# HAEMATOLOGICAL MALIGNANCIES

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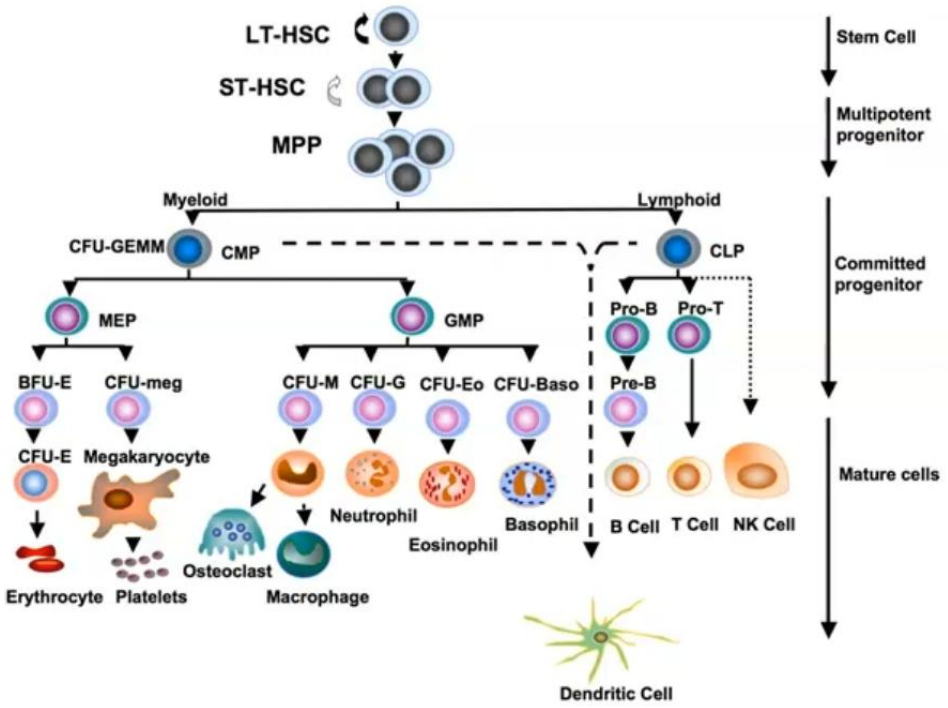
# Blood Cell Formation

