# HAEMATOLOGY

- Chronic Leukemias,
- Multiple Myeloma,
- Myelodysplastic Syndrome

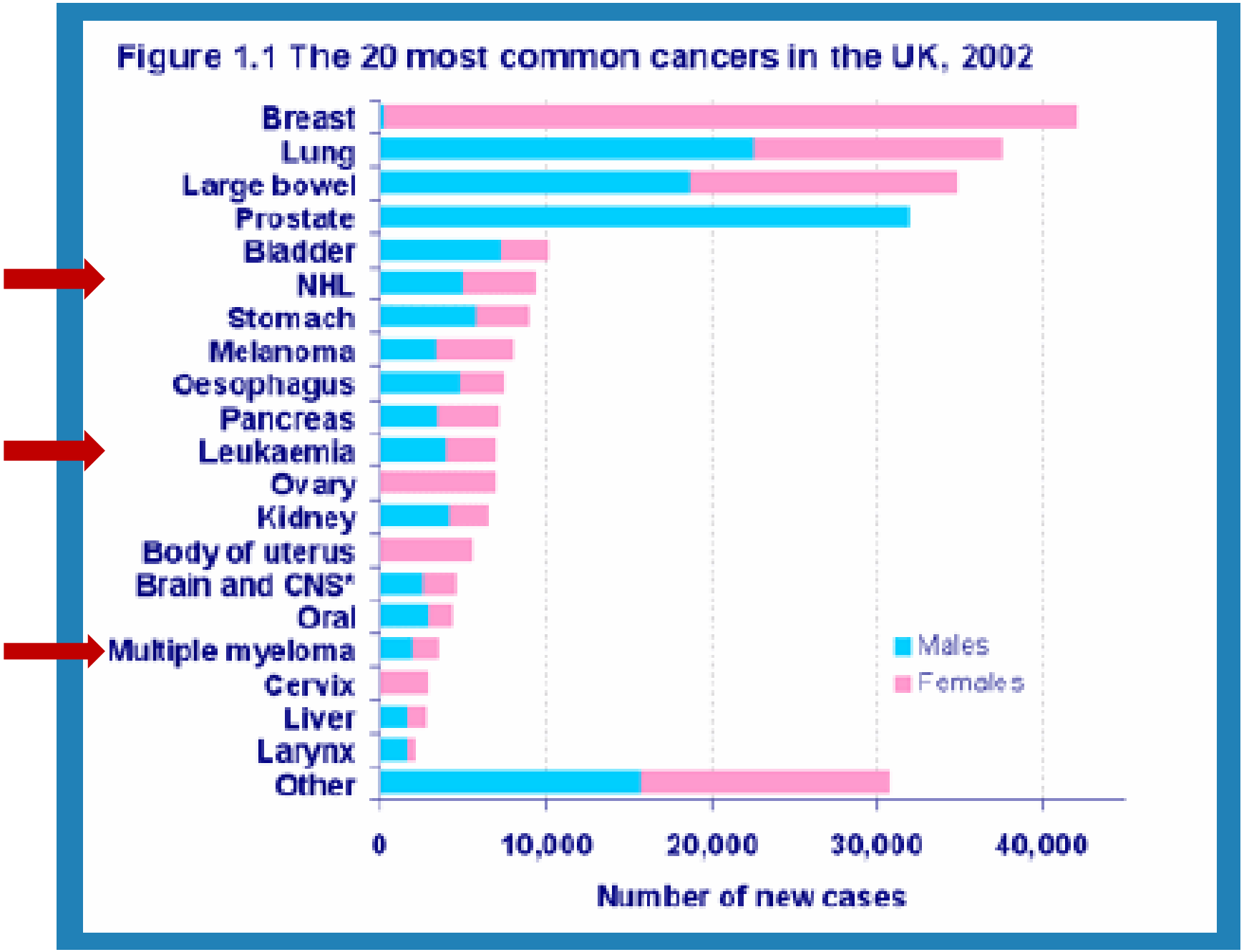


Figure 1.1 The 20 most common cancers in the UK, 2002
Breast
Lung
Large bowel
Prostate
Bladder
NHL
Stomach
Melanoma
Oesophagus
Pancreas
Leukaemia
Ovary
Kidney
Body of uterus
Brain and CNS*
Oral
Multiple myeloma
Cervix
Liver
Larynx
Other
Males
Females
0
10,000
20,000
30,000
40,000
Number of new cases

# Lymphoma

Lymphoma is a type of cancer involving lymphocytes.

