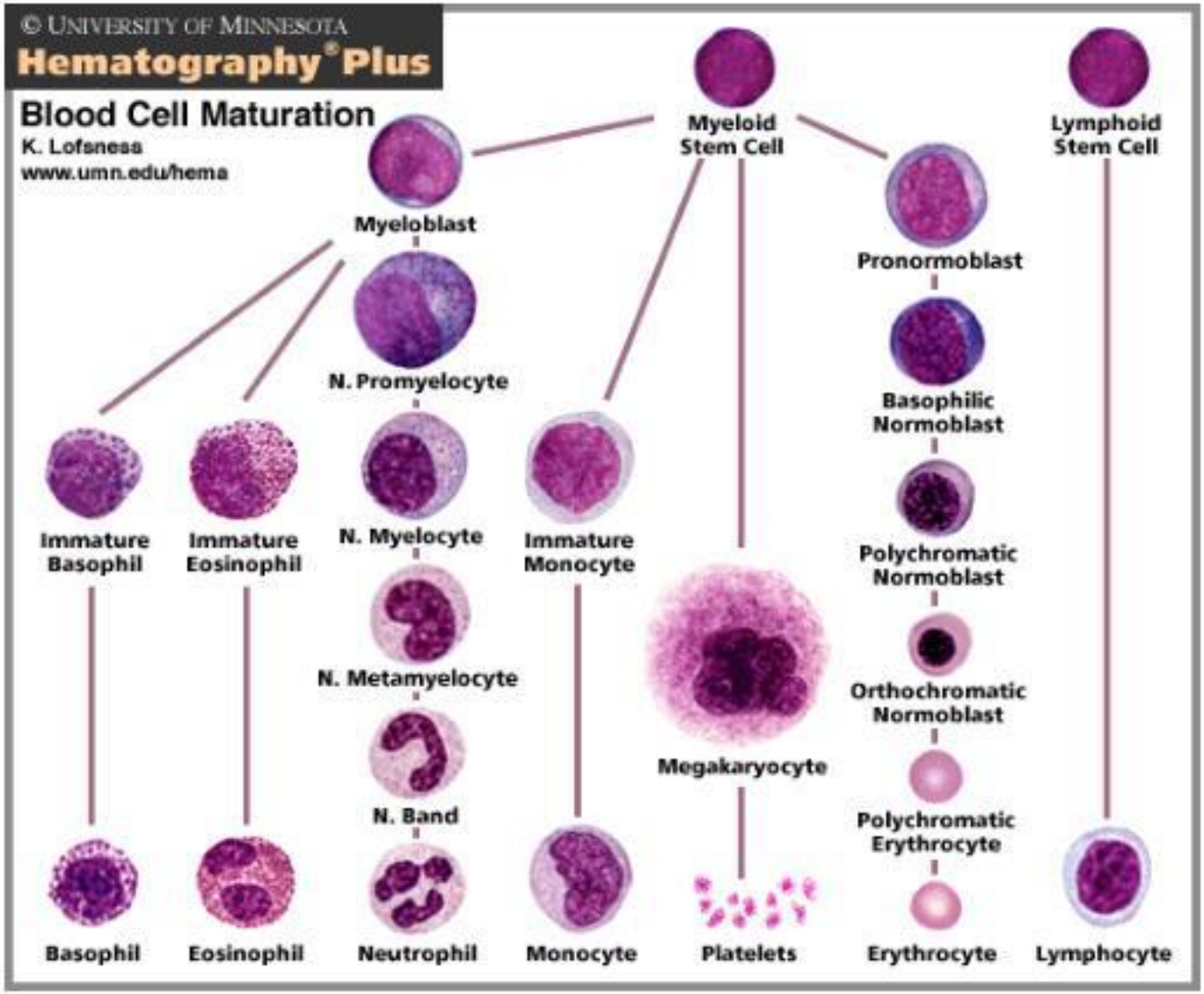
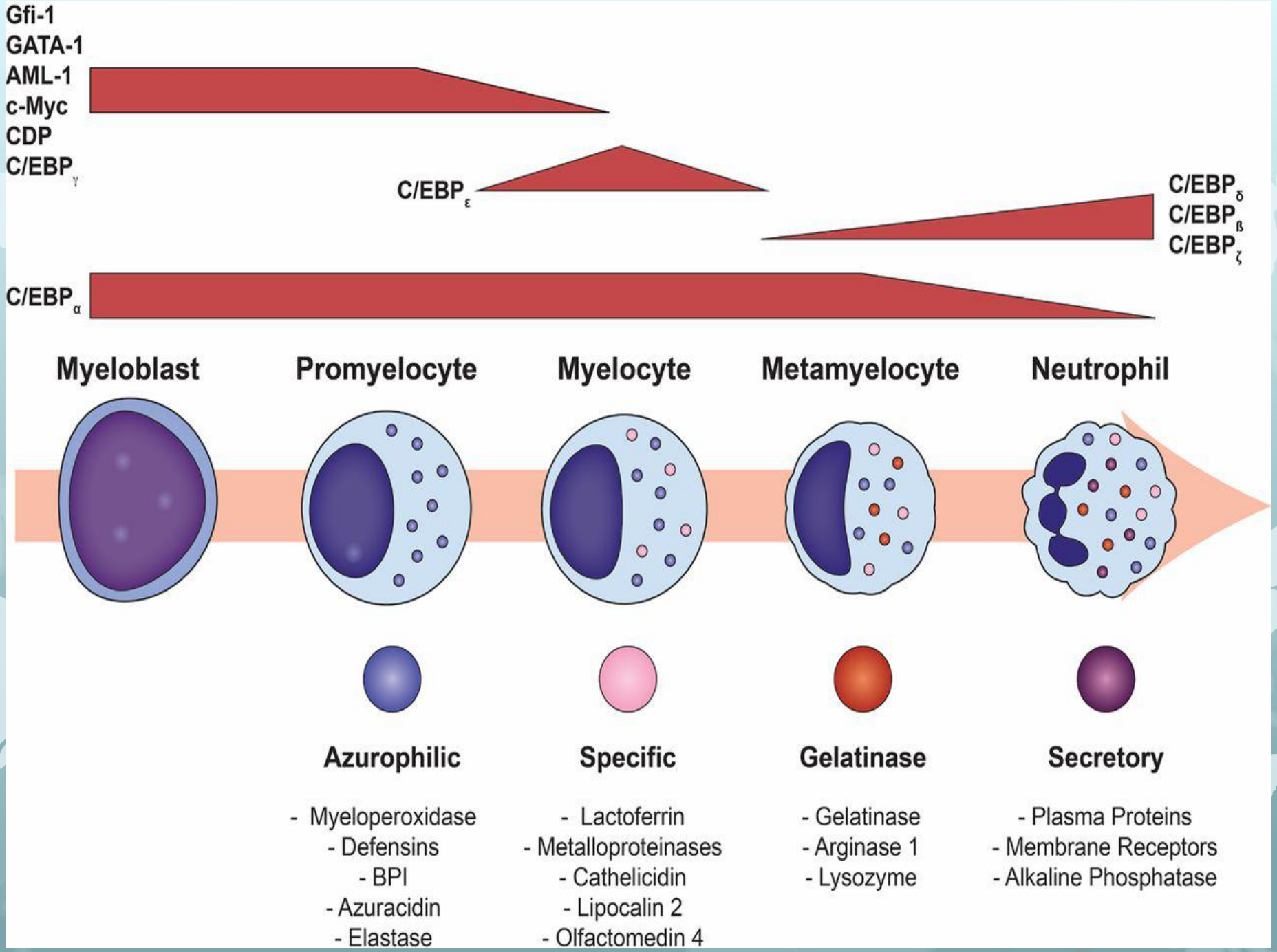
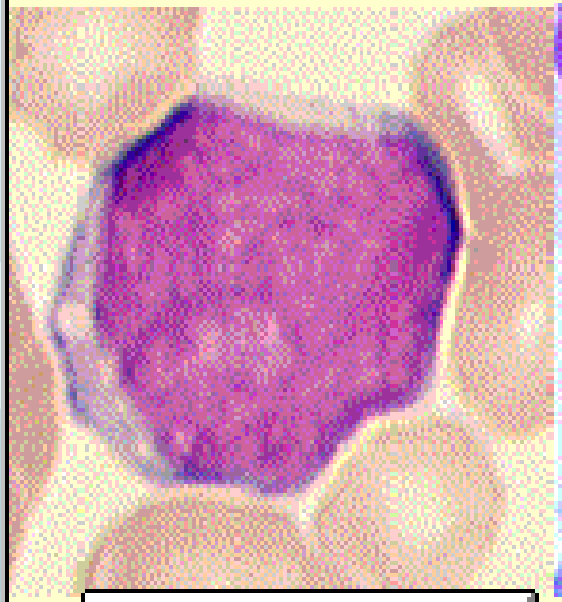
Chronic Myeloid Leukemia (CML)

