Dr. Khaled Al-Qaoud

Chapter 14 & 18

Chronic Leukemia Myeloid and Lymphoid

Types of Leukaemia

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	Acute : No maturation beyond blast	Chronic : Maturation beyond blast
Lymphocytic (B or T lineage)	ALL	CLL
Myeloid – granulocytes Erythroids Monocytes Platelets	AML	CML

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Chronic Leukemia

- Distinguished from acute leukemia by the slower progression.
- More difficult to cure than acute leukemias
- Can be divided into:
  - Chronic myeloid leukemia (CML)
  - Chronic lymphoid leukemia (CLL)

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Introduction- CML

- Incidence :1 per 100,000 (UK)
- Accounts for 7-15% of all leukaemia in adults
- Median age : 53 years
- All age groups, including children, can be affected

Introduction- CML

- Etiology
  - Not clear
  - Little evidence of genetic factors linked to the disease
  - Increased incidence
    - Survivors of the atomic disasters at Nagasaki & Hiroshima
    - Post radiation therapy

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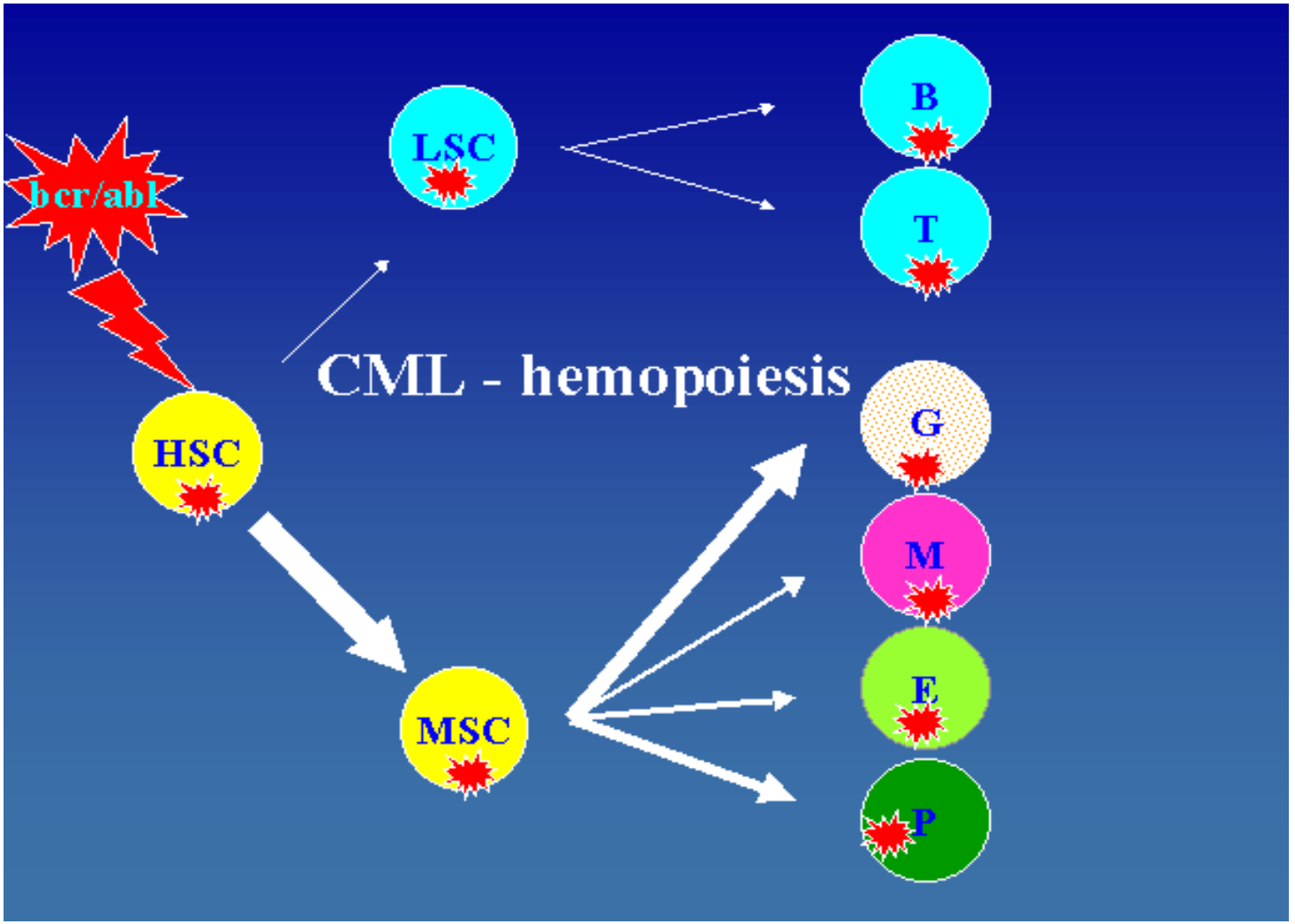
Leukaemogenesis