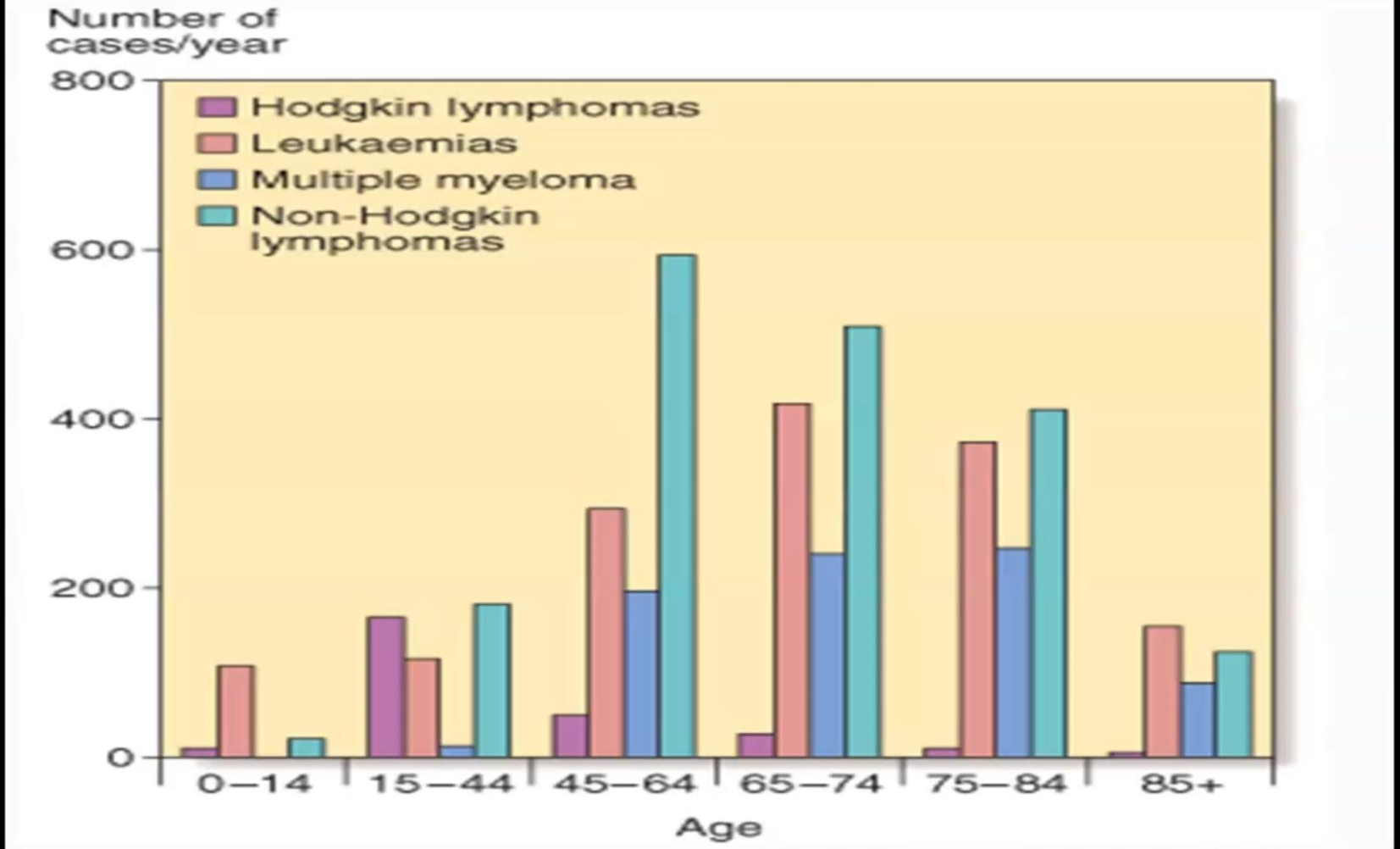


# General Concepts

- Disease of elderly patients
  - Exceptions ALL & Hodgkin Lymphoma
- Mature differentiated cells involved
  - Low growth fraction
  - Indolent neoplasms
  - Low-grade lymphoma, chronic leukaemia

# General Concepts

- Involvement of pluripotent stem cells
  - The highest growth fractions of all human neoplasms
  - Rapidly progressive life-threatening illnesses
  - Acute leukaemias or high-grade lymphomas




Variation in the incidence of different haematological malignancies in the UK by age.

# General classification

- Leukaemias
- Lymphomas
- Paraproteinemias
- Myeloproliferative disorders

# Leukaemias

- Malignant disorders of the haematopoietic stem cell compartment
- ALL disease of children
- Chronic leukaemia mainly in old age

# Classification of Leukaemias

- Acute lymphoblastic leukaemia (ALL)
- Acute myeloid leukaemia (AML)
- Chronic lymphocytic leukaemia (CLL)
- Chronic myeloid leukaemia (CML)

# Acute vs. Chronic Leukemia

- Acute Leukemia (AML and ALL)
  - excess myeloblasts or lymphoblasts
  - short clinical course (weeks to months)

- Chronic Leukemia (CML and CLL)
  - accumulation of mature granulocytes or lymphocytes
  - longer clinical course (several to many years)

# Acute Leukemia

- A clonal, molecular abnormality of hematopoietic blast cells resulting in a failure of differentiation & uncontrolled cell proliferation

- Accumulation of leukemic blast cells results in marrow replacement, organ infiltration and metabolic effects

# Acute Leukemia:

## AML versus ALL

- Adults - 85% of acute leukemia is AML
- Children-85% of acute leukemia is ALL
- Leukemic Blast morphology
  - AML: cytoplasmic granules, Auer rods, more cytoplasm, 2-5 nucleoli
  - ALL: no cytoplasmic granules, minimal cytoplasm, 1-2 nucleoli

# Acute Leukemia: Clinical Manifestations

- Constitutional & Metabolic effects:
  - Weight loss
  - Fever
  - Hyperkalemia
  - Hyperuricemia

# Acute Leukemia:

## Hematology Laboratory Findings

- ***Decreased, normal or elevated WBC***
- Anemia
- Thrombocytopenia
- Blasts on peripheral blood smear (often)
- Hypercellular bone marrow with 20% or more blasts (normal is < 5%)

# Acute Leukemia: Clinical Manifestations

- Marrow replacement, organ infiltration & metabolic effects

- Marrow replacement
  - Neutropenia: infection
  - Anemia: pallor, fatigue, dyspnea
  - Thrombocytopenia: abnormal bruising and bleeding

