

Diyala University – collage of medicine
Hematology -5th stage
Dr.zahraa najah alzuhairi
Lec 10

Chronic myeloid leukemia

By

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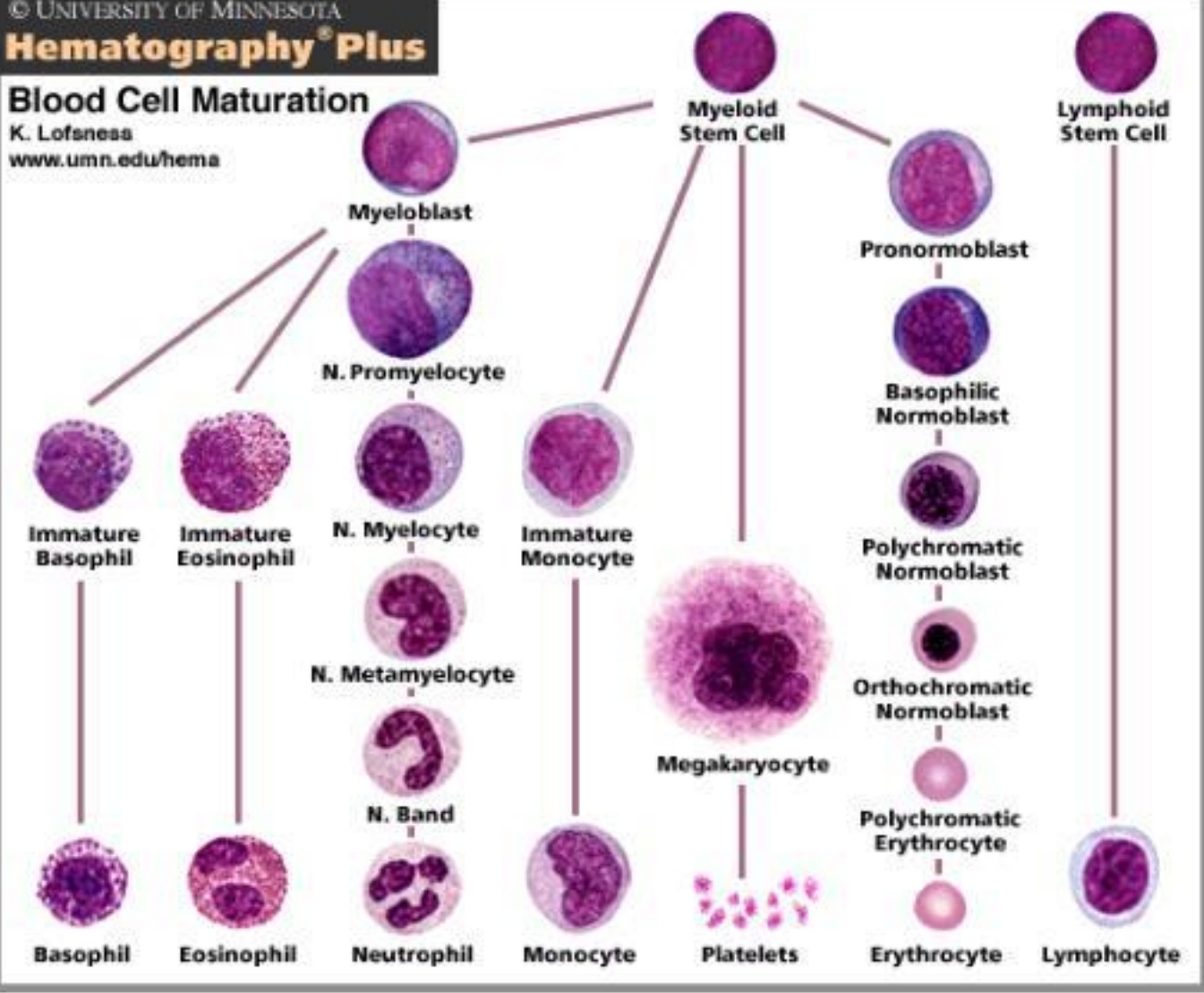
Chronic Myeloid Leukemia (CML)

Definition :

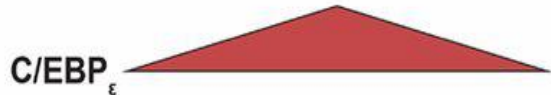
- ❑ **Also known** as chronic myelogenous leukemia and chronic granulocytic leukemia
- ❑ It is a **clonal disease** that results from an **acquired genetic** change in a pluripotential haemopoietic stem cell.
- ❑ This **altered stem cell proliferates** and **produce a population of differentiated cells**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

Blood Cell Maturation

K. Lofsness
www.umn.edu/hema



Gfi-1
 GATA-1
 AML-1
 c-Myc
 CDP
 C/EBP $_{\gamma}$



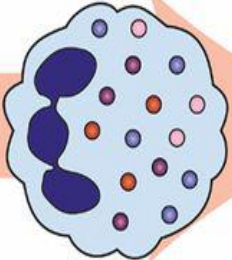
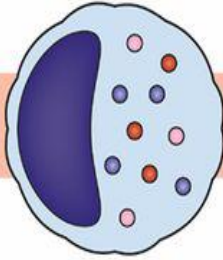
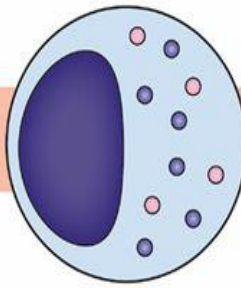
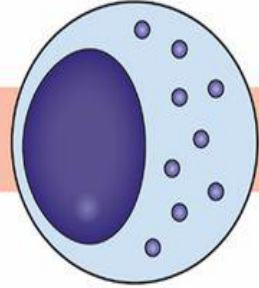
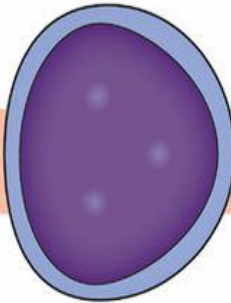
Myeloblast