Cancer occurs when normal cells undergo a transformation whereby they grow and multiply uncontrollably.

Lymphomas fall into 1 of 2 major categories:
-Hodgkin lymphoma (HL, previously called Hodgkin's disease) and
-all other lymphomas (non-Hodgkin lymphomas or NHLs).

Lymphoma represents about 35 different malignant transformation of either lymphocytes B or T cells or their subtypes.

| | **B Cell Disorders** |
|---|---|
| 1 | B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma |
| 2 | B cell prolymphocytic leukaemia |
| 3 | Lymphoplasmacytic lymphoma |
| 4 | Splenic marginal zone lymphoma |
| 5 | Hairy cell leukaemia |
| 6 | Plasma cell myeloma including plasmacytoma |
| 7 | Extra nodal marginal zone B-cell lymphoma<br>of mucosa associated lymphoid tissue type (MALT-Lymphoma) |
| 8 | Nodal marginal zone B-cell lymphoma |
| 9 | Follicular lymphoma, |
| 10 | Mantle cell lymphoma |
| 11 | Diffuse Large B-cell lymphoma |
| | Mediastinal (thymic) lymphoma |
| | Intravascular large B-cell lymphoma |
| | Primary effusion lymphoma |
| 12 | Burkitt lymphoma/leukaemia |

| | **T & NK Disorders** |
|---|---|
| 13 | Extranodal NK/T cell lymphoma nasal type |
| 14 | Enteropathy-type intestinal T-cell lymphoma |
| 15 | Hepatosplenic T-cell lymphoma |
| 16 | Angioimmunoblastic T-cell lymphoma (AILD) |
| 17 | Anaplastic large cell lymphoma (ALCL) |
| 18 | Peripheral T-cell lymphomas, unspecified |
| 19 | Precursor T-lymphoblastic lymphoma/leukaemia |
| 20 | Blastic NK cell lymphoma |
| 21 | T-cell prolymphocytic leukaemia |
| 22 | T-cell large granular lymphocytic leukaemia |
| 23 | Aggressive natural killer cell leukaemia |
| 24 | Adult T-cell lymphoma/leukaemia (ATL/L) |

| | **Hodgkin Lymphoma** |
|---|---|
| 25 | Classical |
| | Nodular sclerosis |
| | Lymphocyte rich classical |
| | Mixed cellularity |
| | Lymphocyte depleted |
| 26 | Nodular lymphocyte predominance |

| | **Macrophage/ Histiocytic Neoplasms** |
|---|---|
| 27 | Histiocytic sarcomas |
| 28 | Langerhans' cell histiocytosis |
| 29 | Langerhans' cell sarcoma |
| 30 | Interdigitating dendritic cell sarcoma/tumour |
| 31 | Follicular dendritic cell sarcoma/tumour |
| 32 | Dendritic cell sarcoma not otherwise specified |

# Chronic lymphocytic leukemia (CLL)

- 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 -markers of B-cell lineage (CD19, CD20 and CD23).

- T cell CLL can occur rarely

# Chronic lymphocytic leukemia

- Is the most common form of leukemia in North America and Europe, but is extremely rare in the Orient
- Typically occurs in older patients, with the highest incidence being in those aged 50 to 55 years
- Affects men twice as often as  women

# Etiology

- The cause of CLL is unknown
- There is increased incidence in farmers, rubber manufacturing workers, asbestos workers, and tire repair workers
- Genetic factors have been postulated to play a role in high incidence of CLL in some families

