# CHRONIC LEUKEMIAS

## CHRONIC MYELOID LEUKEMIA (CML)

definition :-

myeloproliferative stem cell disorder resulting in proliferation of all hematopoietic cells manifested mainly in the granulocytic series .

## Epidemiology & Incidence :-

* disease of middle & old ages (30– 80 ).
* annual incidence : 1.8 / 100,000 .
* accounts for 20% of all leukemias .
* occurs in all races .

## Natural History :-

the disease has three phases

*A chronic phase : presents 85% of cases , usually asymptomatic , responsive to treatment

* An accelerated phase : in which the disease is progressing towards the acute phase manifested with persistent leukocytosis splenomegaly , ↓↑ PLTs .

*Blast crisis : in which the disease is transforms into acute leukemia either myeloblastic (70%) or lymphblstic ( 30% ) of cases .

TABLE 1

## Phases of chronic myelogenous leukemia

| Characteristic | Chronic | Accelerated | Blastic |
|---|---|---|---|
| Blasts (%) | 1–15 | ≥ 15 | ≥ 30 |
| Basophils (%) | Increased | ≥ 20 | Any number |
| Platelets | Increased or normal | Increased or decreased | Decreased |
| Bone marrow | | Myeloid hyperplasia | |
| Duration | 4–6 years | Up to 1 year | 3–6 months |

Based on information in references 3 and 4.

# Pathophysiology

translocation between the long arms of chromosomes 22 and 9; t(9;22)

↓

Relocation of *ABL* oncogene from the long arm of chromosome 9 to the long arm of chromosome 22 in the *BCR* region

↓

*BCR/ABL* fusion gene encodes a chimeric protein with strong tyrosine kinase activity.

↓

chronic myelogenous leukemia (CML) phenotype

http://emedicine.medscape.com/article/199425-overview

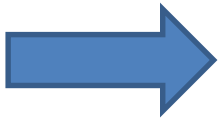
## Clinical features & Symptoms :-

- Asymptomatic ( 25 %) at diagnosis .
- Fatigue , Lethargy , Anorexia .
- weight loss , sweating .
- Abdominal fullness , Abdominal pain .
- breathlessness .

Clinically : pallor , gout

splenomegaly(90%) , friction rub .

hepatomegaly ( 50 % ) .

lymphadenopathy  blast crisis .