Promyelocyte

Myelocyte

Metamyelocyte

Neutrophil



Azurophilic

Specific

Gelatinase

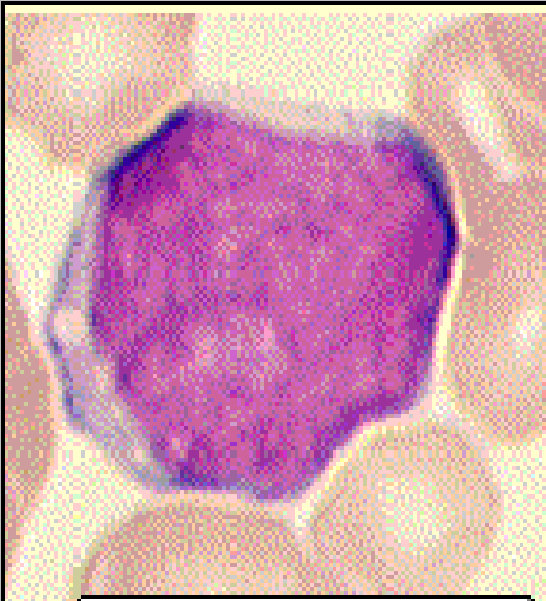
Secretory

- Myeloperoxidase
- Defensins
- BPI
- Azuracidin
- Elastase

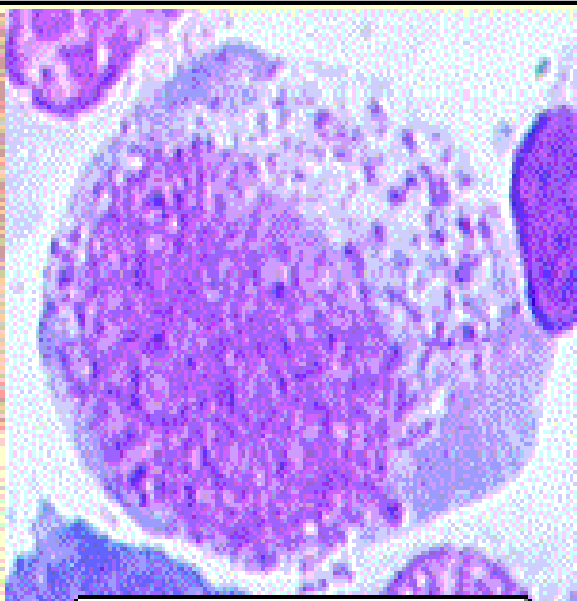
- Lactoferrin
- Metalloproteinases
- Cathelicidin
- Lipocalin 2
- Olfactomedin 4

- Gelatinase
- Arginase 1
- Lysozyme

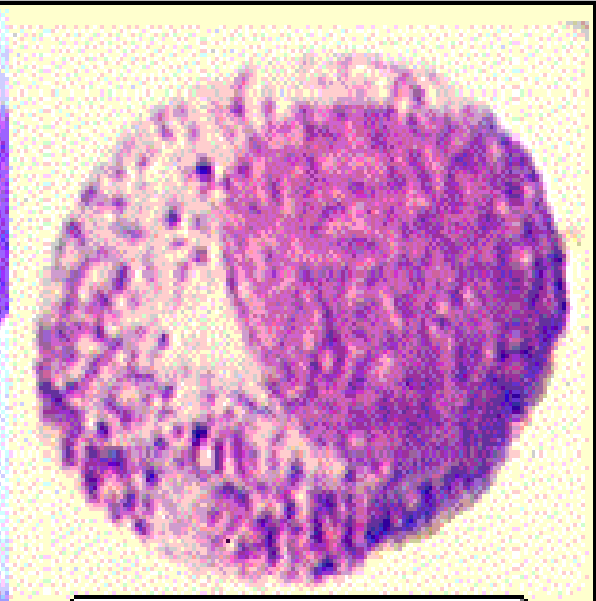
- Plasma Proteins
- Membrane Receptors
- Alkaline Phosphatase



Myeloblast



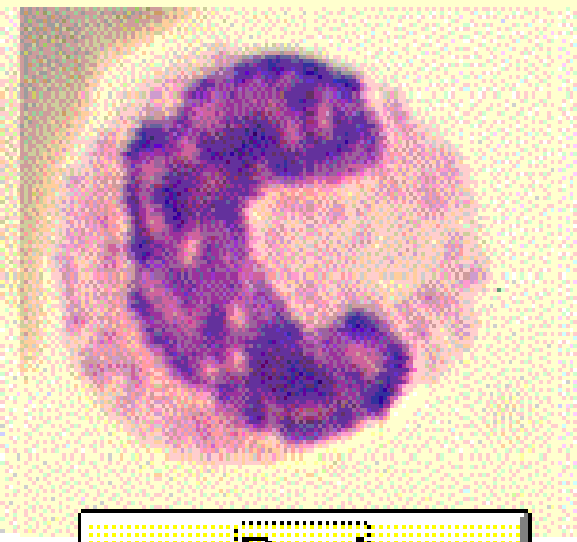
Promyelocyte



Myelocyte



Metamyelocyte



Band



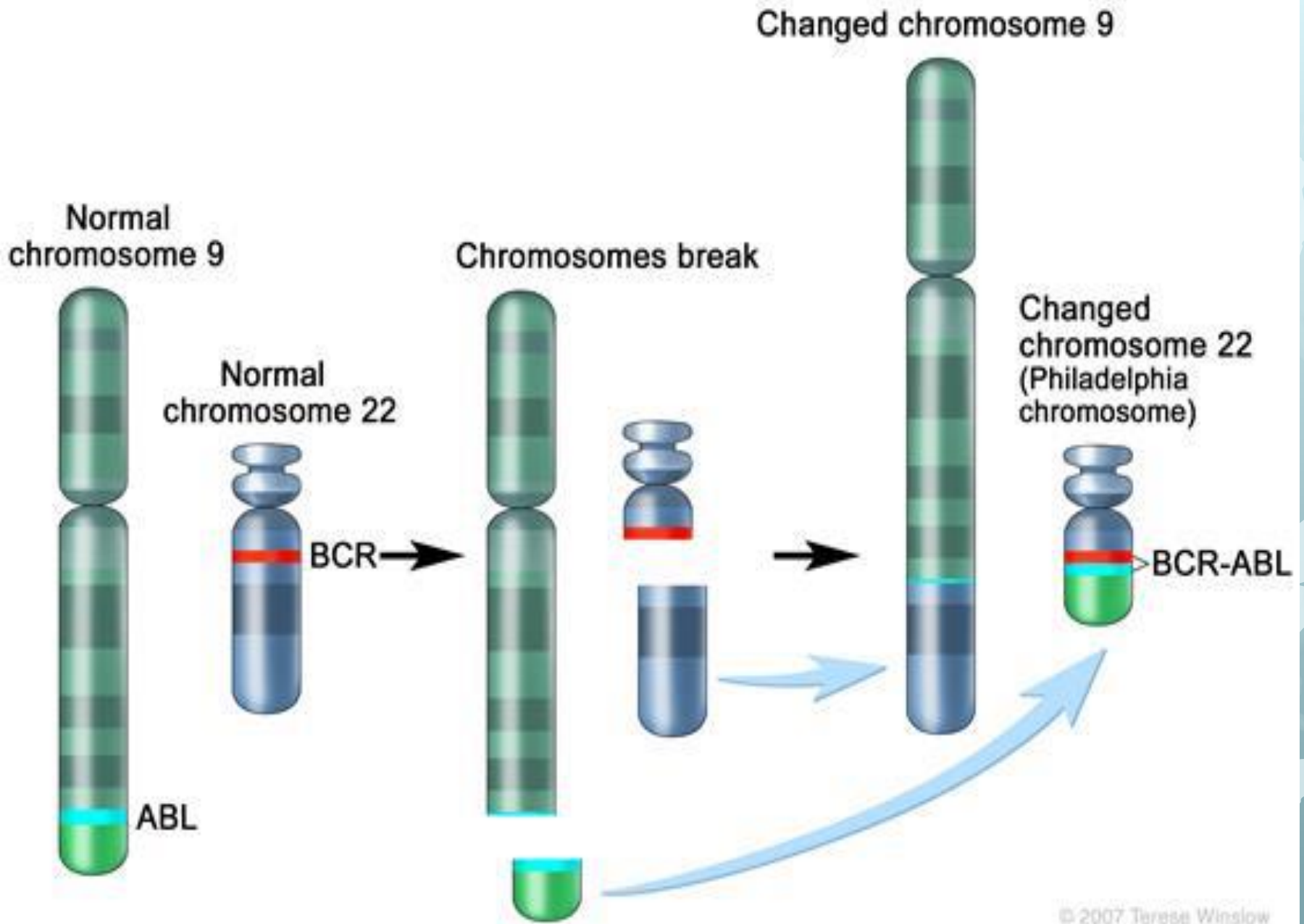
Segment

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.