Definition :

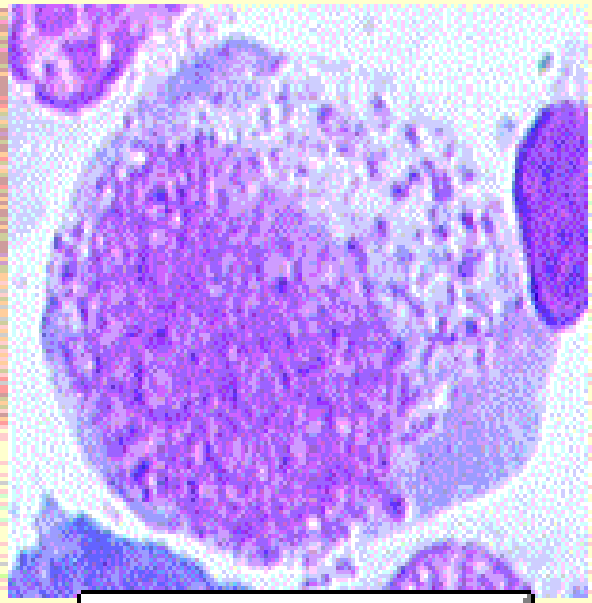
- **Also known** as chronic myelogenous leukemia and chronic granulocytic leukemia
- It is **a clonal disease** that results from an **acquired genetic** change in a pluripotential haemopoietic stem cell or progenitor cells.
- This **altered stem cell proliferates** and **produce a population of differentiated cells** that gradually displaces normal haemopoiesis and leads to a **greatly expanded total myeloid mass.**


© University of Minnesota
Hematography® Plus
Blood Cell Maturation
K. Lofsness
www.umn.edu/hema
Myeloid Stem Cell
Lymphoid Stem Cell
Myeloblast
Pronormoblast
N. Promyelocyte
Basophilic Normoblast
Immature Basophil
Immature Eosinophil
N. Myelocyte
Immature Monocyte
Polychromatic Normoblast
N. Metamyelocyte
Orthochromatic Normoblast
Megakaryocyte
N. Band
Polychromatic Erythrocyte
Basophil
Eosinophil
Neutrophil
Monocyte
Platelets
Erythrocyte
Lymphocyte

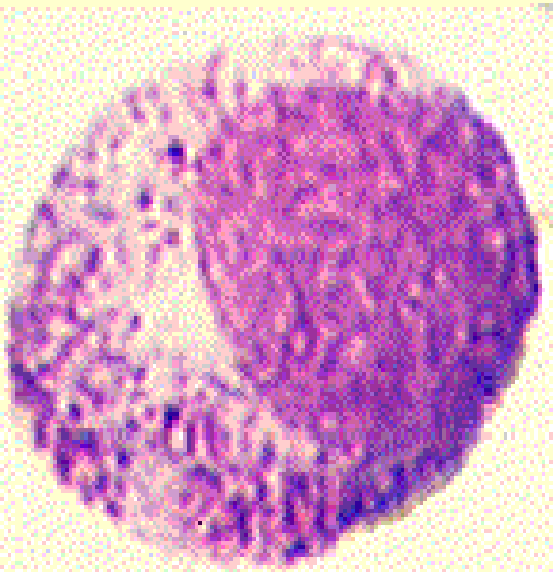

Gfi-1
GATA-1
AML-1
c-Myc
CDP
C/EBP γ
C/EBP ε
C/EBP δ
C/EBP ß
C/EBP ζ
C/EBP α
Myeloblast
Promyelocyte
Myelocyte
Metamyelocyte
Neutrophil
Azurophilic
- Myeloperoxidase
- Defensins
- BPI
- Azuracidin
- Elastase
Specific
- Lactoferrin
- Metalloproteinases
- Cathelicidin
- Lipocalin 2
- Olfactomedin 4
Gelatinase
- Gelatinase
- Arginase 1
- Lysozyme
Secretory
- Plasma Proteins
- Membrane Receptors
- Alkaline Phosphatase