# Etiology (2)

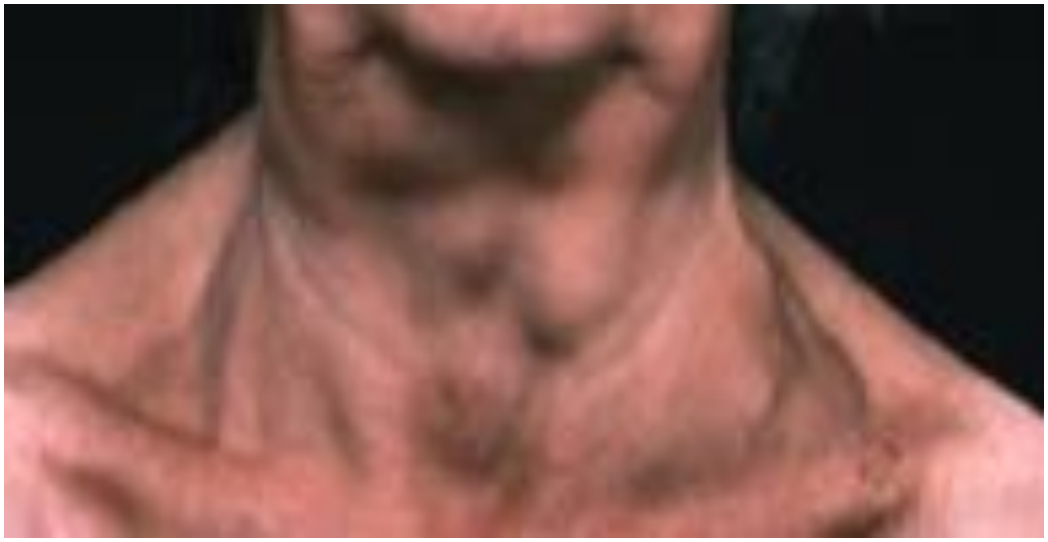
- Cytogenetics
  - clonal chromosomal abnormalities are detected in approximately 50% of CLL patients
  - the most common clonal abnormalities are:
    - trisomy 12
    - structural abnormalities of chromosomes 13, 14 and 11
  - patients with abnormal karyotypes have a worse prognosis
- Oncogenes
  - in most cases of CLL is overexpressed the proto-oncogene c-fgr 9a member of the src gene family of tyrosine kinases

# Clinical findings (1)

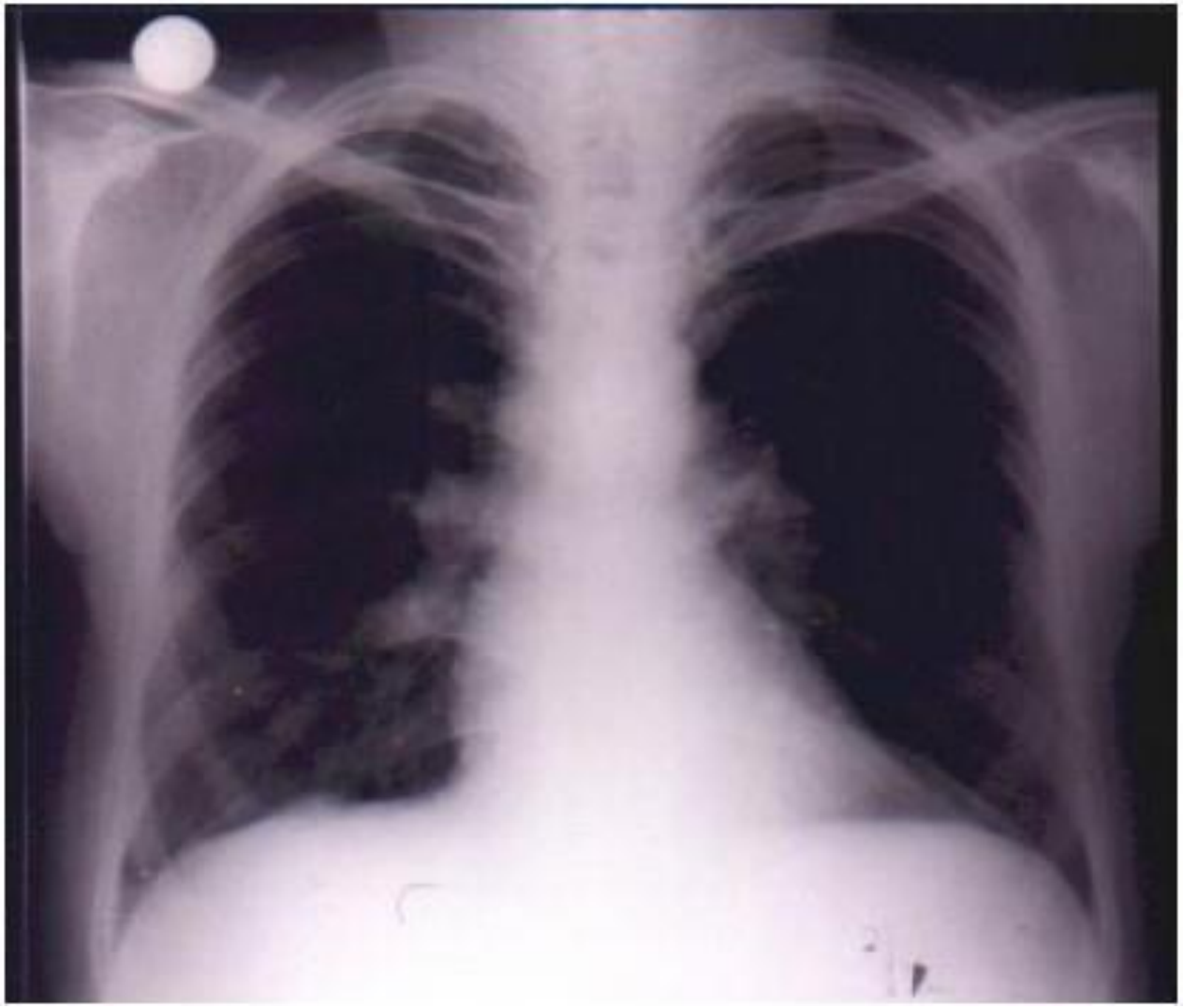
- Approximately 40% of CLL patients are asymptomatic at diagnosis
- In symptomatic cases the most common complaint is fatigue
- Less often the initial complaint are enlarged nodes or the development of an infection (bacterial)