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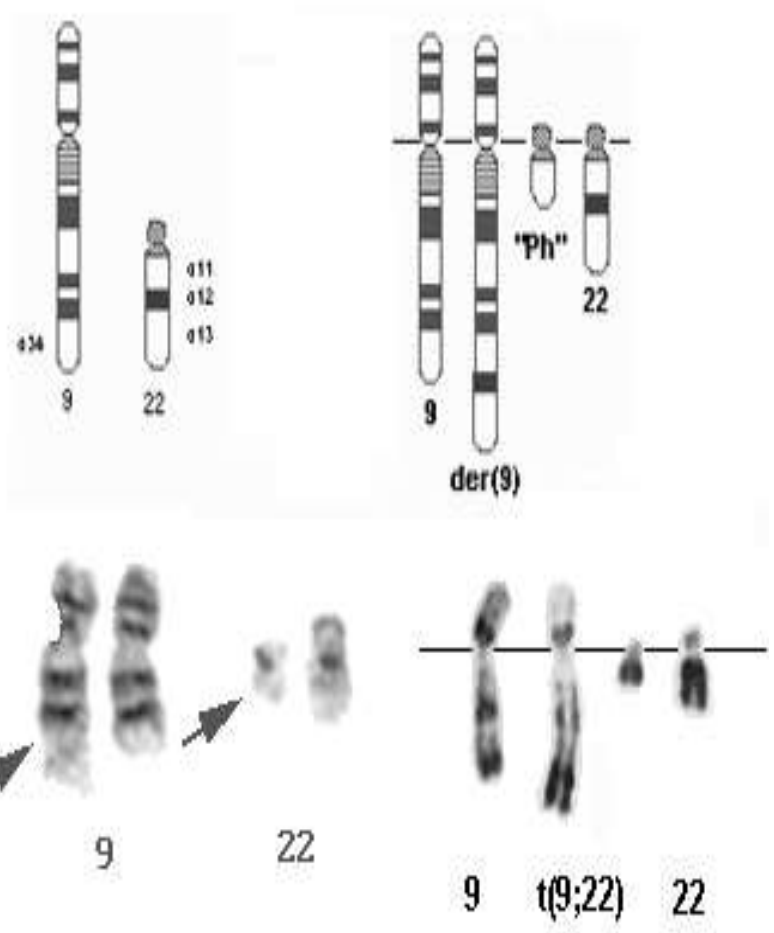
Leukaemogenesis

- Philadelphia chromosome is an acquired cytogenetic anomaly that is characterizes in all leukaemic cells in CML
- 90-95% of CML pts have Ph chromosome
- Reciprocal translocation of chromosome 22 and chromosome 9