# Acute Leukemia: Clinical Manifestations

- Organ infiltration
  - Bone pain
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Gingival hypertrophy
  - Leukemic meningitis

## 24.37 WHO CLASSIFICATION OF ACUTE LEUKAEMIA

**Acute myeloid leukaemia with recurrent genetic abnormalities**

- AML with t(8;21) gene product AML/ETO
- AML with eosinophilia inv(16) or t(16;16), gene product CBFβ/MYH11
- Acute promyelocytic leukaemia t(15;17), gene product PML/RARA
- AML with 11q23 abnormalities (MLL)

**Acute myeloid leukaemia with multilineage dysplasia**

- e.g. Following a myelodysplastic syndrome

**Acute myeloid leukaemia and myelodysplastic syndromes, therapy-related**

- e.g. Alkylating agent or topoisomerase II inhibitor

**Acute myeloid leukaemia not otherwise specified**

- e.g. AML with or without differentiation, acute myelomonocytic leukaemia, erythroleukaemia, megakaryoblastic leukaemia, myeloid sarcoma

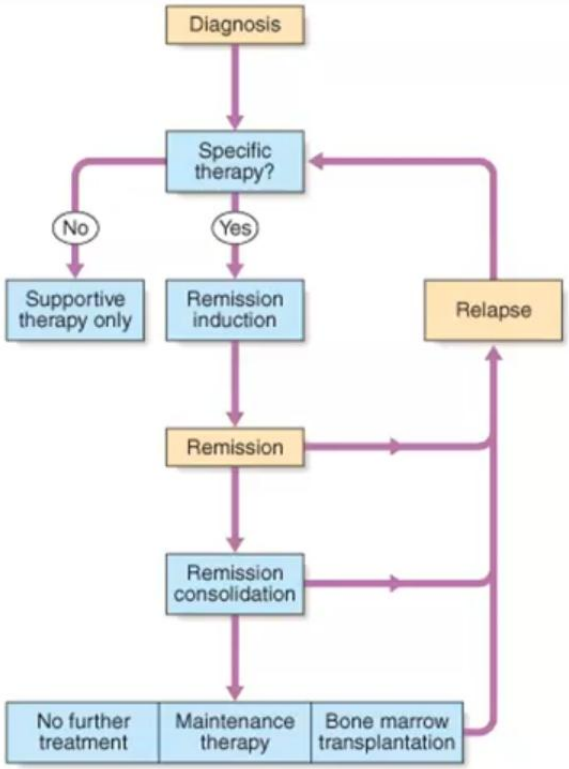
**Acute lymphoblastic leukaemia**

- Precursor B ALL
- Precursor T ALL

# AML:
# FAB classification

- **F**rench **A**merican **B**ritish classification
- Mo-M7 based on morphology, and special cytochemical studies
- Historically, distinguishing AML Mo from ALL was a major clinical problem

# Treatment strategy in acute leukaemia



## 24.39 DRUGS COMMONLY USED IN THE TREATMENT OF ACUTE LEUKAEMIA

| Phase | ALL | AML |
|---|---|---|
| **Induction** | Vincristine (i.v.) | Daunorubicin (i.v.) |
| | Prednisolone (oral) | Cytarabine (i.v.) |
| | L-asparaginase (i.m.) | Etoposide (i.v. and oral) |
| | Daunorubicin (i.v.) | |
| | Methotrexate (intrathecal) | |
| **Consolidation** | Daunorubicin (i.v.) | Cytarabine (i.v.) |
| | Cytarabine (i.v.) | Amsacrine (i.v.) |
| | Etoposide (i.v.) | Mitoxantrone (i.v.) |
| | Methotrexate (i.v.) | |
| **Maintenance** | Prednisolone (oral) | |
| | Vincristine (i.v.) | |
| | Mercaptopurine (oral) | |
| | Methotrexate (oral) | |

# Chronic lymphocytic leukemia

- Is characterised by the accumulation of nonproliferating mature-appearing lymphocytes in the blood, marrow, lymph nodes, and spleen
- In most cases, the cells are monoclonal B lymphocytes that are CD5+
- T cell CLL can occur rarely

# Clinical findings

- Approximately 40% of CLL patients are asymptomatic at diagnosis
- In symptomatic cases the most common complaint is fatigue
- Less often the initial complaint are enlarged nodes or the development of an infection (bacterial)