## Investigations :-

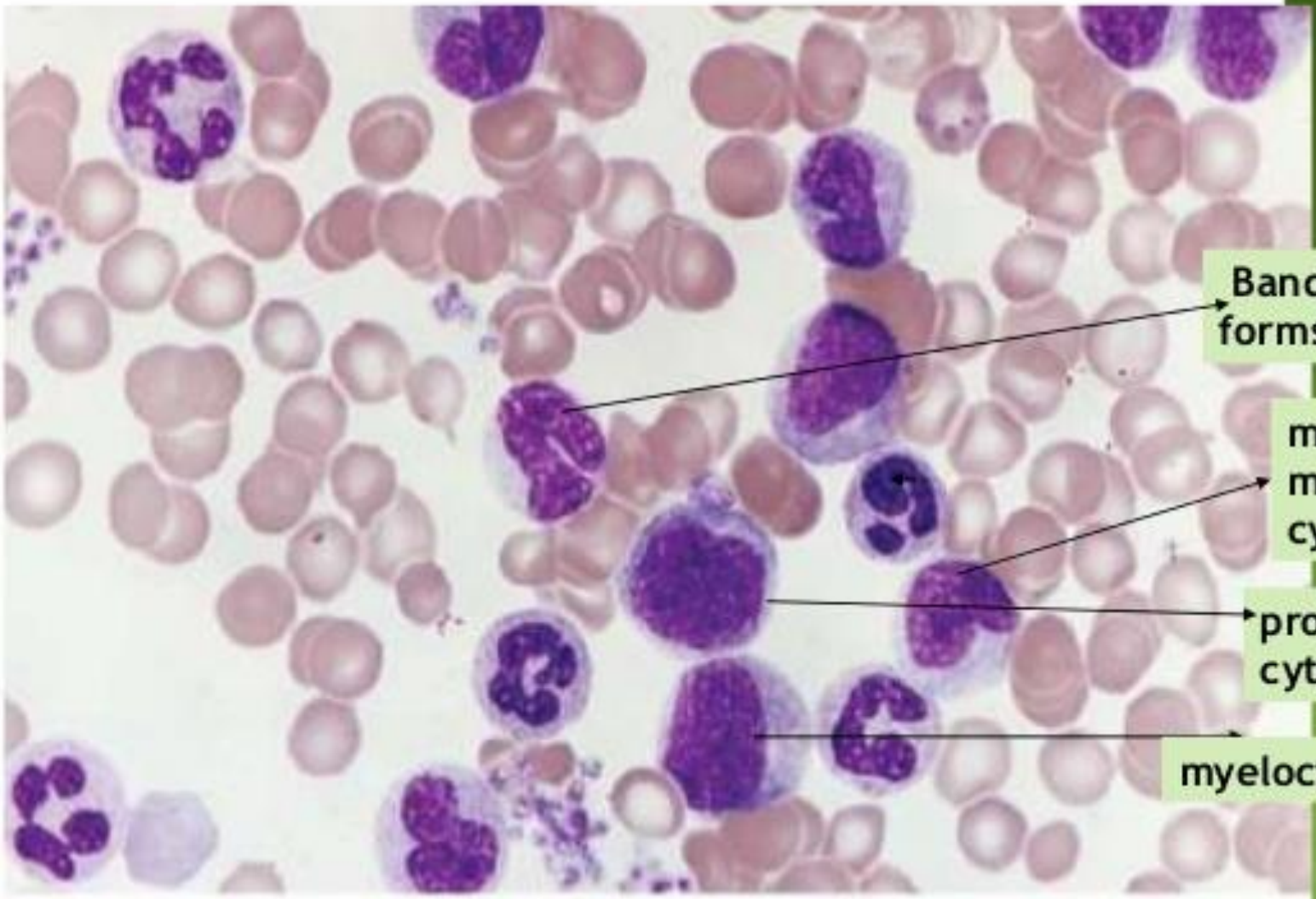
1- CBC& PBF : “ shift to left ”.

NNA ,leukocytosis : full range of immature granulocytes (myelocytes , metamyelocytes , myeloblasts, basophilia, eosinophilia, with increased No. of NRBCs , thrombocytosis.

2- Bone Marrow Aspiration :

confirms the diagnosis & disease phase .