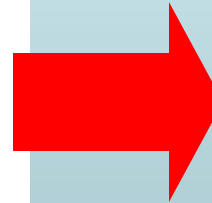
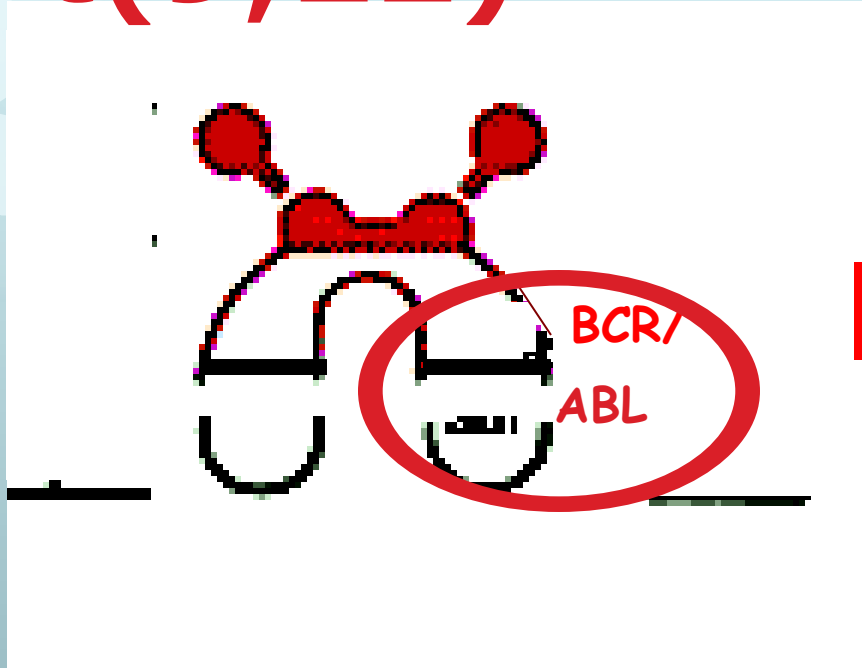
Pathogenesis & course of disease

- ❑ **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)

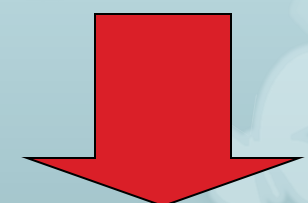


Pathogenesis of CML

t(9;22)