# Clinical findings (2)

- Most symptomatic patients have enlarged lymph nodes (more commonly cervical and supraclavicular) and splenomegaly
- The lymph nodes are usually discrete, freely movable, and nontender
- Hepatomegaly may occure
- Less common manifestation are infiltration of tonsils, mesenteric or retroperitoneal lymphadenopathy, and skin infiltration
- Patients rarely present with features of anemia, and bruising or bleeding



Enlarged cervical lymph nodes



Enlargement hilar lymph nodes

# Laboratory findings (1)

- The blood lymphocyte count above 5,0 G/L
- In most patients the leukemic cells have the morphologic appearance of normal small lymphocytes
- In the blood smears are commonly seen ruptured lymphocytes (“basket” or “smudge” cells)
- Careful examination of the blood smear can usually differentiate CLL, and the diagnosis can be confirmed by immunophenotyping

Pacjent: [redacted]
Oddzial: POR HEMATOLOGICZNA

Zlecenie: 86
Nr pacjenta:

| Badanie | Wynik badania | | J.miary | Wart.referencyjne | |
|---|---|---|---|---|---|
| WBC | | 159.9 | 10^3/uL | ( 4.0 | - 10.0 ) |
| %NEUT | | 4.4 | % | ( 40 | - 72 ) |
| %LYMPH | | 80.3 | % | ( 18 | - 48 ) |
| %MONO | | 0.5 | % | ( 2.5 | - 10.0 ) |
| %EOS | | 0.1 | % | ( 0.5 | - 6.0 ) |
| %BASO | | 2.3 | % | ( 0.0 | - 1.5 ) |
| %LUC | | 14.7 | % | ( 0.0 | - 4.0 ) |
| #NEUT | 6.96 | | 10^3/uL | ( 1.9 | - 7.5 ) |
| #LYMPH | | 128.4 | 10^3/uL | ( 0.9 | - 4.5 ) |
| #MONO | 0.85 | | 10^3/uL | ( 0.1 | - 1.0 ) |
| #EOS | 0.11 | | 10^3/uL | ( 0.05 | - 0.50 ) |
| #BASO | | 3.67 | 10^3/uL | ( 0.0 | - 0.2 ) |
| #LUC | | 23.52 | 10^3/uL | ( 0.0 | - 0.4 ) |
| RBC | | 3.37 | 10^6/ul | ( 4.0 | - 5.5 ) |
| HGB | | 10.7 | g/dL | ( 12 | - 16 ) |
| HCT | | 32.6 | % | ( 37 | - 47 ) |
| MCV | 96.7 | | fL | ( 81 | - 99 ) |
| MCH | 31.7 | | pg | ( 27 | - 34 ) |
| MCHC | 32.7 | | g/dL | ( 31 | - 37 ) |
| CHCM | 31.8 | | g/dL | ( 31 | - 37 ) |
| RDW | 12.3 | | % | ( 11.5 | - 14.5 ) |
| HDW | 2.39 | | g/dL | ( 2.2 | - 3.2 ) |
| PLT | 137 | | 10^3/uL | ( 130 | - 350 ) |
| MPV | 7.6 | | fL | ( 7.0 | - 12.0 ) |
| PCT | | 0.10 | % | ( 0.12 | - 0.36 ) |
| PDW | 51.3 | | % | ( 40.0 | - 60.0 ) |
| Atypical Lymph | | +++ | | | |
| BLASTS | | ++ | | | |