# CML PERIPHERAL SMEAR CHRONIC PHASE

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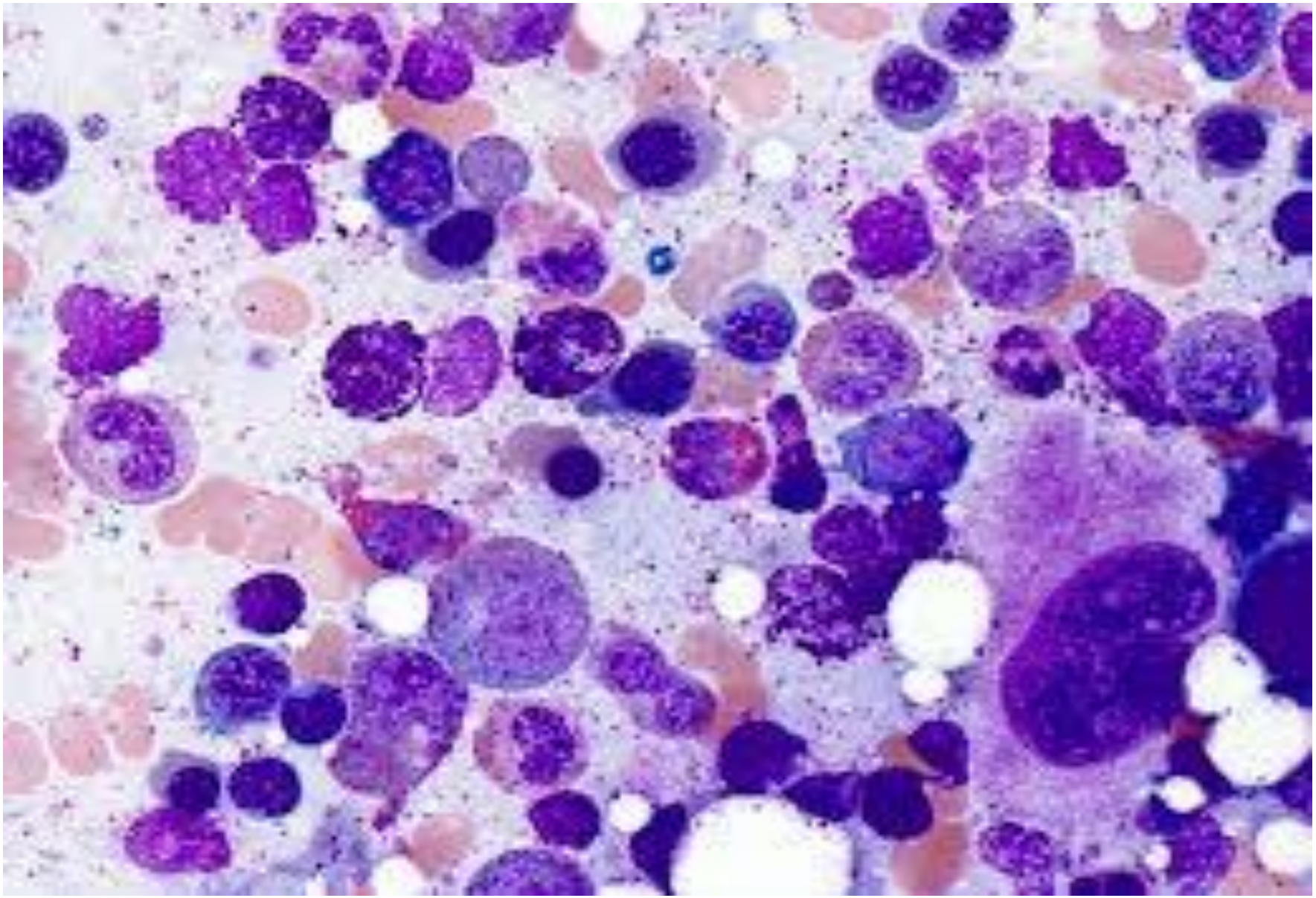