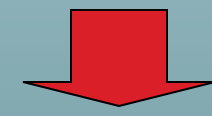
8.5kb mRNA



P210 protein

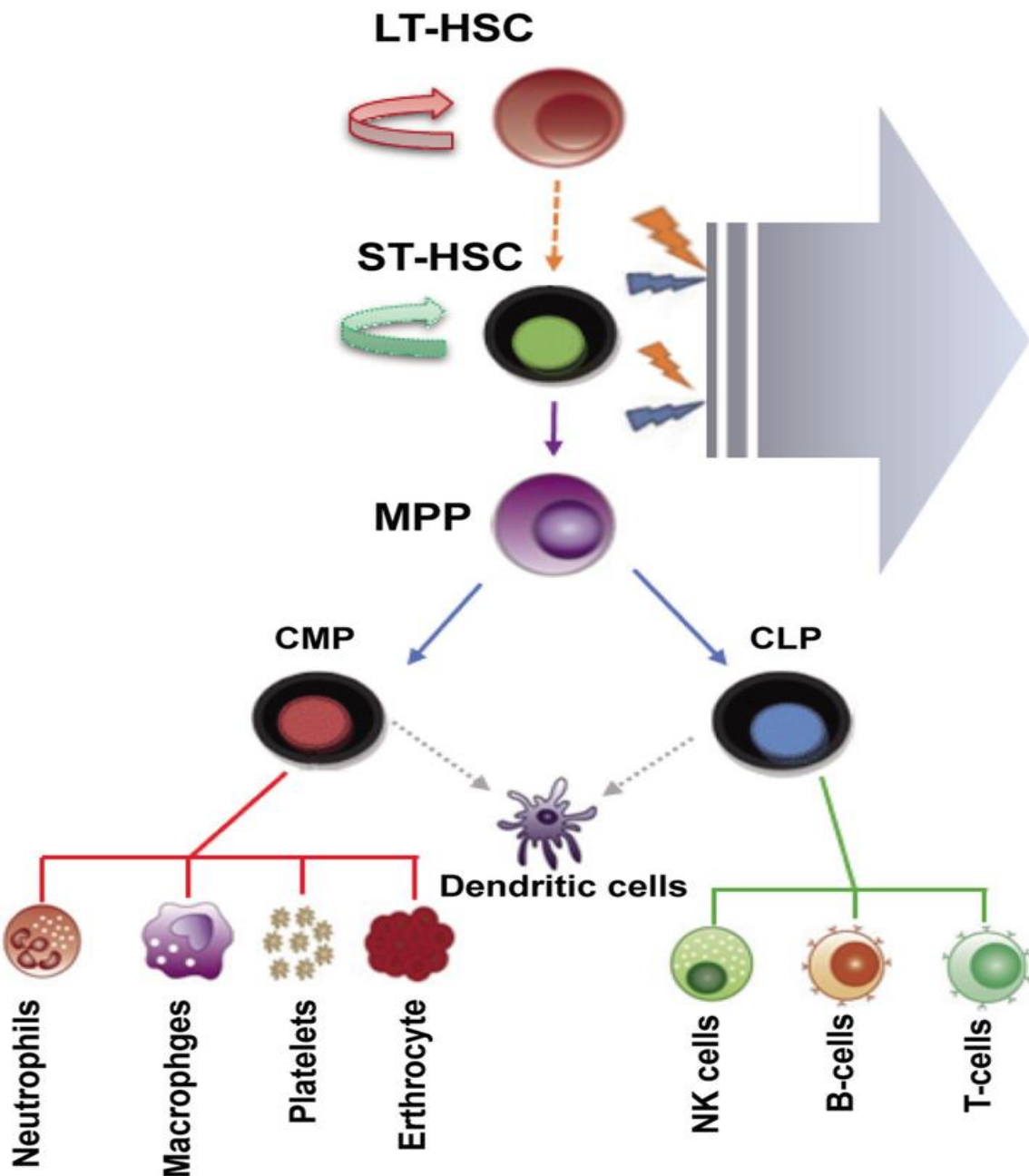


Tyrosine Kinase activity

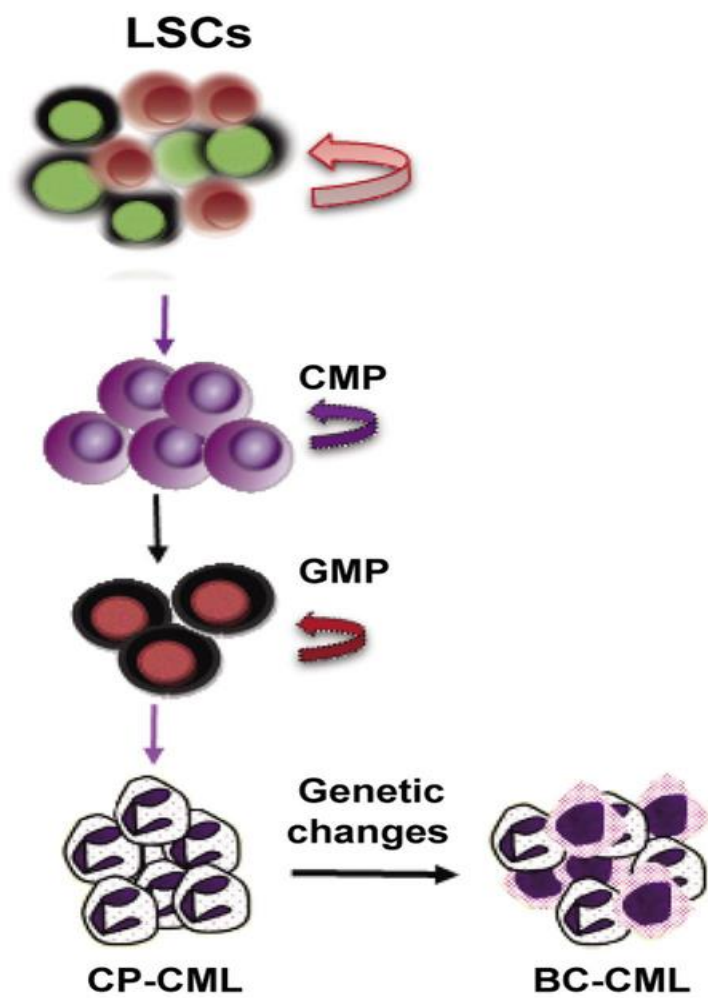


Proliferative advantage to Myeloid cells in CML

HSC



CML



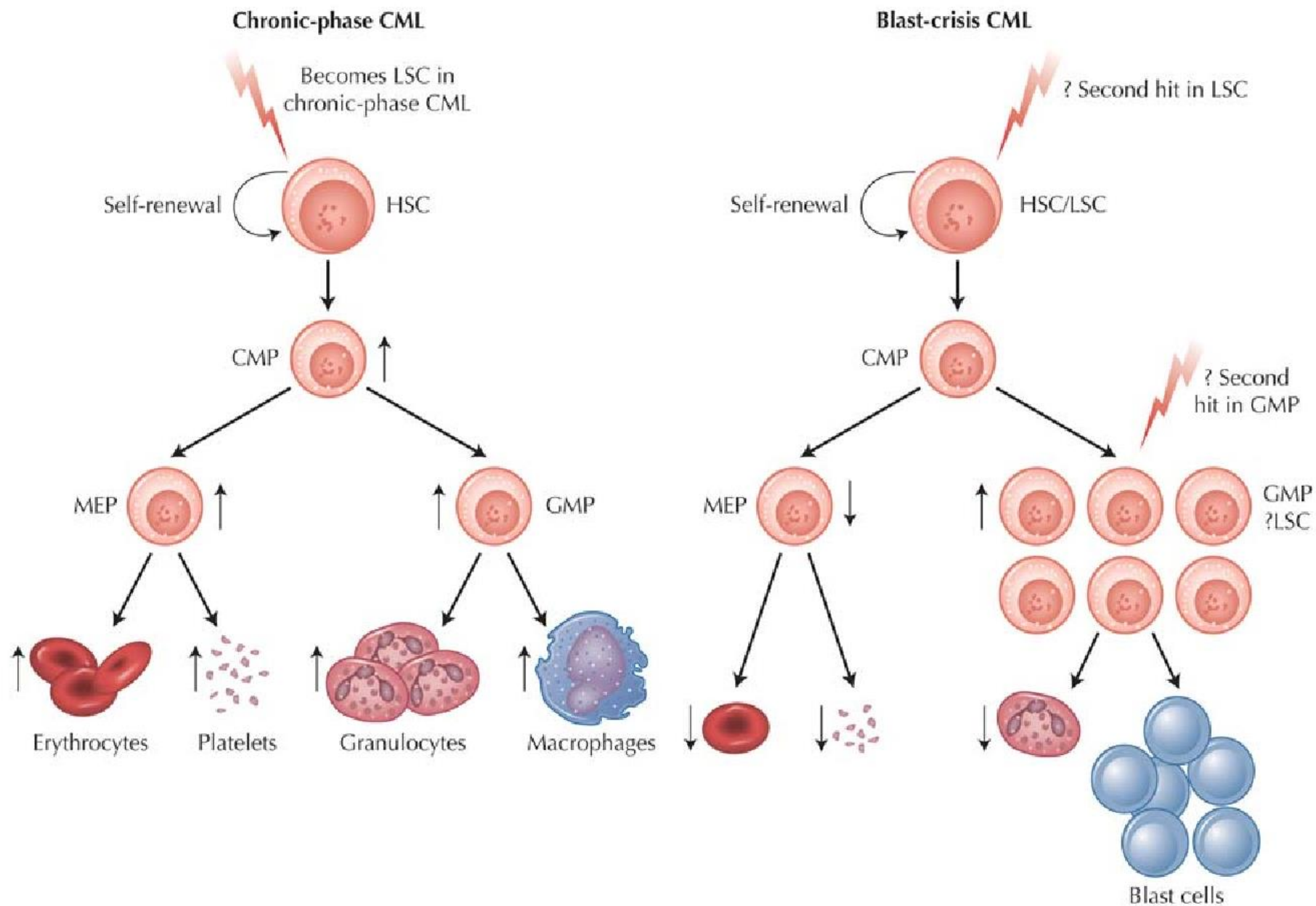


Figure 1. Comparison of aberrant hematopoiesis in chronic phase chronic myelogenous leukemia (CML) compared with blast crisis CML.

- ❑ 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 \geq 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	<ul style="list-style-type: none"> • PB or BM blast 15–29% • PB or BM blast + promyelocytes $\geq 30\%$ • PB basophils $\geq 20\%$ • Platelets $\leq 100 \times 10^9/L$ unrelated to therapy • Clonal evolution 	<ul style="list-style-type: none"> • PB or BM blast 10–19% • PB basophils $\geq 20\%$ • Platelets $\leq 100 \times 10^9/L$ unrelated to therapy • Platelets $> 1000 \times 10^9/L$ unresponsive to therapy • Clonal evolution on treatment • Increasing spleen size and increasing WBC count unresponsive to therapy
Blast crisis	<ul style="list-style-type: none"> • PB or BM blast $\geq 30\%$ • Extramedullary blast proliferation, apart from spleen 	<ul style="list-style-type: none"> • 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.