Philadelphia Chromosome

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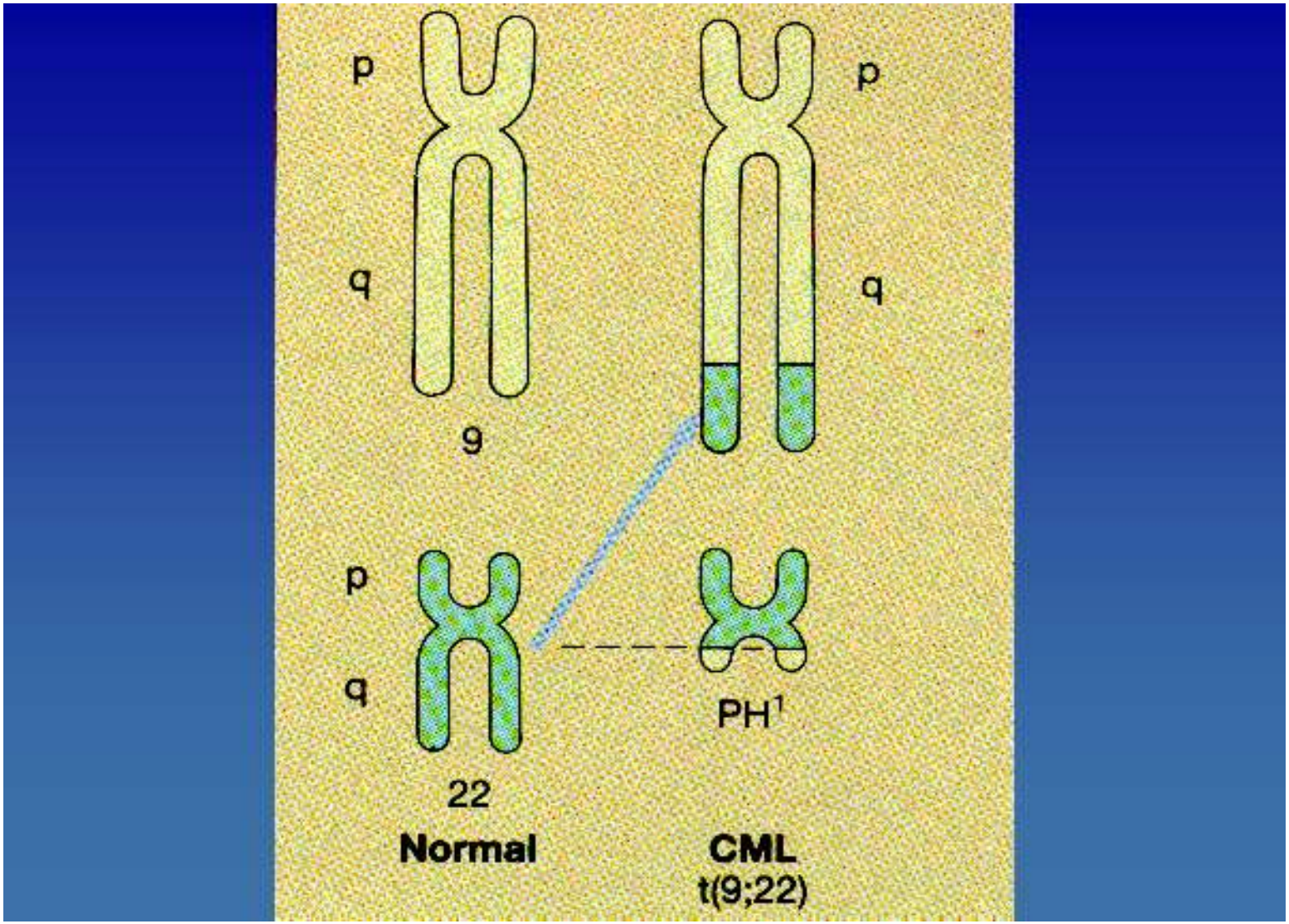
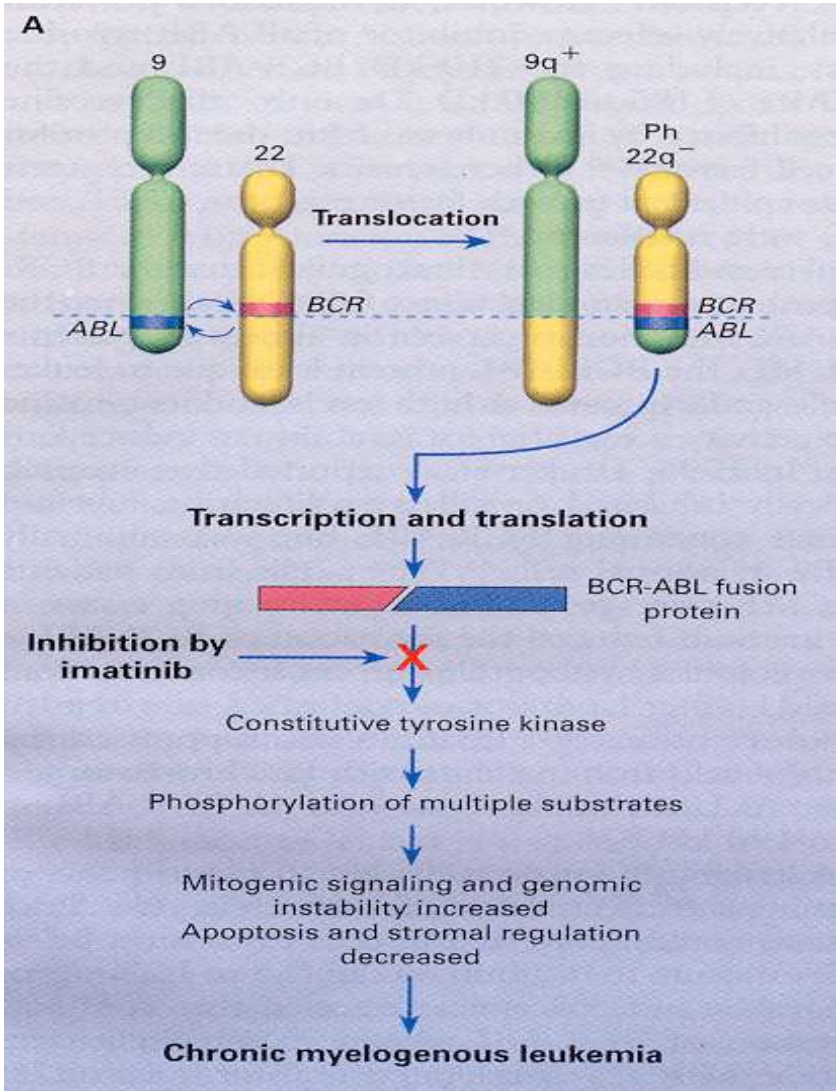