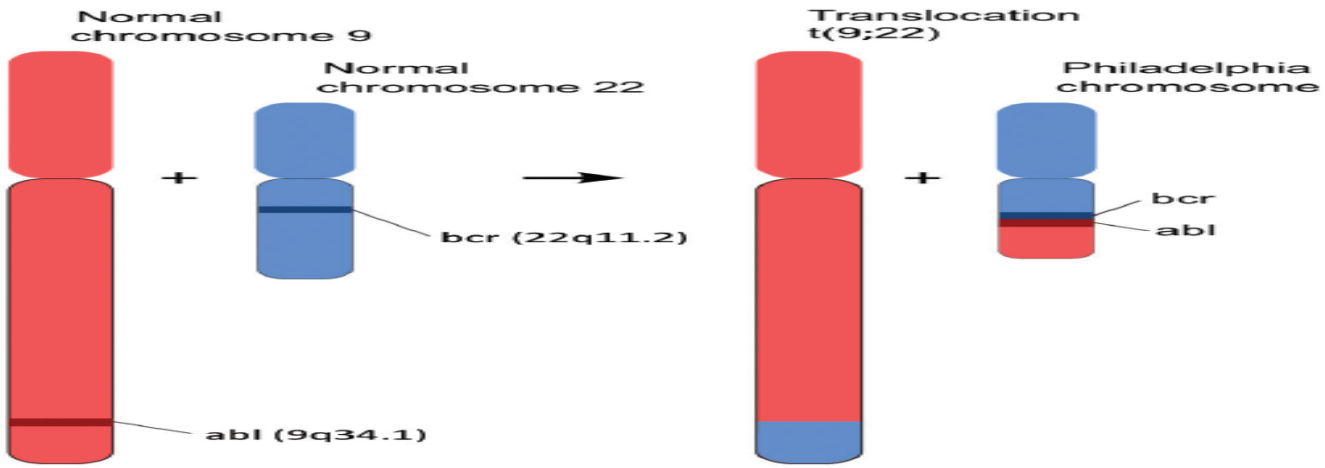
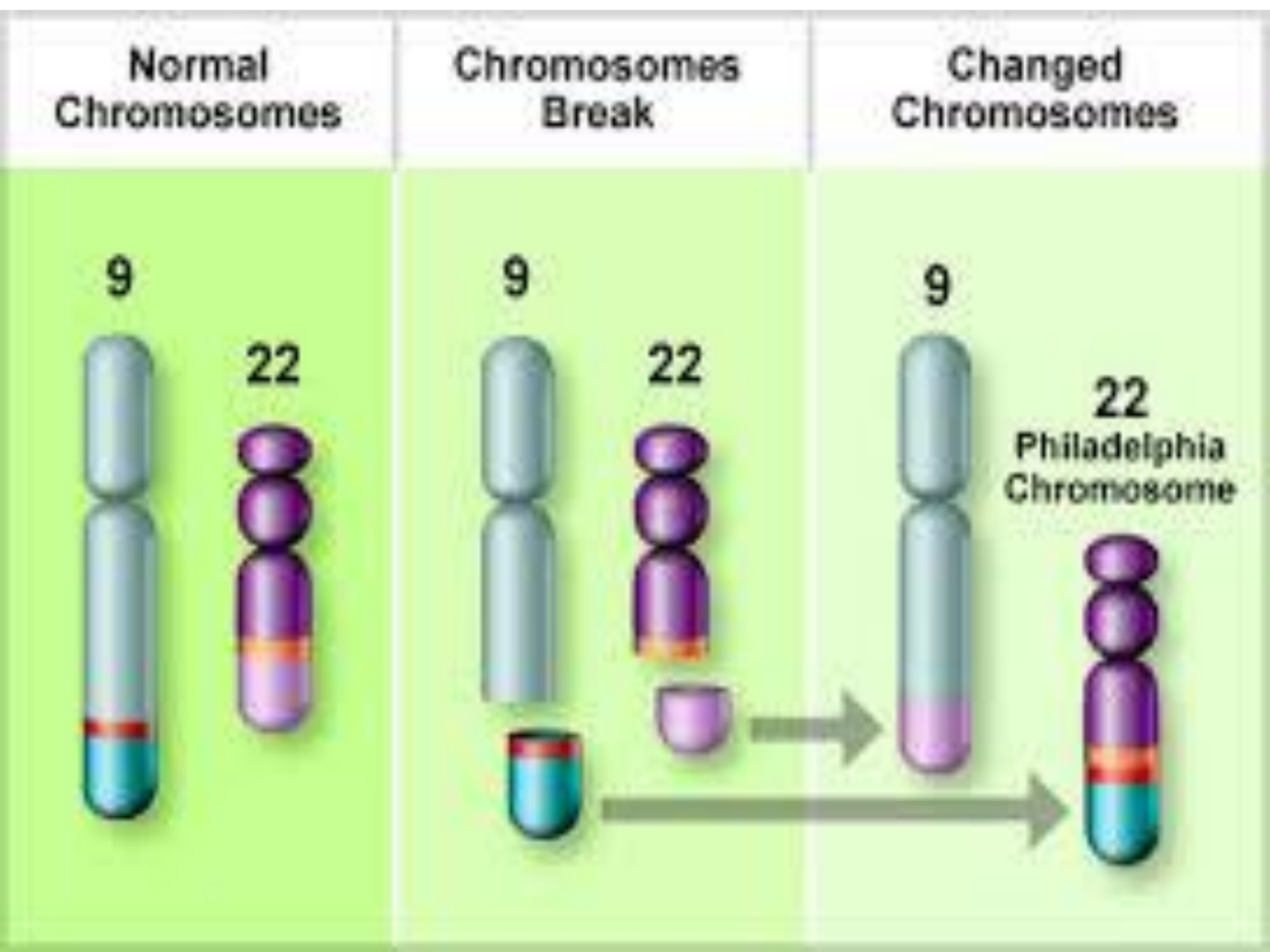
# Bone Marrow