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# The diagnostic criteria for CLL

1) A peripheral blood lymphocyte count of greater than 5 G/L, with less than 55% of the cells being atypical
2) The cell should have the presence of Bcell-specific differentiation antigens (CD19, CD20, and CD24) and be CD5(+)
3) A bone marrow aspirates showing greater than 30% lymphocytes

# Staging

- Rai Classification for CLL
  - 0 - lymphocytosis (>5 G/L)
  - I - lymphocytosis + lymphadenopathy
  - II - lymphocytosis + splenomegaly +/-lymphadenopathy
  - III - lymphocytosis + anemia (Hb <11g%) +/- lymphadenopathy or splenomegaly
  - IV - lymphocytosis + thrombocytophenia (Plt <100G/L) +/- anemia +/-lymphadenopathy +/- splenomegaly

# Staging

- Binet Classification for CLL
  - A. < 3 involved areas, Hb > 10g%, Plt > 100G/L
  - B. > 3 involved areas, Hb > 10g%, Plt > 100G/L
  - C. - any number of involved areas, Hb < 10g%, Plt < 100G/L

# Prognosis

- Rai classification

| stage | median survival (years) |
|---|---|
| 0 | >10 |
| I | > 8 |
| II | 6 |
| III | 2 |
| IV | < 2 |

- Binet classification

| stage | median survival (years) |
|---|---|
| A | > 10 |
| B | 7 |
| C | 2 |

# Treatment

- Treatment is reserved for patients with low- or intermediate risk disease who are symptomatic or have progressive disease (increasing organomegaly or lymphocyte doubling time of less than 12 months) and patients with high -risk disease
  - Alkylating agents (chlorambucil, cyclophosphamide)
  - Nucleoside analogs (cladribine, fludarabine)
  - Biological response modifiers
  - Monoclonal antibodies
  - Bone marrow transplantation
  - And systemic complications requiring therapy
    - antibiotics
    - immunoglobulin
    - steroids
    - blood products

# Chronic Myeloid Leukemia

- A myeloproliferative stem cell disorder
- Philadelphia (Ph) chromosome
  - Seen in 95% of patients.Translocation of long arm of q22 to q9.

- Natural History of Disease
  - A chronic phase
  - An accelerated phase (not always seen)
  - Blast crisis

## 24.45 SYMPTOMS AT PRESENTATION OF CHRONIC MYELOID LEUKAEMIA

| Symptom | Present (%) |
|---|---|
| Tiredness | 37 |
| Weight loss | 26 |
| Breathlessness | 21 |
| Abdominal pain and discomfort | 21 |
| Lethargy | 13 |
| Anorexia | 12 |
| Sweating | 11 |
| Abdominal fullness | 10 |
| Bruising | 7 |
| Vague ill health | 7 |

# Management

- Imatinib
- Hydroxycarbamide
- Allogeneic or syngeneic bone marrow transplant from a matched sibling donor
- Treatment of the accelerated phase and blast crisis
- Hydroxyurea(commonest alternative available in pakistan).

# Lymphomas

# Lymphomas

- Hodgkin's Lymphoma (HL)
- Non-Hodgkin lymphoma (NHL)

# Hodgkin's Lymphoma

## 24.50 EPIDEMIOLOGY AND AETIOLOGY OF HODGKIN LYMPHOMA

**Incidence**

- Approximately 4 new cases/100 000 population/year

**Sex ratio**

- Slight male excess (1.5:1)

**Age**

- Median age 31 years; first peak at 20-35 years and second at50-70 years

**Aetiology**

- Unknown. More common in patients from well-educated backgrounds and small families. Three times more likely with a past history of infectious mononucleosis but no causal link to
  Epstein-Barr virus infection proven

## 24.51 WHO PATHOLOGICAL CLASSIFICATION AND INCIDENCE OF HODGKIN LYMPHOMA (HL)

| Type | Histology | Incidence |
|---|---|---|
| Nodular lymphocyte- predominant HL | | 5% |
| Classical HL | Nodular sclerosing | 70% |
| | Mixed cellularity | 20% |
| | Lymphocyte-rich | 5% |
| | Lymphocyte-depleted | Rare |