Leukaemogenesis

- *BCR (breakpoint cluster region)* gene on chromosome 22 fused to the *ABL (Ableson leukemia virus)* gene on chromosome 9
- Ph chromosome is found on myeloid, monocytic, erythroid, megakaryocytic, B-cells and sometimes T-cell proof that CML derived from pluripotent stem cell

Leukaemogenesis

- Molecular consequence of the t(9;22) is the fusion protein BCR–ABL, which has increased in tyrosine kinase activity
- BCR-ABL protein transform hematopoietic cells so that their growth and survival become independent of cytokines
- It protects hematopoietic cells from programmed cell death (apoptosis)



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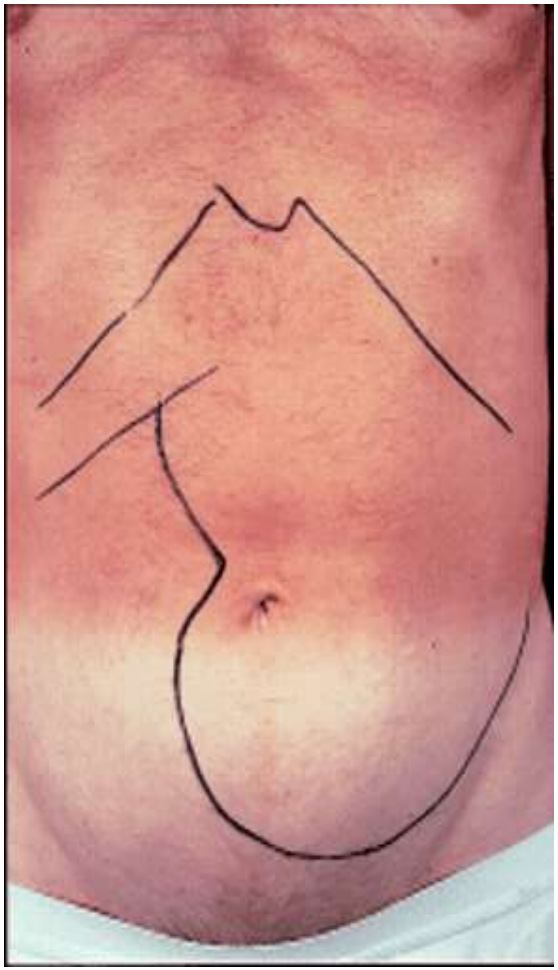
Clinical Features

- Disease is biphasic, sometimes triphasic
- 40% asymptomatic
- Chronic phase
- Splenomegaly often massive
- Symptoms related to hypermetabolism
  - Weight loss
  - Anorexia
  - Lassitude
  - Night sweats
- Features of anaemia
  - Pallor, dyspnoea, tachycardia
- Abnormal platelet function
  - Bruising, epistaxis, menorrhagia
- Hyperleukocytosis
  - thrombosis
  - Increased purine breakdown : gout
  - Visual disturbances
  - Priapism