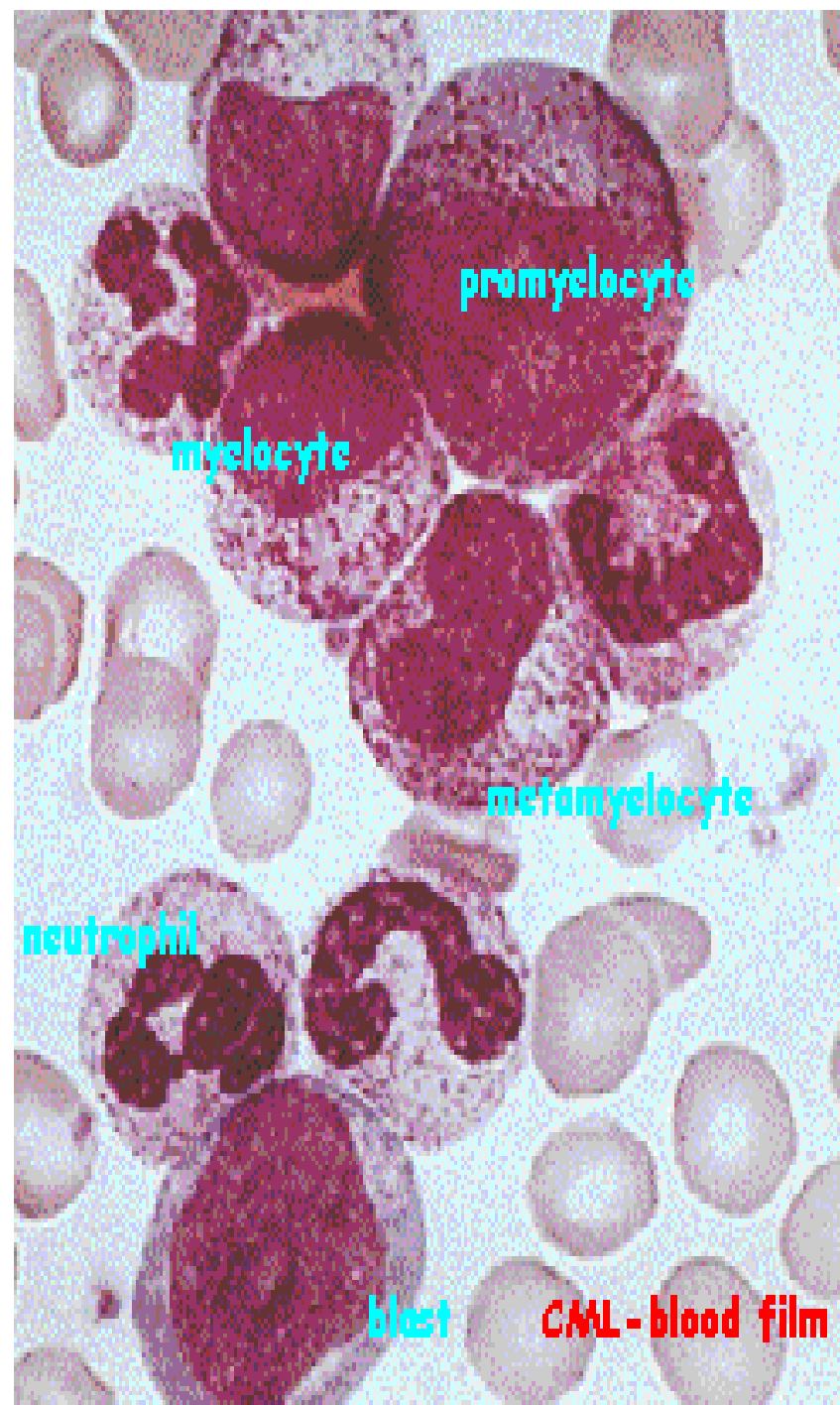


Hematological test in Chronic phase-CML

1. **CBC** : Often anemia , Leukocytosis (usually $20-1000 \times 10^9/L$ 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 appears hypercellular with same findings to peripheral blood. BM examination done for: assess fibrosis, cytogenetic study, assess occult transformation, assess megakaryocytes

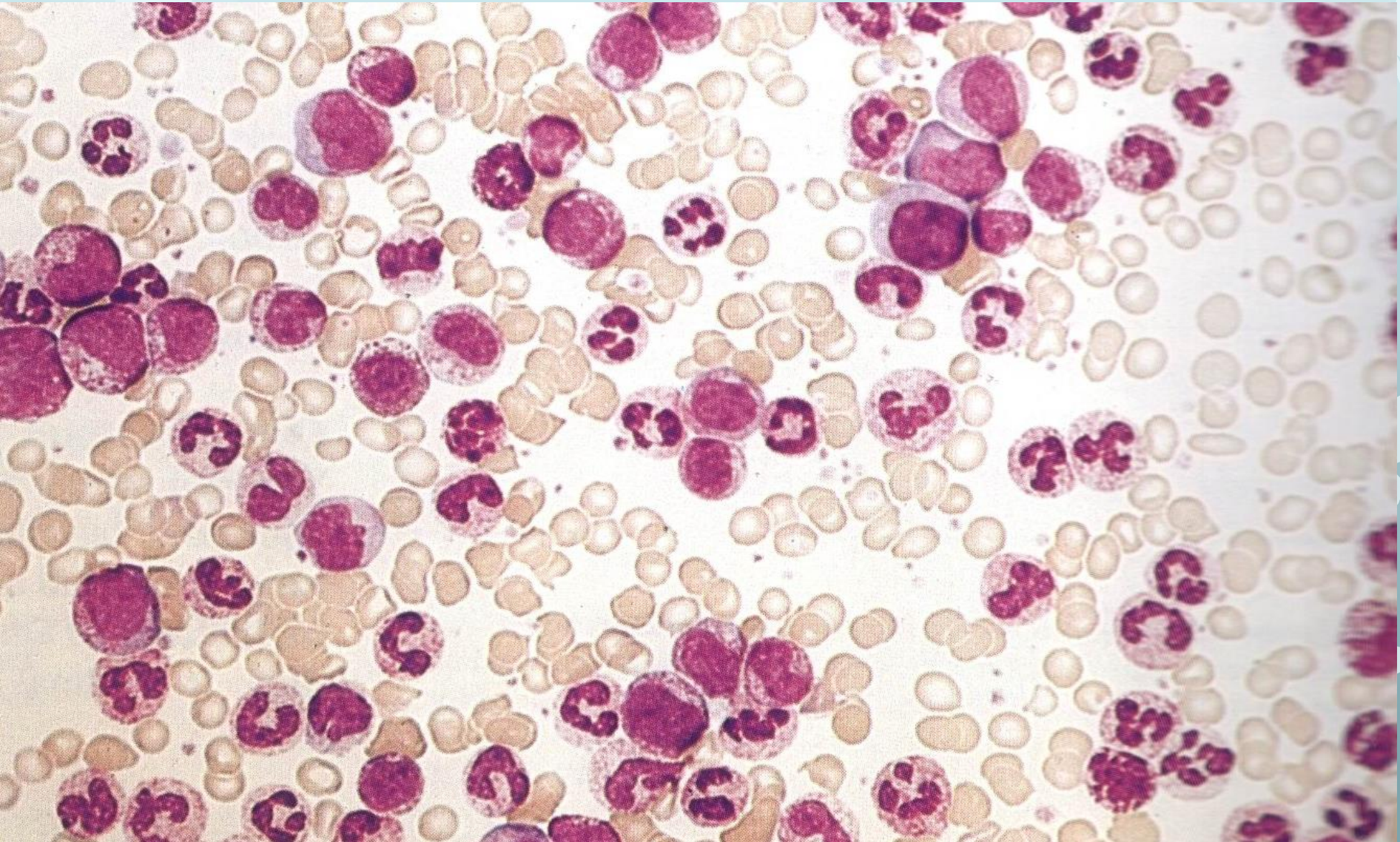
4. **Biochemical findings**: increase in serum UA, Alkaline phosphatase, LDH, B12, histamine, K.