Obraz mikroskopowy

| | | |
|---|---|---|
| BLAST | - | % |
| PROMYELO | - | % |
| MYELO | - | % |
| META | - | % |
| BAND | - | % |
| NEUT | - | 4 % |
| EOSIN | - | % |
| BASO | - | % |
| MONO | - | % |
| PROLYMPH | - | 6 % |
| LYMPH | - | 90 % |
| ATYP LY | - | % |
| NRBC | - | |

Komentarz:
pjed. cienie
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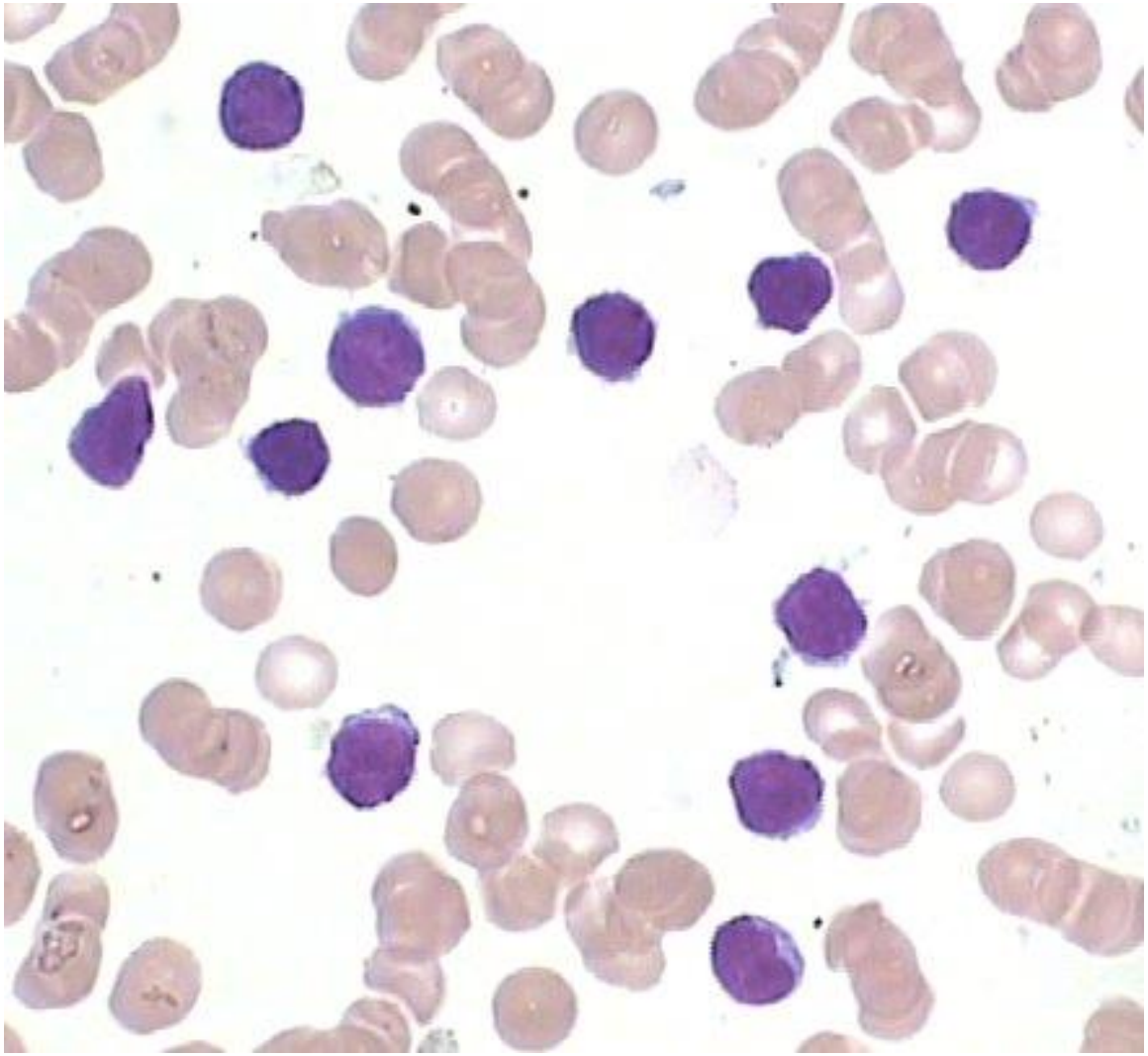
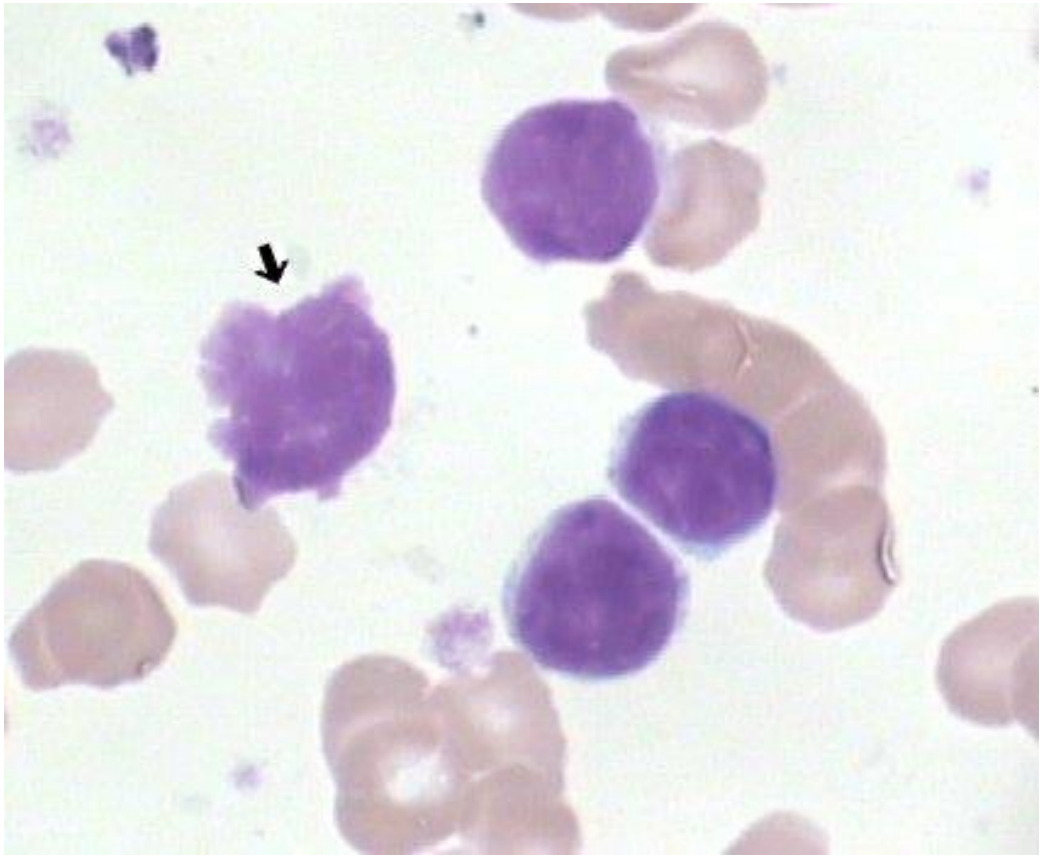
RETIC : /