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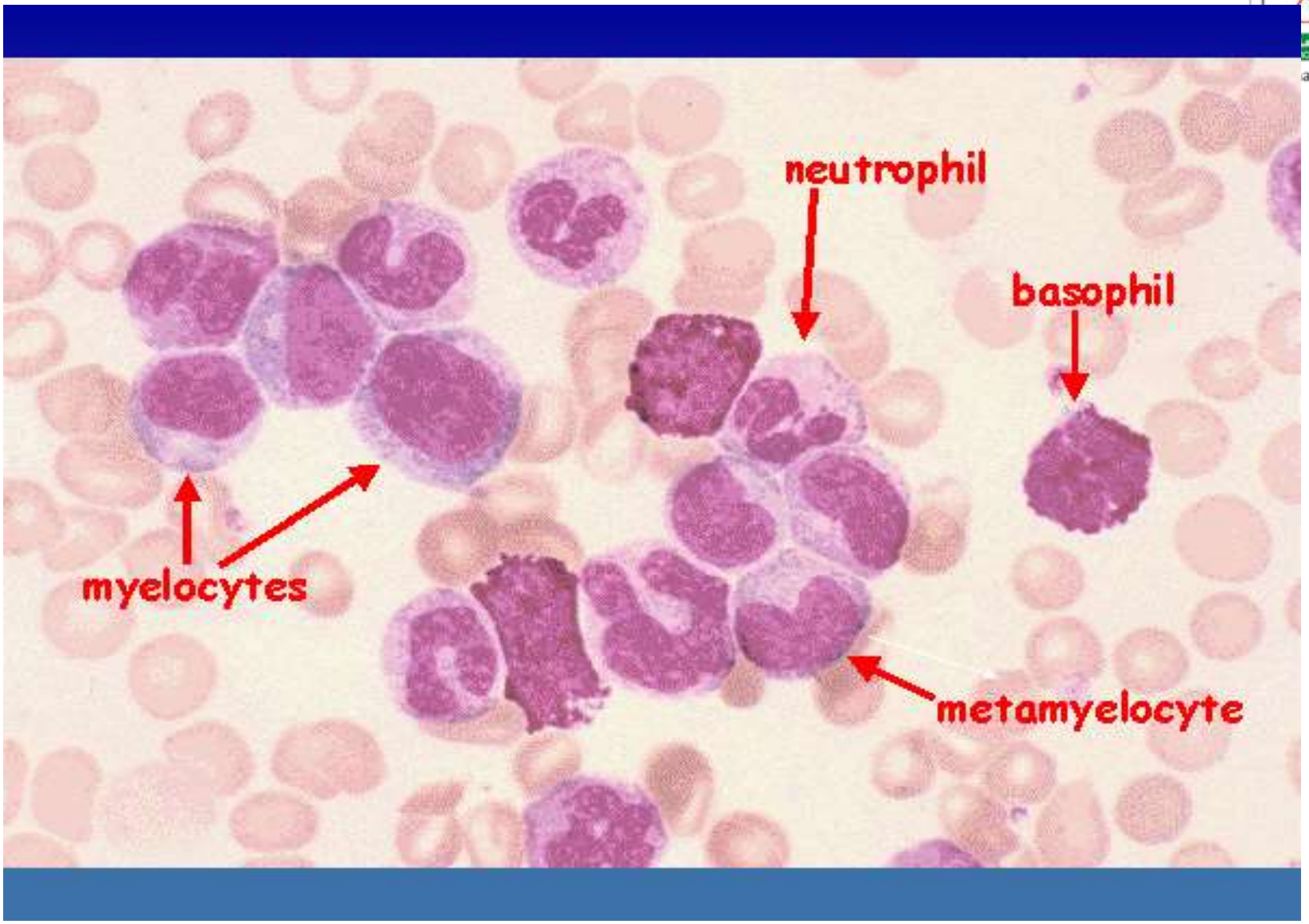
Lab features

- Peripheral blood film
  - Anaemia
  - Leukocytosis (usu >25 x 10^9/L, freq> 100 x 10^9/L
  - WBC differential shows granulocytes in all stages of maturation
  - Basophilia
  - thrombocytosis