## 24.52 CLINICAL STAGES OF HODGKIN LYMPHOMA (ANN ARBOR CLASSIFICATION)

| Stage | Definition |
|---|---|
| I | Involvement of a single lymph node region (I) or extralymphatic site ($IA_E$) |
| II | Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side of (above or below) the diaphragm ($II_E$) |
| III | Involvement of lymph node regions on both sides of the diaphragm with ($III_E$) or without (III) localised extralymphatic involvement or involvement of the spleen ($III_S$) or both ($III_{SE}$) |
| IV | Diffuse involvement of one or more extralymphatic tissues, e.g. liver or bone marrow |
| A | No systemic symptoms |
| B | Weight loss, drenching sweats |
| The lymphatic structures are defined as the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches. | |

## 24.53 THERAPEUTIC GUIDELINES FOR HODGKIN LYMPHOMA

**Indications for radiotherapy**

- Stage I disease
- Stage IIA disease with three or fewer areas involved
- After chemotherapy to sites where there was originally bulkdisease
- To lesions causing serious pressure problems

**Indications for chemotherapy**

- All patients with B symptoms
- Stage II disease with more than three areas involved
- Stages III and IV disease

## 24.54 THE ChlVPP REGIMEN FOR HODGKIN LYMPHOMA

| Drug | Dose |
|---|---|
| Chlorambucil | 6 mg/m$^2$ (up to 10 mg total) days 1-14 orally |
| Vinblastine | 6 mg/m$^2$ (up to 10 mg total) days 1 and 8 i.v. |
| Procarbazine | 100 mg/m$^2$ days 1-14 orally |
| Prednisolone | 40 mg/m$^2$ days 1-14 orally |

# Non-Hodgkin lymphoma

## 24.55 EPIDEMIOLOGY AND AETIOLOGY OF NON-HODGKIN LYMPHOMA

**Incidence**

- 12 new cases/100 000 people/year

**Sex ratio**

- Slight male excess

**Age**

- Median age 65-70 years

**Aetiology**

- No single causative abnormality described
- Lymphoma is a late manifestation of HIV infection (p. 396)
- Specific lymphoma types are associated with EBV, human herpes virus 8 (HHV8) and HTLV infection
- The development of gastric lymphoma can be associated with *Helicobacter pylori* infection
- Some lymphomas are associated with specific chromosome lesions; the t (14:18) translocation in follicular lymphoma results in the dysregulated expression of the *BCL-2* gene product which inhibits apoptotic cell death
- Lymphoma occurs in congenital immunodeficiency states and in immunosuppressed patients post-organ transplantation

# Histologic classification of non-Hodgkin's lymphomas - Working Formulation (WF)

- Low grade
- Intermediate grade
- High grade

# Paraproteinaemias

# Paraproteinaemias

- Monoclonal gammopathy of uncertain significance (MGUS)
- Waldenström macroglobulinaemia
- Multiple myeloma

# Multiple myeloma

**Hyperviscosity**
Retinal bleeds
Bruising
Heart failure
Cerebral ischaemia

**Amyloid**
'Panda' eyes
Nephrotic syndrome
Carpal tunnel syndrome

**Spinal cord compression**
Bony collapse
Extradural mass

Bone pain/fracture

Lytic lesions

Anaemia
Normochromic
Normo- or macrocytic

Pancytopenia

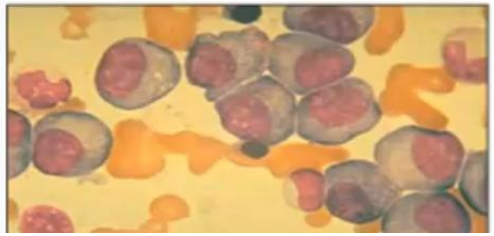
Raised ESR

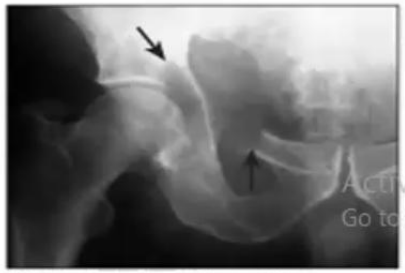
Hypercalcaemia

**Renal failure**
Paraprotein deposition
Hypercalcaemia
Infection
NSAIDs
Amyloid
Dehydration

Bone marrow plasmacytosis
> 30%

**Paraproteinaemia**
IgG/A/D/E
(κ or λ light chains only)
Immune paresis
Bence Jones proteinuria





# Myeloproliferative disorders

- Myelofibrosis
- Primary Thrombocythaemia
- Polycythaemia Rubra Vera (PRV)
- CML