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.**

The background is a light blue gradient with several white butterfly silhouettes scattered across it. The text is centered and written in a bold, magenta font.

Chronic Lymphocytic Leukemia

DEFENITION

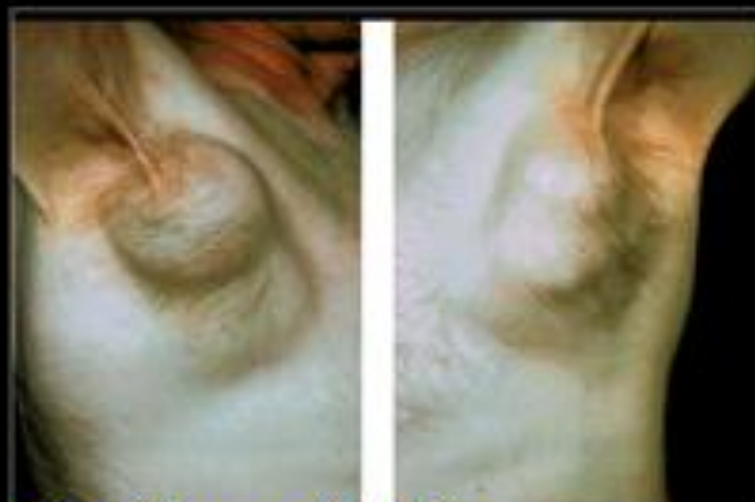
- Is a **neoplastic disease** characterized by the accumulation of small mature-appearing lymphocytes in the blood, bone marrow and lymphoid tissues .
- The neoplastic lymphocytes are in **> 98% of B-cell lineage**, in **< 2% the neoplastic cells are of T-cell lineage** .
- It is disease of **elderly** and middle aged , 90% >50 years of age.
- It occurs 2x more frequently in **males** than females.

Clinical findings

- More than 25% of patients are **asymptomatic** at diagnosis.
- Majority of patients present with Lymphadenopathy, Splenomegaly, less so hepatomegaly, signs & symptoms of **anemia**, or **bleeding manifestations**
- Non-tender Symmetrical **Lymphadenopathy** in ~ 80%:
- Splenomegaly, hepatomegaly, and purpuric spots
- **Reduced Immunity**