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Phases

- Accelerated phase
  - Median duration is 3.5 – 5 yrs before evolving to more aggressive phases
  - Clinical features
    - Increasing splenomegaly refractory to chemo
    - Increasing chemotherapy requirement
  - Lab features
    - Blasts>15% in blood
    - Blast & promyelocyte > 30% in blood
    - Basophil 20% in blood
    - Thrombocytopenia
    - Cytogenetic: clonal evolution

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Phases

- Blastic phase
  - Resembles acute leukaemia
  - Diagnosis requires > 30% blast in marrow
  - 2/3 transform to myeloid blastic phase and 1/3 to lymphoid blastic phase
  - Survival : 9 mos vs 3 mos (lym vs myeloid)

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CML - principles of treatment

- Relieve symptoms of hyperleukocytosis, splenomegaly and thrombocytosis
  - Hydration
  - Chemotherapy (bulsuphan, Hydoxyurea)
- Control and prolong chronic phase (non-curative)
  - alpha interferon+chemotherapy
  - imatinib mesylate
  - chemotherapy (hydroxyurea)

CML - principles of treatment

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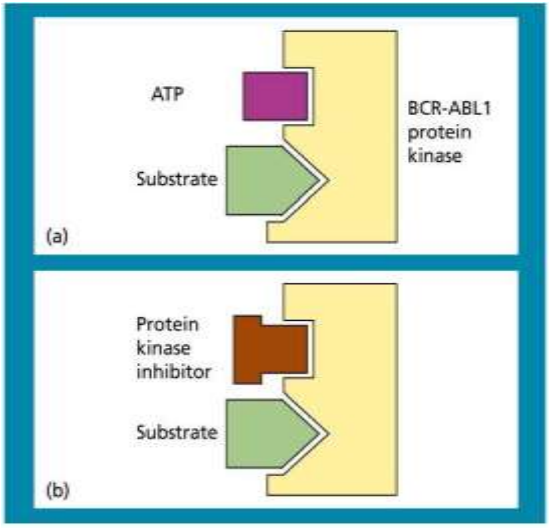
- Treatment cont…
- Eradicate malignant clone (curative)
  - allogeneic transplantation
  - alpha interferon ?
  - imatinib mesylate/STI 571 ?(Thyrosine kinase inhibitor)



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CML - prognosis

- Median survival 3.5 yrs (range 2-8 yrs)
- Interferon + chemotherapy :6 years
- Transplant : 5+ years
- imatinib mesylate ?

Chronic Lymphoblastic Leukemia

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- Characterized by proliferation of mature B or T lymphocytes with chronic persistent lymphocytosis
- They are incuracle
- May have fluctuating course
- Subtypes can be distinguished by morphology, immunophenotyping and cytogenetics

CLL

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- CLL is the most common chronic Lymphoid leukemia
- Has a peak incidence between 60 and 80 years of age
- The cells accumulate in the blood, liver, BM, spleen, and Lymph nodes.

Table 18.1 Classification of the chronic lymphoid leukaemias.

B-cell	T-cell
Chronic lymphocytic leukaemia (CLL)	Large granular lymphocytic leukaemia
Prolymphocytic leukaemia (PLL)	T-cell prolymphocytic leukaemia (T-PLL)
Hairy cell leukaemia (HCL)	Adult T-cell leukaemia/ lymphoma
Plasma cell leukaemia	Sézary syndrome (see Chapter 20)

Source: WHO (2008) classification (see p. 426).

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CLL
Binet Staging

Stage	Organ enlargement*	Hb g/dl	Plateletes (X 109/l
A (50-60%)	0,1,2 areas		
B (30%)	3,4,5 area	>=10	>=100
C (<20%)	(not considered)	<10	<100

* One area= lymph node >1 cm in neck , axillae, inguinal, groins or spleen or liver enlargement

CLL prognosis

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Table 18.3 Prognostic factors in chronic lymphocytic leukaemia.

	Good	Bad
Stage	Binet A (Rai 0–I)	Binet B, C (Rai II–IV)
Sex	Female	Male
Lymphocyte doubling time	Slow	Rapid
Bone marrow biopsy appearance	Nodular	Diffuse
Chromosomes	Deletion 13q14	Deletion 17p
VH immunoglobulin genes	Hypermutated	Unmutated Use of VH3.21
ZAP expression	Low	High
CD38 expression	Negative	Positive
LDH	Normal	Raised

LDH, lactate dehydrogenase.