# 3- Cytogenetic :-

* demonstration of philadelphia chromosome “translocation bet. Chr. 22 & 9”+ve in 90 % .
* demonstration of BCR ABL gene.
* chr. 17p , mutation of TP53 gene.




Normal Chromosomes
Chromosomes Break
Changed Chromosomes
9
22
9
22
9
22
Philadelphia Chromosome

4- Biochemistry :-

- routine LFT , RFT (LDH,UA ).
- low NAP score , high B12 levels .

Differential diagnosis :

- other myeloproliferative disorders
  ( PRV , ET and MF ) .
- leukemoid reaction.

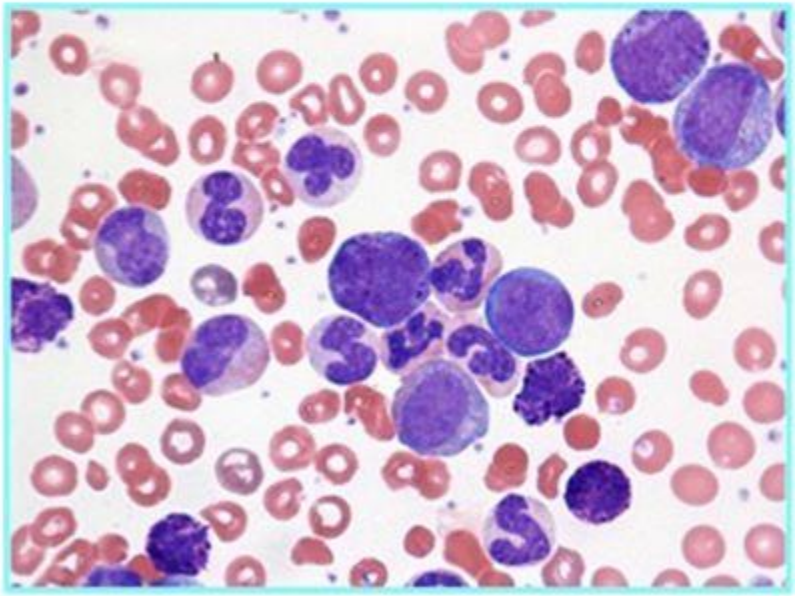
| | Leukemoid | CML |
|---|---|---|
| Clinical | Fever, chills<br>↑ vital signs | Asymptomatic,<br>splenomegaly |
| Peripheral Smear<br>- Toxic granulation<br>- Myelocytes, Blasts | <br>Present<br>Fewer, most neutrophils | <br>Absent<br>Increased |
| - Basophils | Normal | Increased |
| Leukocyte alkaline Phosphatase (LAP) Score | High | Low |
| Genetics | Normal | Philadelphia chromosome t(9;22) |

# Diagnostic Considerations in CML

**A peripheral blood smear or bone marrow aspirate can only give a presumptive diagnosis of CML – one still needs to confirm the presence of the t (9 ; 22)**

**Common Peripheral Blood Findings**

1. Leukocytosis with a 'left shift'
2. Normocytic anemia
3. Thrombocytosis in ~ 50% of patients
4. Absolute eosinophilia
5. Absolute and relative increase in basophils
6. LAP score is low (not frequently employed today)



LAP = leukocyte alkaline phosphatase.

## Management :-

Based on Tyrosine Kinase Inhibitors (TKIs).

chronic phase :-

1- IMATINIB , NILOTINIB , DASATINIB

shows hematological response within a month , complete cytogenetic response with in 3-6 months .

PONATINIB ,BOSUTINIB .