**Non-tender Symmetrical
Lymphadenopathy in ~
80%:**

**Most commonly cervical,
supra-clavicular and**



Axillary LAP



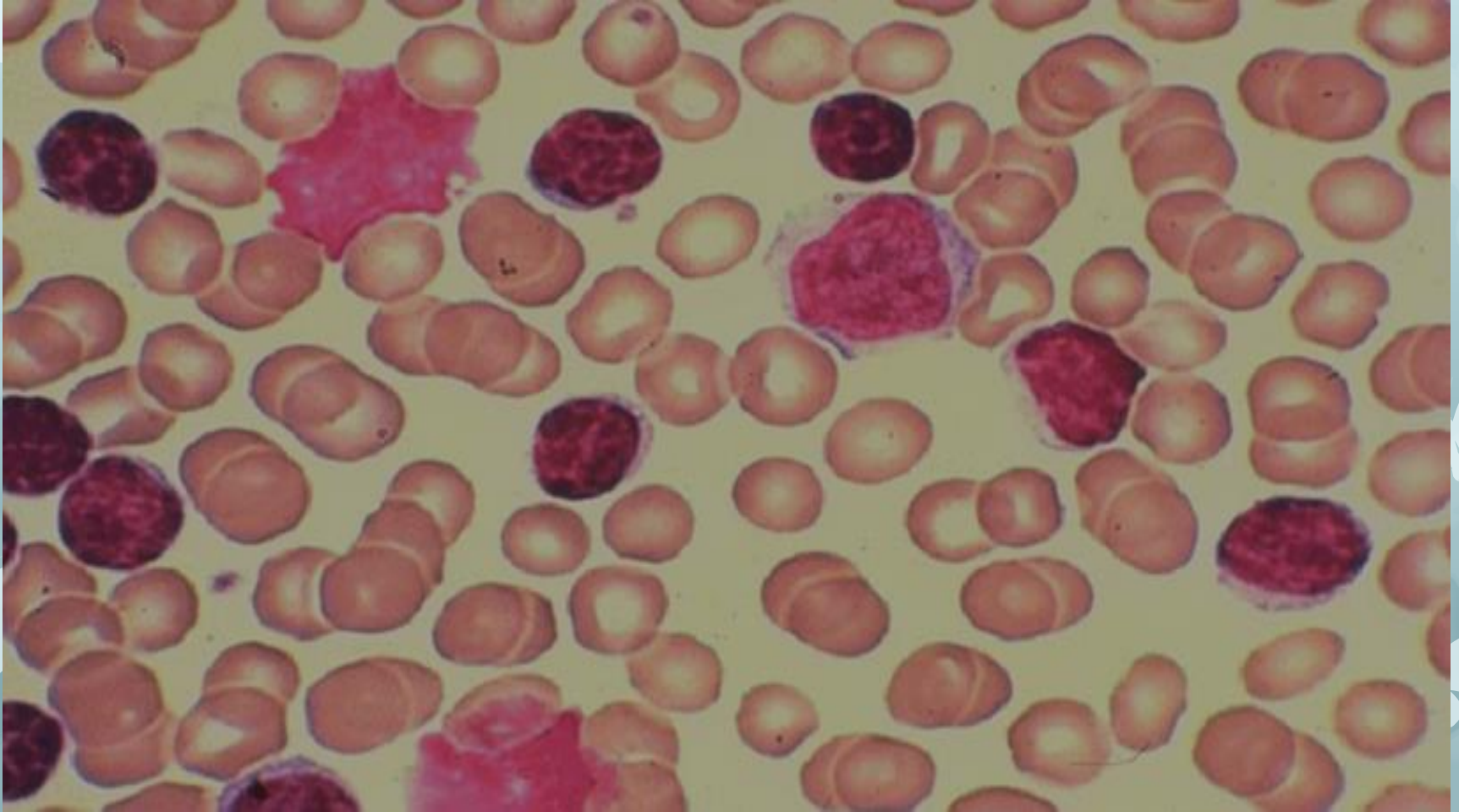
Cervical LAP

**Clinical features
in CLL**

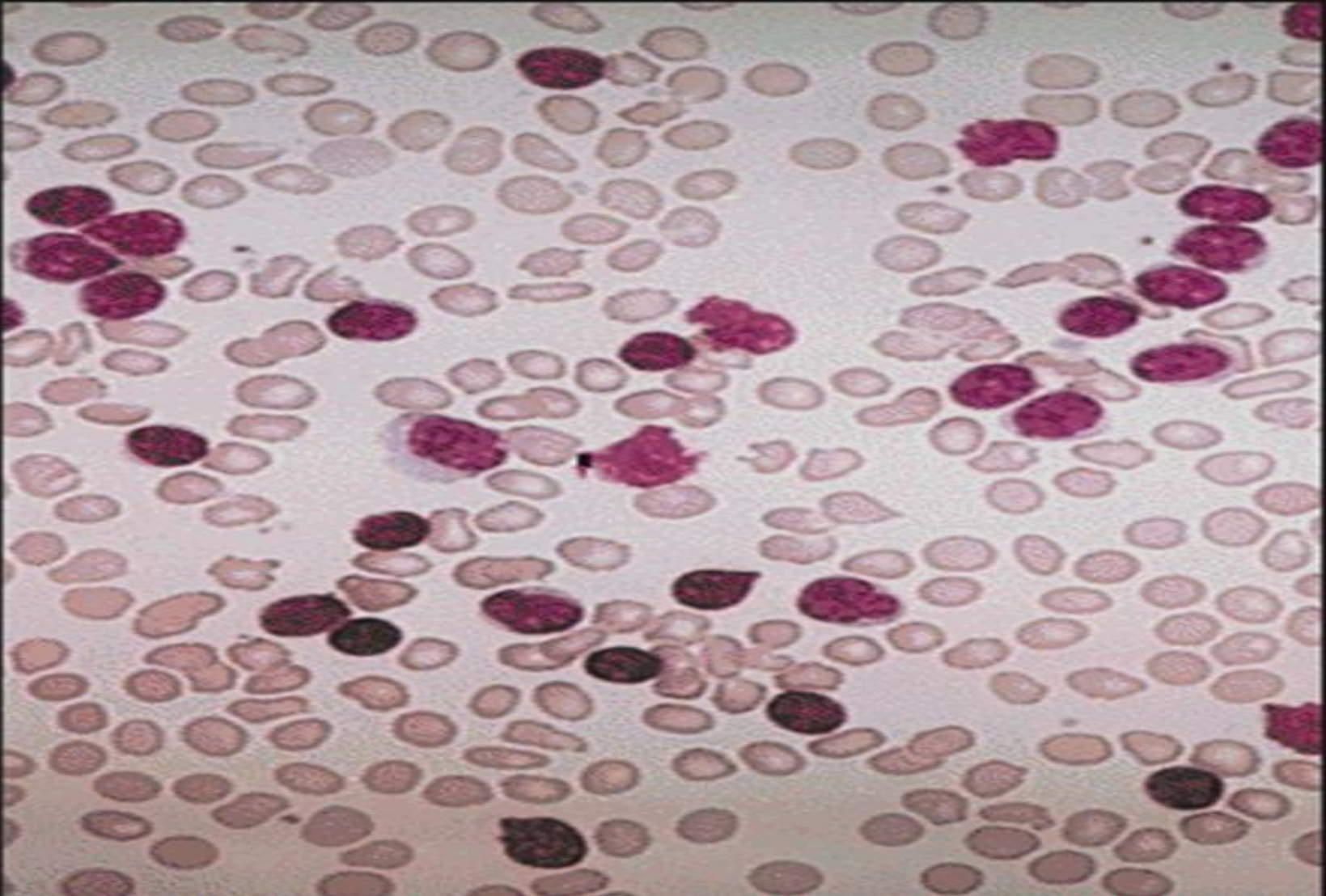
Diagnosis of CLL

- **Lymphocytosis** at least $10 \times 10^9/L$ or $> 5 \times 10^9/L$ if monoclonality (by light chain restriction) is confirmed.
- **Bone marrow Lymphocytes** $>40\%$.
- **Prolymphocytes** $< 10\%$.

Blood Film in CLL



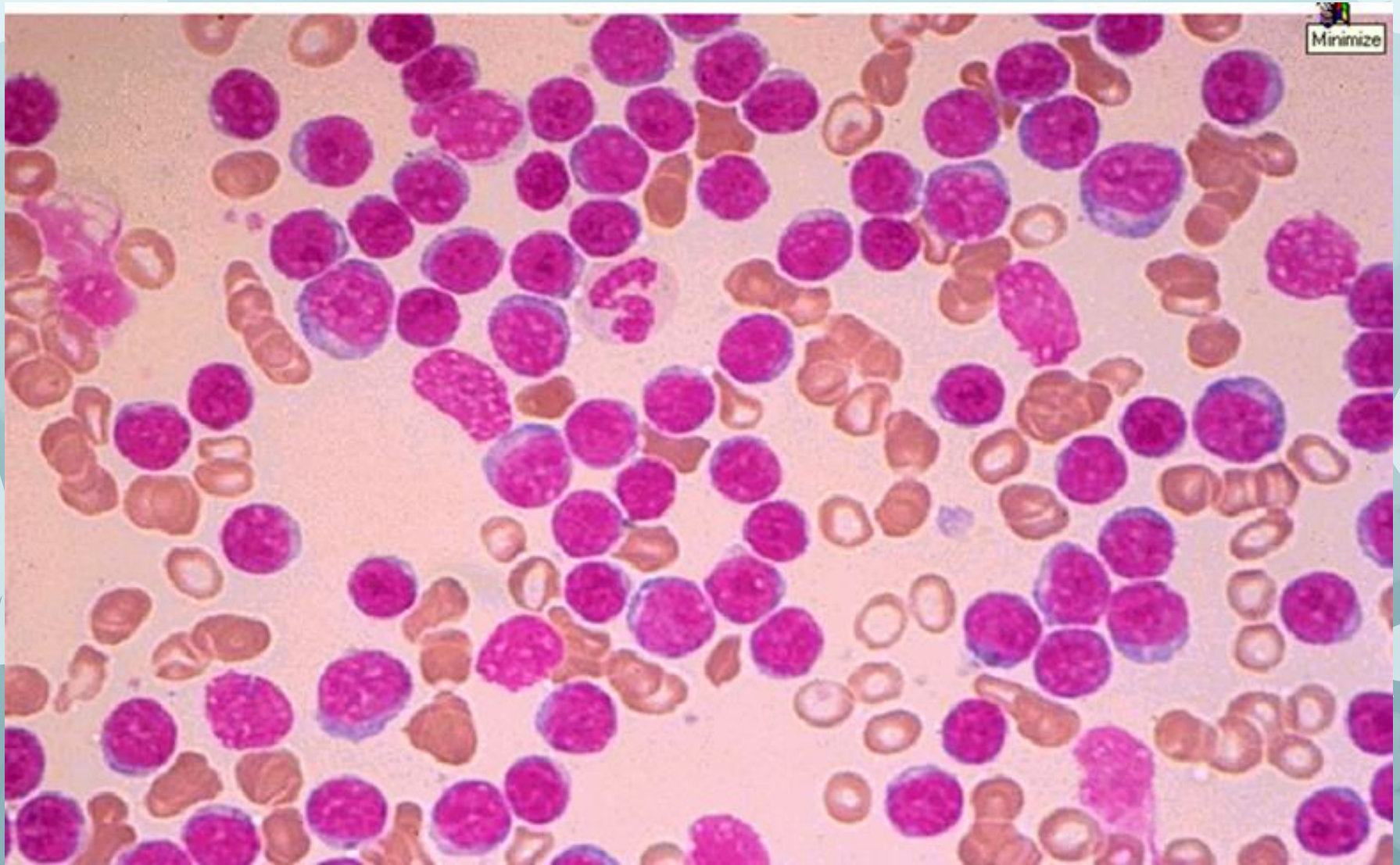
Lymphocytosis $>10\ 000/\text{cmm}$
Frequent smudge Cells