Wykonal: Wiesława Mejpak
st. inż. analityki med.



May-Grunwald-Giemsa-stained peripheral blood. Predominant morphology is the small lymphocyte with thin cytoplasmic rim, giving a low cytoplasm:nuclear ratio



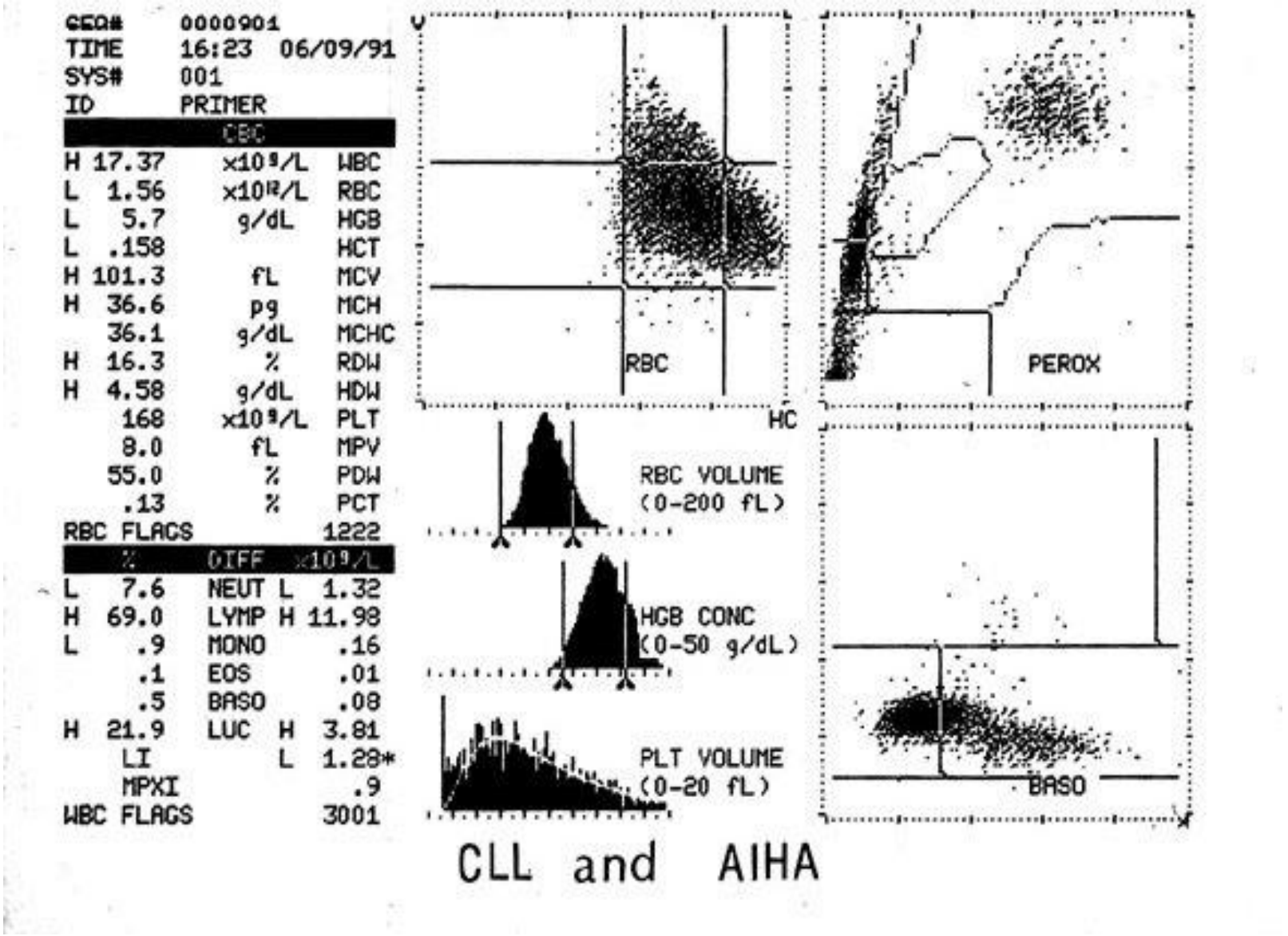
May-Grunwald-Giemsa-stained peripheral blood. High power magnification showing '**smear cell**' (arrowed).

# Laboratory findings (2)

- Clonal expansion of B (99%) or T(1%) lymphocyte
  - In B-cell CLL clonality is confirmed by
    - the expression of either κ or λ light chains on the cell surface membrane
    - the presence of unique idiotypic specificities on the immunoglobulins produced by CLL cells
    - by immunoglobulin gene rearrangements
    - typical B-cell CLL are unique in being CD19+ and CD5+

- 10 - 25% of patients with CLL develop autoimmune hemolytic anemia, with a positive direct Coombs' test

- The marrow aspirates shows greater than 30% of the nucleated cells as being lymphoid




**Autoimmuhemolitic anaemia (AIHA)**

# 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

# Investigations

- Pretreatment studies of patients with CLL should include examination of:
  - complete blood count
  - peripheral blood smear
  - reticulocyte count
  - Coomb's test
  - renal and liver function tests
  - serum protein electrophoresis
  - immunoglobulin levels
  - plasma β2 microglobulin level
- The immunophenotyping should be carried out to confirm the diagnosis
- Bone marrow biopsy and cytogenetic analysis is not routinely performed in CLL