(inhibit BCR ABL tyrosine kinase activity ) .

the response is monitored every 3 months (by PCR) for ph. Chr. and mRNA for BCR-ABL transcript

Major molecular response: absence of ph. Chr. and reduction of BCR-ABL transcript by 3-5 logs,

complete molecular response : undetectable level of BCR-ABL .

2- Allogeneic HSCT : reserved for patients who fail TKI therapy .

3- Hydroxycarbamide used for palliative cyto-reduction.

4- Interferon for women planning pregnancy .

5- good hydration , allopurinol .

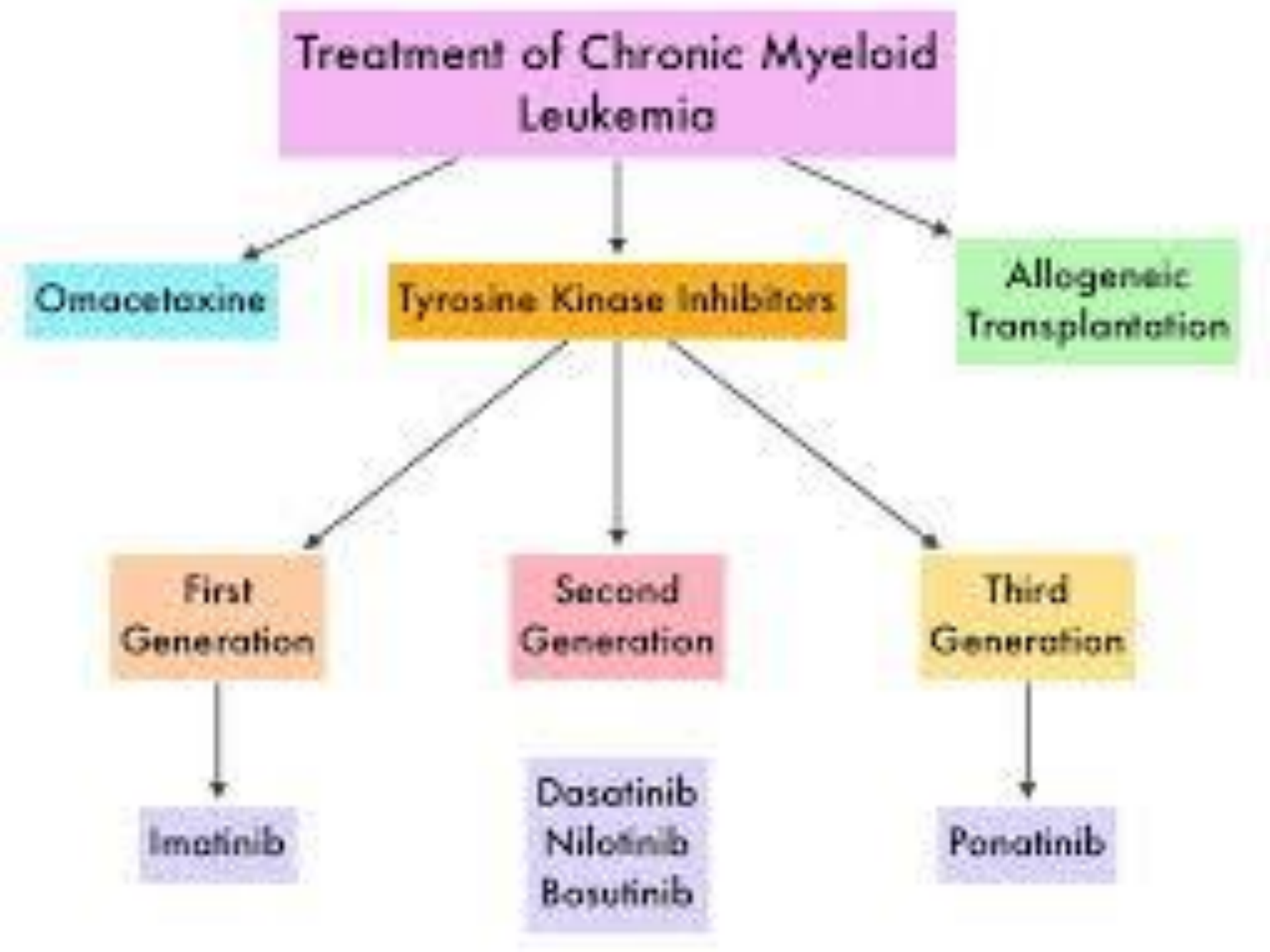
Accelerated phase :-

NILOTINIB or DASATINIB with dose adjustment .