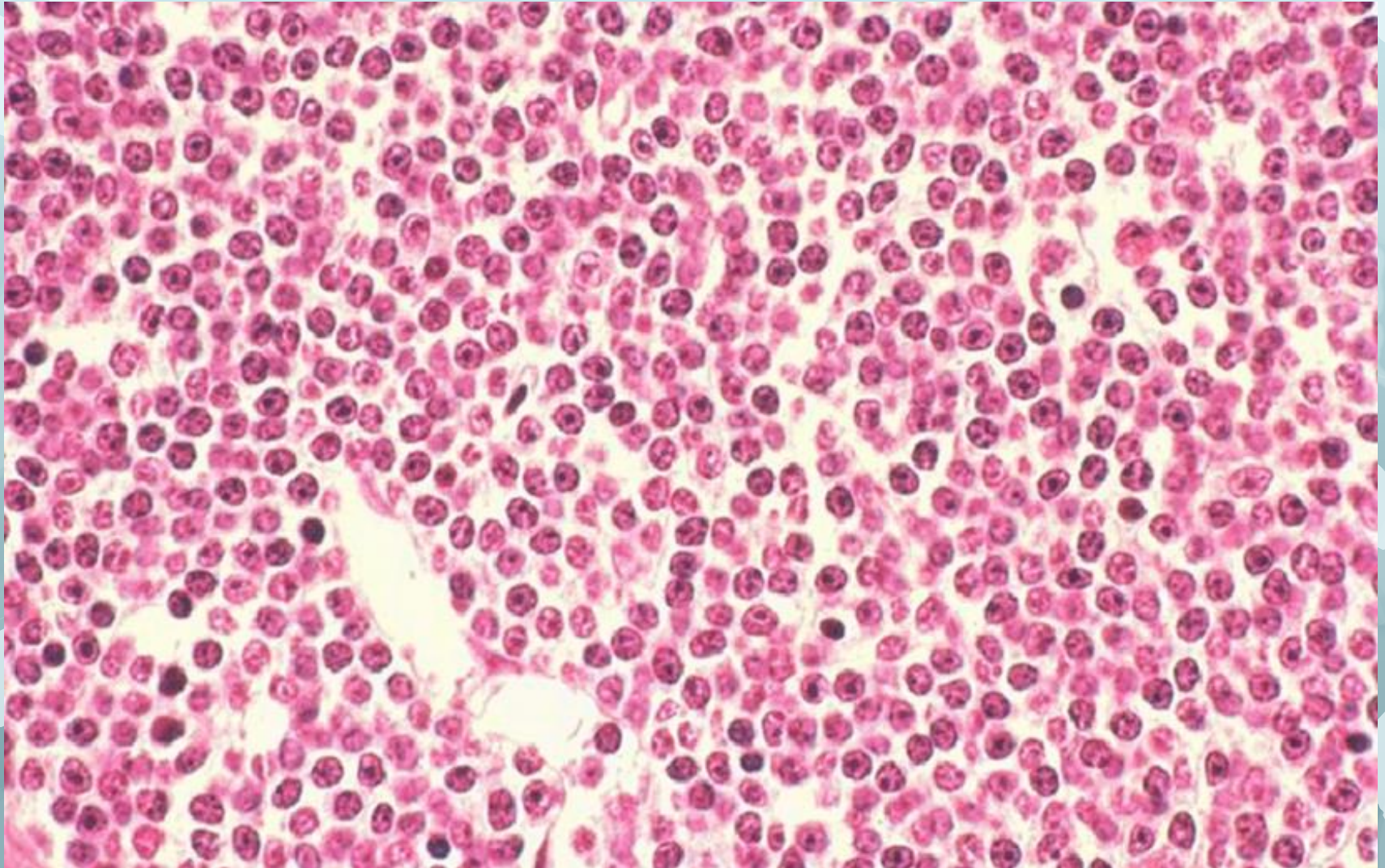
Bone marrow study:

-aspirate

-biopsy



Bone marrow biopsy in advanced CLL



Binet Clinical staging:

	<u>Median Survival</u>
• <u>Stage A</u> : Blood and marrow lymphocytosis and less than 3 areas of palpable lymphoid enlargement	> 7 years
• <u>Stage B</u> : Blood and marrow lymphocytosis and 3 or more areas of lymphoid enlargement.	2-5 years
• <u>Stage C</u> : Any of the above with <u>Anaemia</u> (Hb < 11g/dl in males or 10 g/dl in females), or thrombocytopenia (Platelets < 100 000/ <u>cmm</u>)	< 2 years

Treatment of CLL :

- ❑ The following are guidelines for treatment:
 - **In stage A** : observe, if any progression treat, otherwise do not.
 - **Since most Stage B cases** tend to progress, it is advisable to treat.
 - **Stage C** is a definite indication for treatment.
- Treatment modalities available :
 - ✓ Either minimally toxic single agents like Chlormabucil, Fludarabine (Purine analogue).
 - ✓ Or Combinations of Fludarabine with cytotoxics.
 - ✓ Or combinations of cytotoxics like CHOP, COP,
 - ✓ More recently esp. if Younger than 55yr, BMT

Prognostic factors in CLL

- Clinical staging.
- Histological patterns. This is the best single prognostic factor in CLL.
- Lymphocyte counts : $> 50 \times 10^9/L$ poor prognosis.
- Lymphocytes doubling times: If less than 12 months (poor).
- Karyotyping:
 - Age: More than 60yr and Male sex (poor prognosis)
 - Response to treatment

A white, hand-drawn style speech bubble sticker is centered on a corkboard background. The text 'Thank you!!' is written in a bold, black, sans-serif font. The word 'Thank' is on the top line, and 'you!!' is on the bottom line, slightly indented to the right. The corkboard has a natural, textured appearance with small, light brown granules.

Thank
you!!