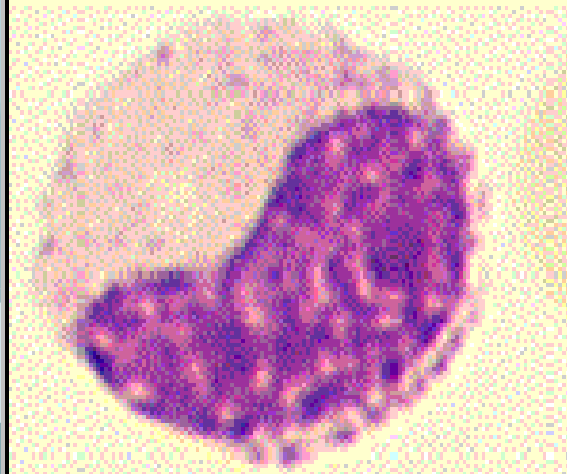
Myeloblast



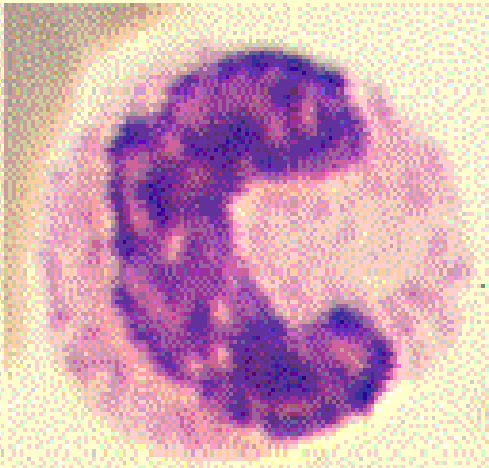
Promyelocyte



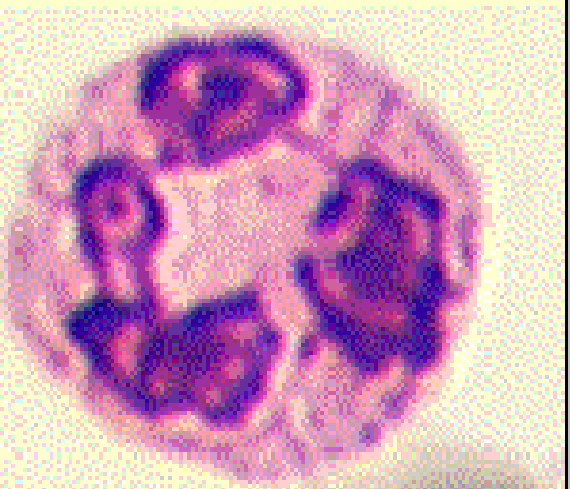
Myelocyte



Metamyelocyte



Band



Segment

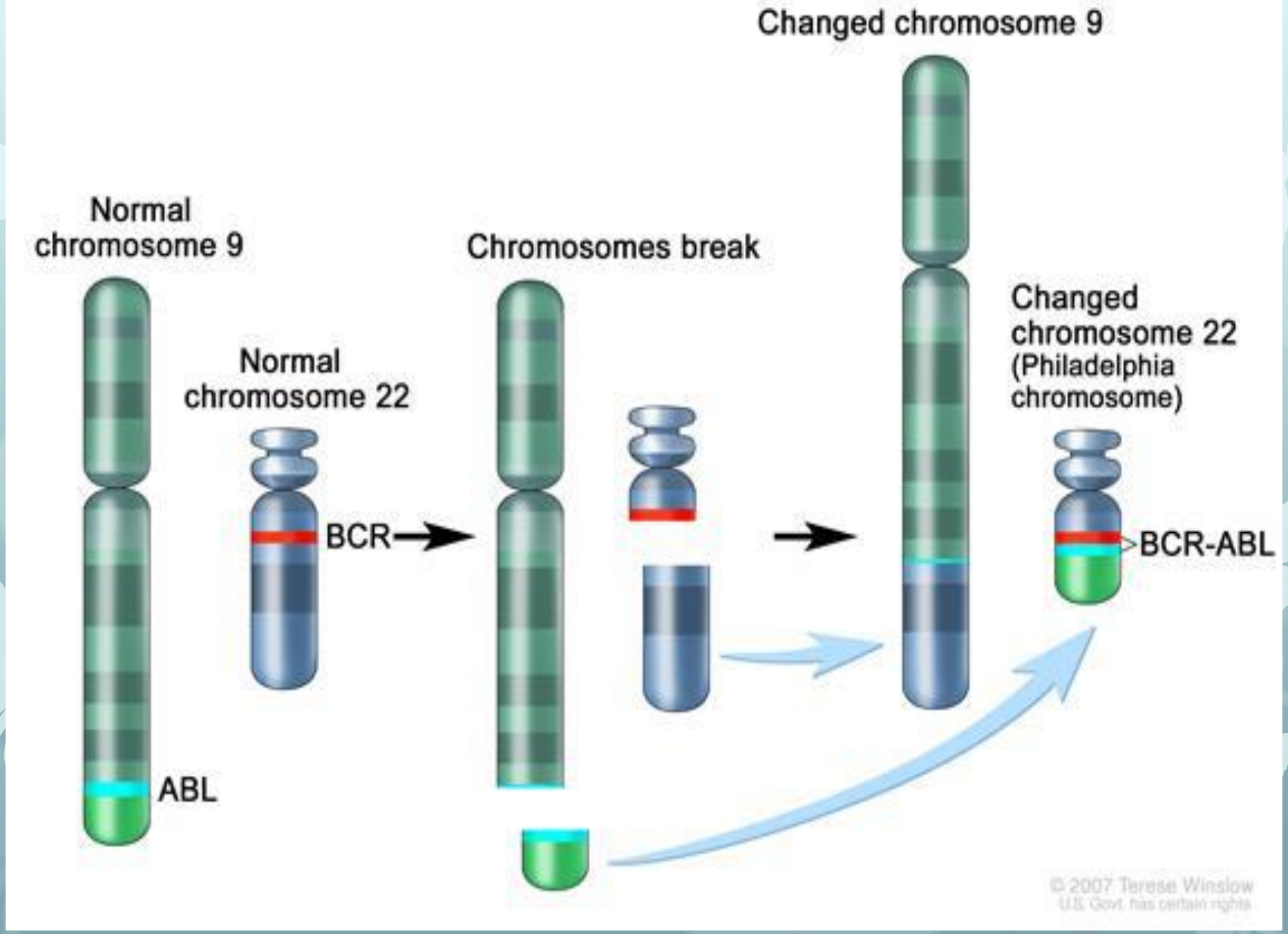
Etiology & Incidence:

- **Etiology**: In most cases no known predisposing factors, but ionizing radiation and less so benzene have been implicated. In general all cases regarded as sporadic and no predisposing factors are identified

- **Incidence**: Rare disease with a frequency of 1.25 per 100,000. CML is **rare below 20 yrs** but occur in all decade of life ,with a median age of onset of 50-60 yrs. The incidence is slightly **higher in male** than females.

Pathogenesis & course of disease

- **Cause** by acquired genetic change
- characterized by reciprocal translocation between the long arms of chromosome 9 and 22, resulting in the **Philadelphia (Ph) chromosome**, creating the fusion oncogene BCR–ABL1.
- This genetic event that encodes for **a constitutively active tyrosine kinase** occurs in a haemopoietic progenitor and confers proliferative and antiapoptotic effects.
- The natural history of untreated CML is **triphasic** . (Chronic ,accelerated and blastic phases)


Changed chromosome 9
Normal chromosome 9
Chromosomes break
Normal chromosome 22
Changed chromosome 22 (Philadelphia chromosome)
BCR
BCR-ABL
ABL
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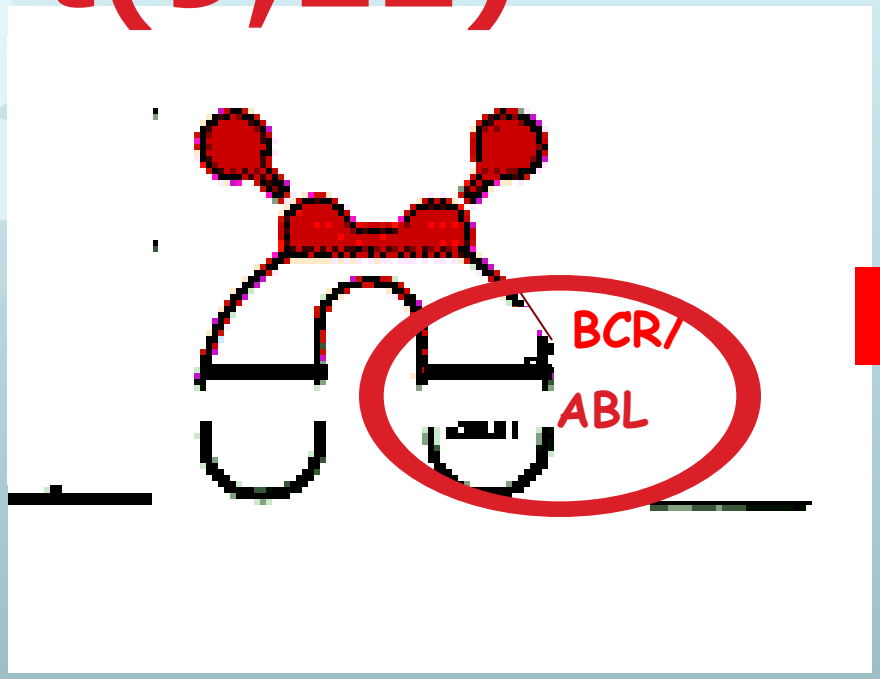
Pathogenesis of CML

t(9;22)