## Definitions of response

| Response | Definition |
|---|---|
| Clinical response | Disappearance of all symptoms and signs |
| Complete hematological response | WBC <10 × $10^3$/L<br>Basophil <5%<br>No myelocyte, promyelocyte, myeloblast<br>Platelets <450 × $10^3$/L<br>Spleen nonpalpable |
| MMR | Detectable disease with ratio of BCR–ABL to ABL ≤0.1% (≥3 log reduction) |

MMR – Major molecular response; WBC – White blood cells


Treatment of Chronic Myeloid Leukemia
Omacetaxine
Tyrosine Kinase Inhibitors
Allogeneic Transplantation
First Generation
Second Generation
Third Generation
Imatinib
Dasatinib
Nilotinib
Bosutinib
Ponatinib

Blast transformation :-

* treated as acute leukemia according to the type of leukemia , with the addition of 2nd. or 3rd. generation of TKI.
* in young patients Allo. HSCT is indicated.
* in old patients palliative treatment with hydroxycarbamide with or with out low dose S/C cytosar.

# TKIs For the Treatment of CML

- First-generation TKI
  - Imatinib
  - Nilotinib, dasatinib*
- Second-generation TKIs
  - Dasatinib
  - Nilotinib
  - Bosutinib†
- Third-generation
  - Bosutinib
  - Ponatinib‡
  - Omecetaxine

*Can be used in the frontline; †Can be used in the secondline at the discretion of the clinician; ‡FDA is requires several new safety measures for ponatinib to address the risk of life-threatening blood clots and severe narrowing of blood vessels.

Wei G, et al. *J Hematol Oncol*. 2010;3:47.[7]