CLL

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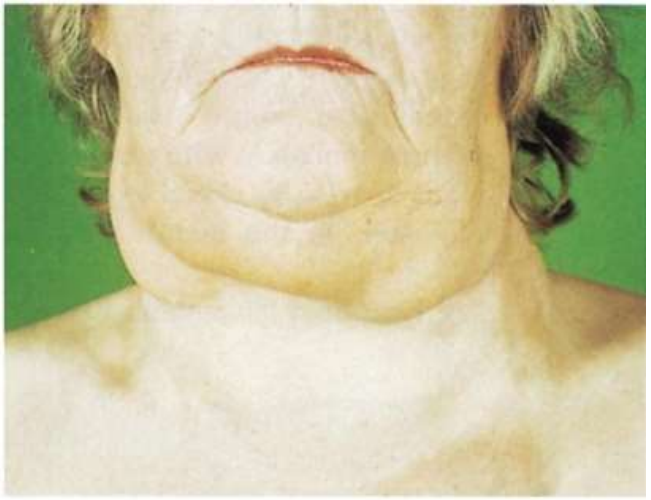
- Bilateral cervical lymphadenopathy in a 67 years old woman
- Hb 12.5 mg/dl
- WBC: 150X109/l
- Lymphocytes: 146X109/l
- Platelets: 120 X109/l



Diagnosis of CLL using Flow cytometry

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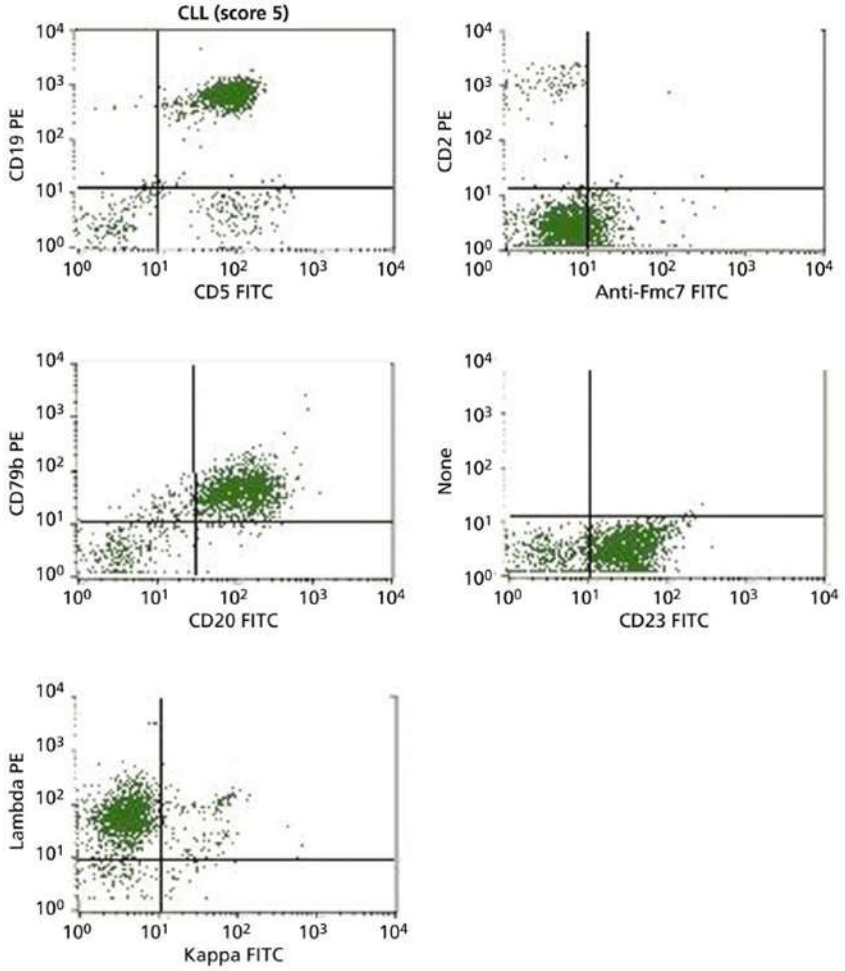
- Immunophenotypic analysis of CLL by flow cytometric analysis
- The cells are CD19+, CD5+, CD20+, CD23+, CD79+ and lambda light chain



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