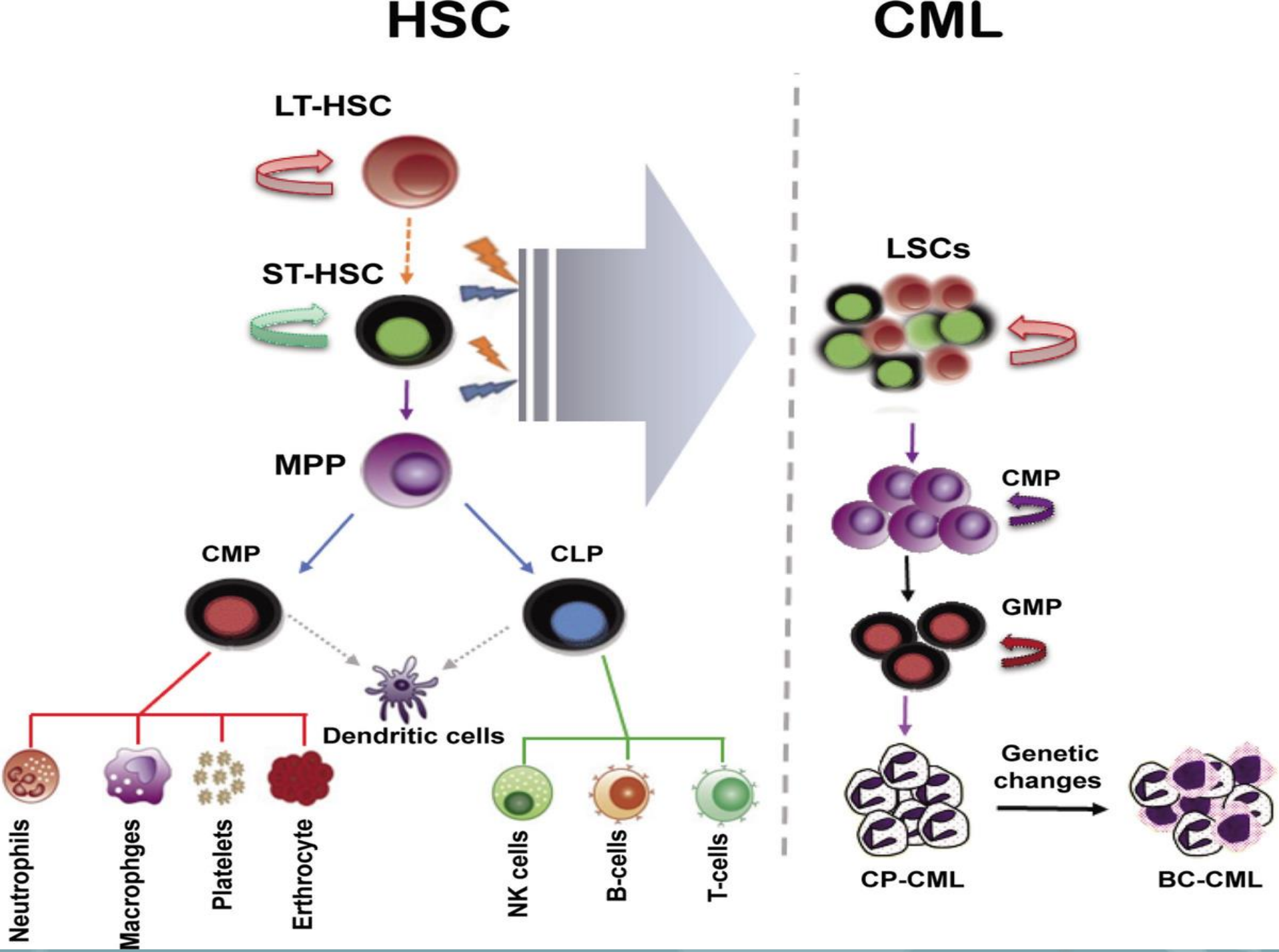


8.5kb mRNA

P210 protein

Tyrosine Kinase activity

Proliferative advantage to Myeloid cells in CML


HSC
CML
LT-HSC
ST-HSC
MPP
CMP
CLP
Dendritic cells
Neutrophils
Macrophges
Platelets
Erthrocyte
NK cells
B-cells
T-cells
LSCs
CMP
GMP
CP-CML
Genetic changes
BC-CML