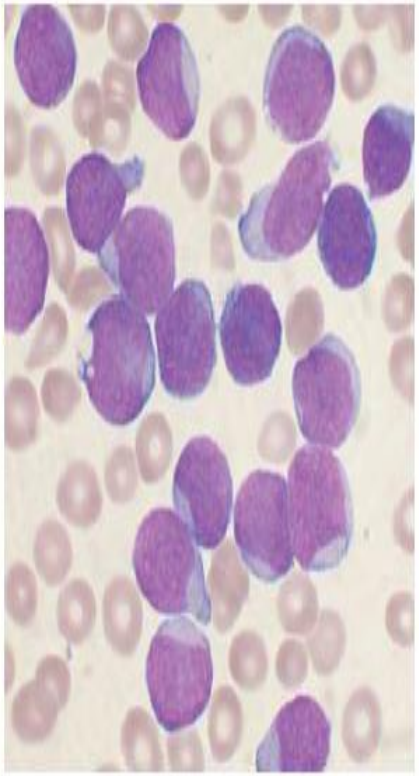
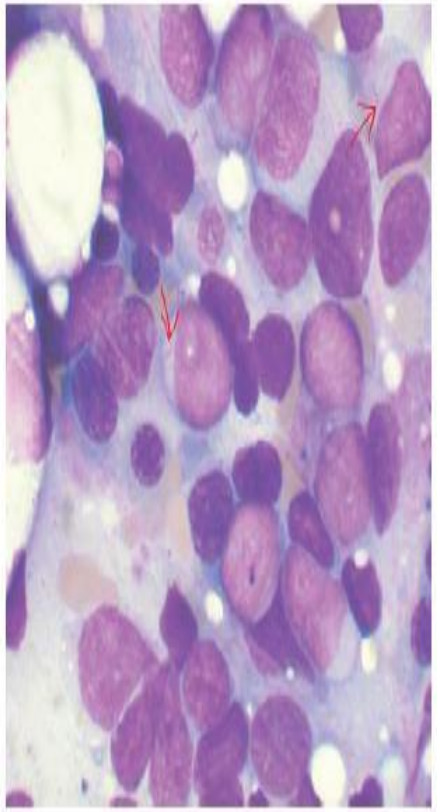
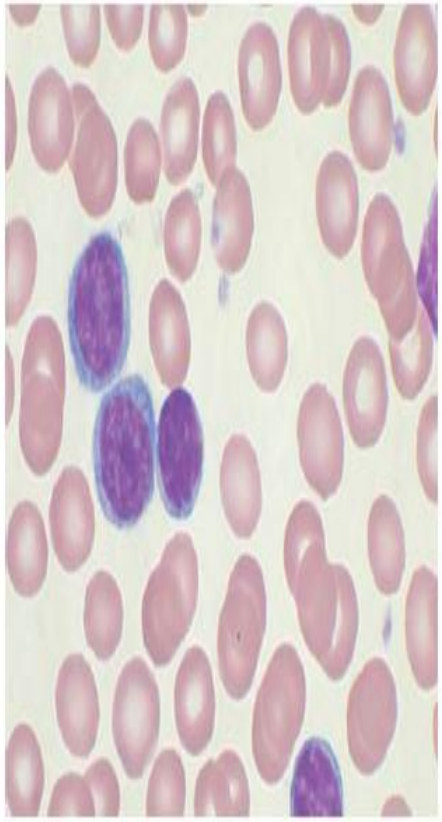
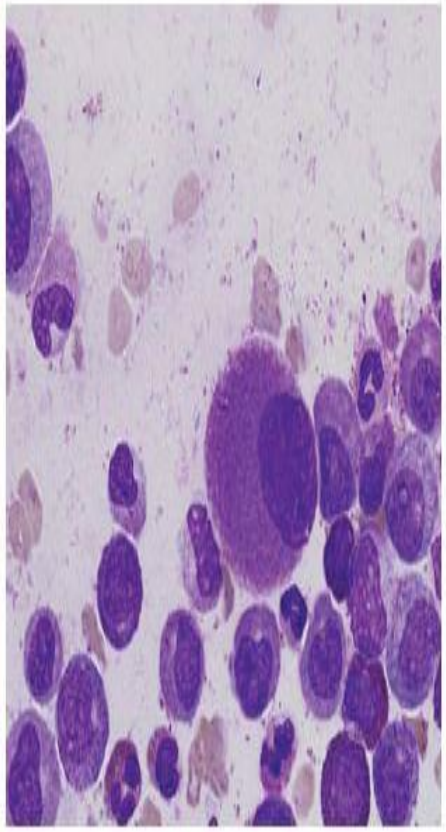
# Childhood CML :

composed 3% of pediatric leukemia , annual incidence 1/ million , have more aggressive features ,more cases are diagnosed at CP, AP , their spleen is more larger than adults leukocytosis range is also > than adults , have lower cytogenetic response to treatment : hydrea , TKI ,

unlike adults SCT is more applied .

.

## TABLE 2. DIAGNOSTIC PERIPHERAL BLOOD SMEAR OF LEUKOCYTE[6]

| ALL (B cells) | AML (Auer rods) | CLL (B cells) | CML (Ph+) |
|---|---|---|---|
|  |  |  |  |

ALL indicates acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; Ph+, Philadelphia chromosome positive.

# Acute vs. chronic leukemia

- **Leukemias are classified according to cell of origin:**
- Lymphoid cells
  - ALL - lymphoblasts
  - CLL – mature appearing lymphocytes
- Myeloid cells
  - AML – myeloblasts
  - CML – mature appearing neutrophils

- **On a CBC, if you see:**
- Predominance of blasts in blood
  - consider an acute leukemia
- Leukocytosis with mature *lymphocytosis*
  - consider CLL
- Leukocytosis with mature neutrophilia
  - consider CML