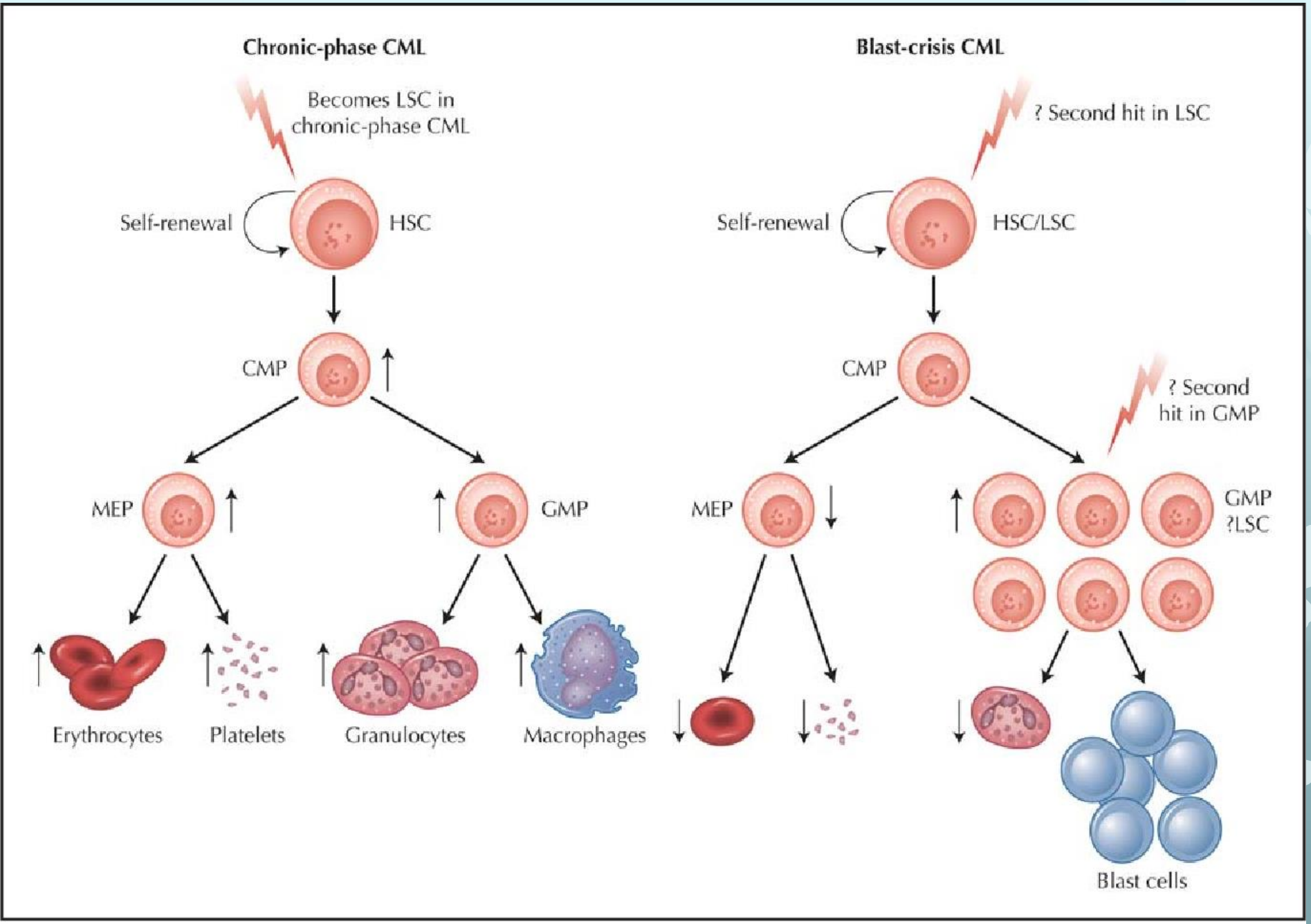


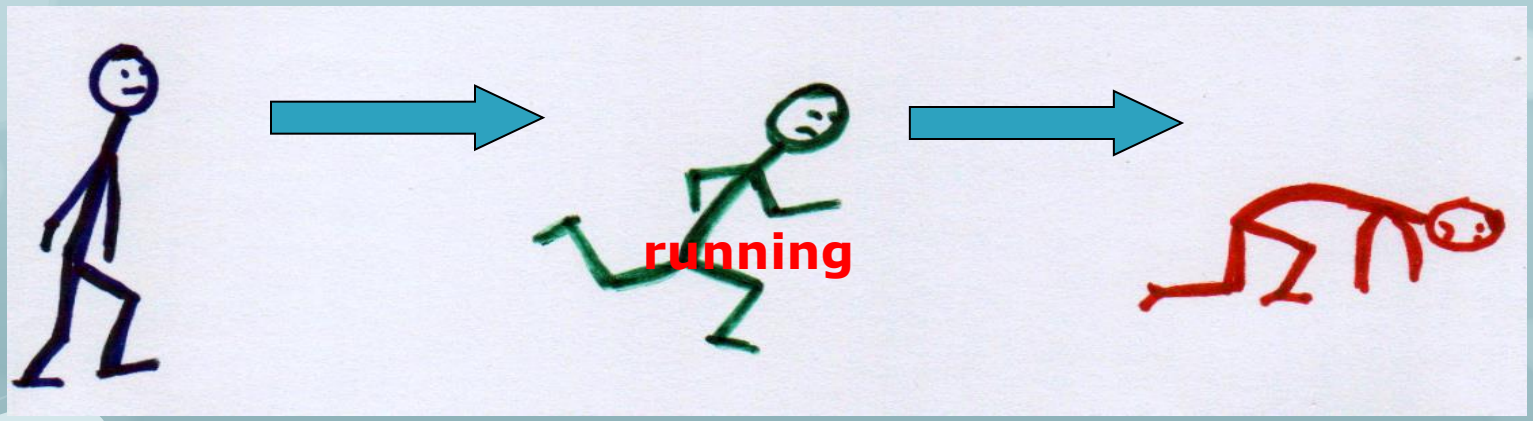
Figure 1. Comparison of aberrant hematopoiesis in chronic-phase chronic myelogenous leukemia (CML) compared with blast-crisis CML

- It most commonly presents in **chronic phase (CP),** characterized by **markedly increased** myeloid activity, resulting in increased numbers **of morphologically and functionally normal** granulocytes, predominantly comprised of neutrophils and myelocytes.
- **Basophilia** is a distinct feature of CML, although eosinophilia is also usually present. Thrombocytosis is commonly seen.
- Without effective treatment, patients may progress from chronic phase into **accelerated phase (AP)**

- where myelopoiesis is increasingly ineffective with a rising blast count, ending in **blastic phase (BP)** when the blast percentage rises further in the context of marrow failure.
- **In CML-BP** (blast crisis, blastic transformation), the disease clinically resembles acute leukemia and the outcome is dismal.
- **Amplification of BCR–ABL1** may result from duplication of the Ph chromosome, which, along with trisomy 8, i(17q) and trisomy 19, leads to increased risk of blastic transformation and together these are referred to as major route cytogenetic lesions.

Phases of CML :

- Chronic Phase .
- Accelerated phase.
- Blastic phase.



- Usually patients will present in the chronic phase, and within a 2-7 year period they will transform to the fatal blastic phase, with or without passing through the accelerated phase. 50% transform directly from chronic phase to blast crisis.

- **Chronic phase:** ability to reduce splenic size and restore and maintenance normal blood count with therapy.
- **Acceleration phase:**
  - blasts 10-19%
  - basophils ≥ 20%.
  - persistent TCP or thrombocytosis.
  - increase in splenic size or WBC count.
  - megakaryocyte clusters or sheets with marked reticuline or collagen fibers in BM.
- **Blastic Phase:**
  - Blasts in peripheral blood and/or marrow more than 20%.
  - Extramedullary blast proliferation or large cluster of blast in the marrow.

- Transformation **mainly to AML (about 70%)** and may be ALL.

Parameter	Chronic Phase	Accelerated Phase	Blast Crisis
White blood cells	≥ 20	↑	↑
BM Blasts MO	< 15%	15% - 20%	≥ 20%
Basophils	< 20%	≥ 20%	–
Platelets	↑ or normal	↓ or ↑	↓
Marrow cellularity	↑	↑	↑
Cytogenetics	Ph+	Ph+	Ph+
Bcr-abl	+	+	+

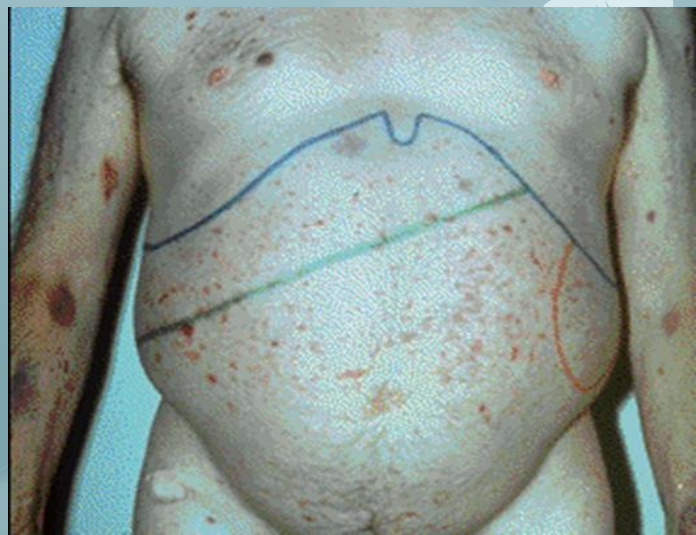
Table 24.1 Definition of advanced phase CML disease.

	ELN	WHO
Accelerated phase	• PB or BM blast 15–29% • PB or BM blast + promyelocytes ≥30% • PB basophils ≥20% • Platelets ≤100 × 10^9/L unrelated to therapy • Clonal evolution	• PB or BM blast 10–19% • PB basophils ≥20% • Platelets ≤100× 10^9/L unrelated to therapy • Platelets >1000 × 10^9/L unresponsive to therapy • Clonal evolution on treatment • Increasing spleen size and increasing WBC count unresponsive to therapy
Blast crisis	• PB or BM blast ≥30% • Extramedullary blast proliferation, apart from spleen	• PB or BM blast 20% • Extramedullary blast proliferation, apart from spleen • Large foci or clusters of blasts in the bone marrow biopsy

BM, bone marrow; PB, peripheral blood

Clinical features of Chronic phase CML:

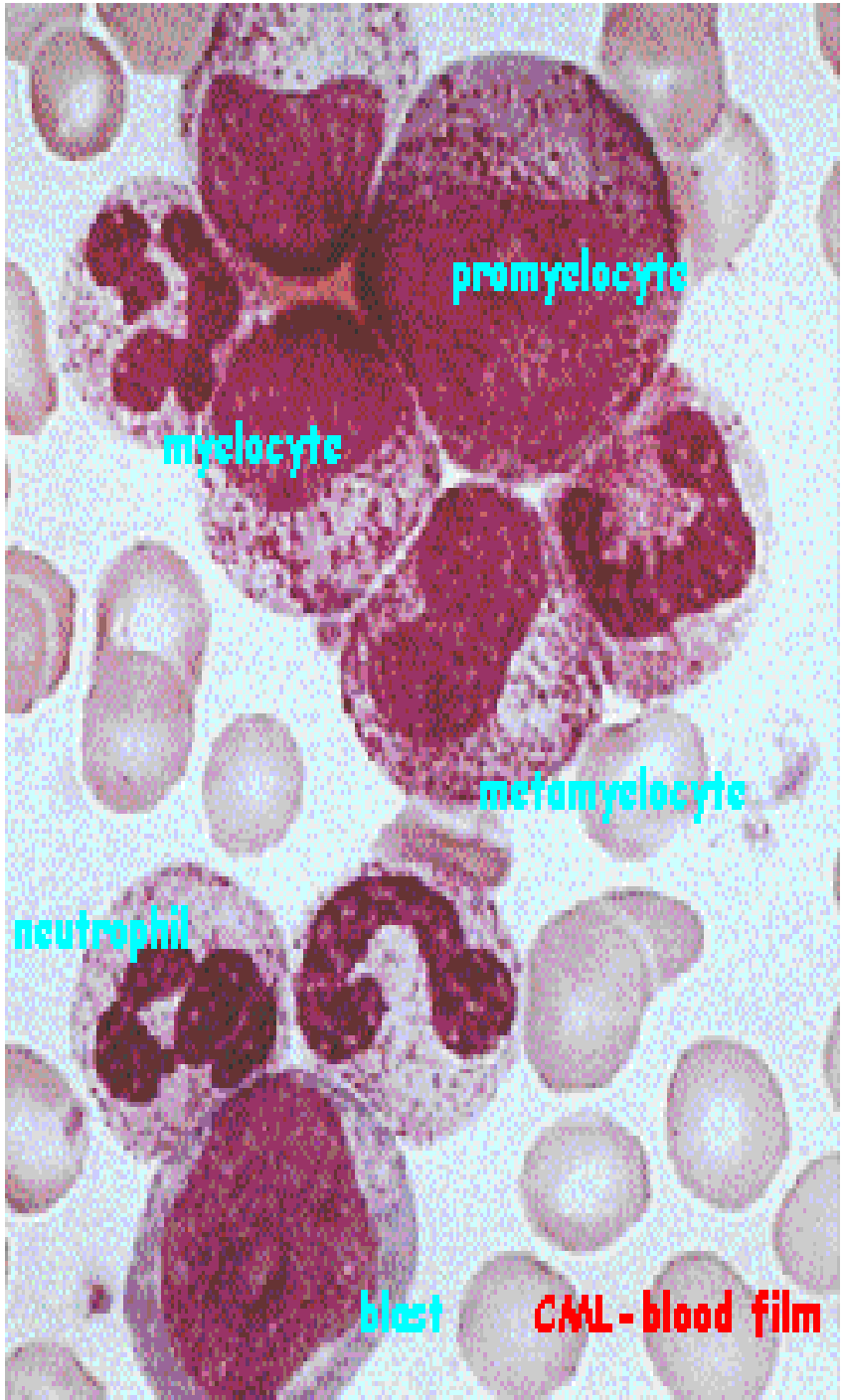
- The majority of patients (around 95%) are diagnosed in **CML CP**.
- Constitutional **non-specific symptoms**.
- Abdominal mass **(Splenomegaly)**.
- 20-50% are **asymptomatic**.
- **O/E**:
  - Massive Splenomegaly in 90%.
  - Hepatomegaly in ~ 50%.
  - Bone pain.



Hematological test in Chronic phase-CML

1. **CBC** : Often anemia , Leukocytosis (usually 20-1000 x 10^9/L and increased Platelets.
2. **Blood film** :
   - shows the full spectrum of granulocytic maturation, from the segmented neutrophil up to blasts.
   - The most predominant cells are neutrophils and myelocytes.
   - Basophils are often increased and sometimes eosinophils are also prominent.
   - Blasts should be less than 10 % in chronic phase.

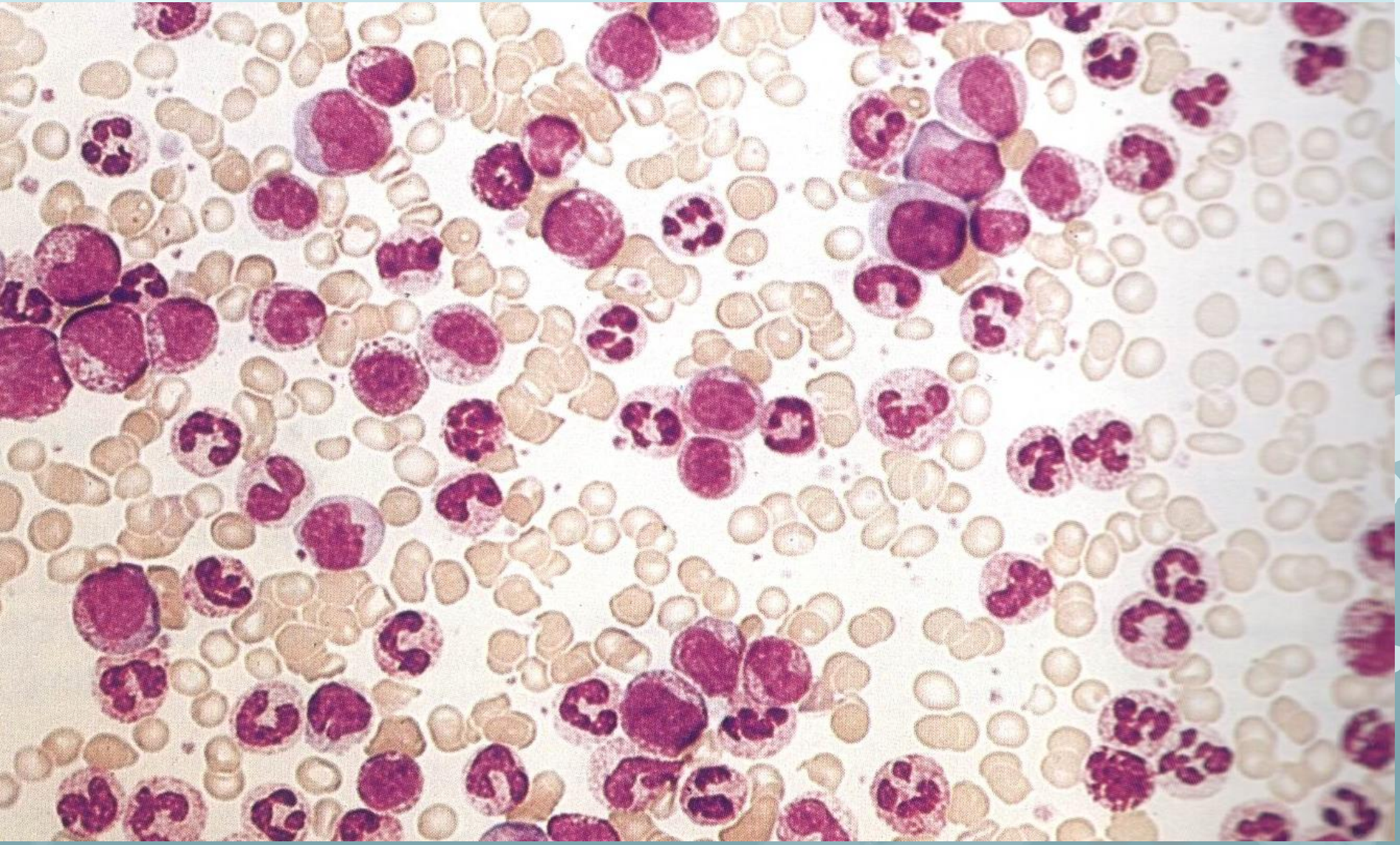
3. **Bone marrow examination** is not usually of additional diagnostic value in CML. It appear hypercellular with same findings to peripheral blood. BM examination **done for**: assess fibrosis, cytogenetic study, assess occult transformation, assess megakaryocytes
4. **Biochemical findings**: increase in serum UA, Alkaline phosphatase, LDH, B12, histamine,K.



Blood Picture in CML :

1. Increase in total leucocyte count, due to the increase in the granulocytes (all stages), with peaks of neutrophils and myelocytes, but blasts are less than 10% usually.
2. Platelets usually increased.
3. Mild anaemia is usual.
4. Basophils and eosinophils maybe increased.

Blood film in CML



Confirmatory diagnostic tests in CML:

- Neutrophil Alkaline phosphatase(NAP) **is low or zero**; helps differentiate from other causes of neutrophilia and left shift in which NAP is normal or high.

  NAP score increase in infection, pregnancy, other MPD, leukemoid reaction. (normal score 20-100).

- Chromosomal studies (cytogenetic analysis) : Show the Philadelphia Chromosome, which is a reciprocal translocation t(9:22), seen in 90-95% of classical CML.
- DNA Studies (molecular analysis): the t(9:22) leads to the BCR/ABL gene rearrangement, which is more specific of CML this done by RT-QPCR.

Ph. Chromosome present in:

1. CML 90-95%. good prognosis.
2. Adult ALL 20% Poor prognosis.
3. Child ALL 2%. Poor prognosis.
4. AML 1%. Poor prognosis.

Poor prognostic factors

1. Old age
2. Features of transformation/acceleration
3. Ph –ve CML
4. Ph + with treatment
5. Poor response to treatment
6. Deletion 9q
7. Rapid rate of shorting telomers in leukemic cells

Principles of Treatment of CML

- **In chronic phase** :
  1. Supportive measures.
  2. SCT for young patient with appropriate donors.
  3. Drugs:
     - Tyrosine kinase inhibitors (**Imatinib** mesylate-Gleevec®).
     - Hydroxyurea.
     - Interferon α.
- **In Blastic phase** : treat as acute leukemia.

- Median survive is 5-6 yrs with treatment, death usually from AL transformation, hge, infections.

Bone marrow transplantation is clearly curative. In fact, it is the only proven cure for chronic myeloid leukemia, even now. However, only 30% to 40% of patients with chronic myeloid leukemia have an appropriate donor. Beyond that, the mortality (death rate) from the procedure ranges from 20% to 30%, depending upon the age of the recipient.

Imatinib mesylate is an ABL tyrosine kinase inhibitors give 400 mg daily in newly diagnosed patients in chronic phase produces:

- complete hematological response in 96%
- major cytogenetic response in 83%
- complete cytogenetic response in 68%
- only 3% achieve a molecular remission

Side Effects

- The majority of patients who received Gleevec® in clinical studies did experience side effects. Most side effects were mild or moderate.
- The most **common side effects** were **fluid retention** (swelling around the eyes, of the legs, etc.), **nausea**, **muscle cramps**, **diarrhea**, **vomiting**, **muscle and bone pain**, fatigue, rash, and abdominal pain.


Thank
you!!