# 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

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- 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

Symptoms B -night sweats and fever

# 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

- WATCH AND WAIT

- Treatment is reserved for patients with:

1. low- or intermediate risk disease who are symptomatic or have progressive disease (increasing organomegaly or lymphocyte doubling time of less than 12 months),

2. patients with high -risk disease

# Treatment

- Alkylating agents (chlorambucil, cyclophosphamide)
- Nucleoside analogs (cladribine, fludarabine)
- Monoclonal antibodies
  (anti CD 20- rituximab, anti CD 52 – alemtuzumab)
- Bone marrow transplantation (young patient with aggressive CLL) – very rare
- And systemic complications requiring therapy
  - antibiotics
  - immunoglobulin
  - steroids
  - blood products

# Multiple Myeloma

- Definition:

  B-cell malignancy characterised by abnormal proliferation of plasma cells able to produce a monoclonal immunoglobulin ( M protein )

- Incidence:

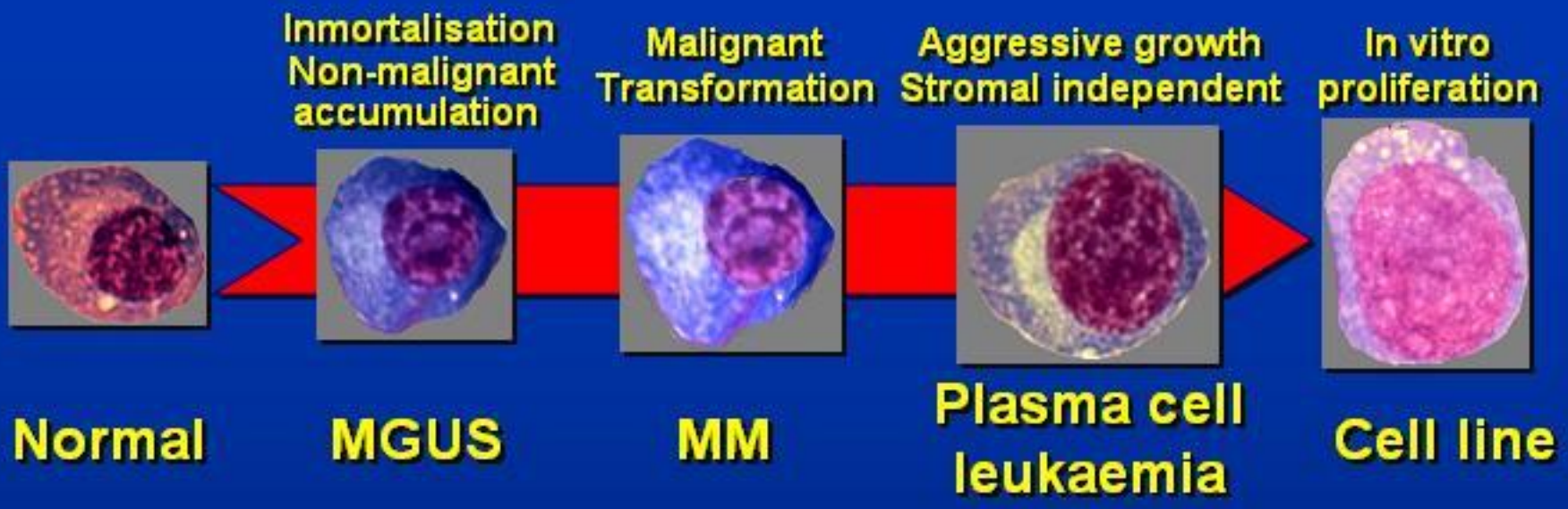
  3 - 9 cases per 100000 population / year

  more frequent in elderly

  modest male predominance

- Clinical forms:
  multiple myeloma
  solitary plasmacytoma
  plasma cell leukemia
- M protein:

  - is seen in 99% of cases in serum and/or urine
    IgG > 50%,  IgA 20-25%, IgE i IgD 1-3%
    light chain 20%
  - 1% of cases are nonsecretory




Karyotypic Instability / Rb del./RAS mut.

**Primary IGH Translocations**

t(11;14), t(4;14)
t(14;16), t(6;14)

**Secondary IGH Translocations**

t(8;14), t(2;8)
t(8;22), t(14;20)

San Miguel J. *Hematol J*. 2003;4(suppl 3):201-207.

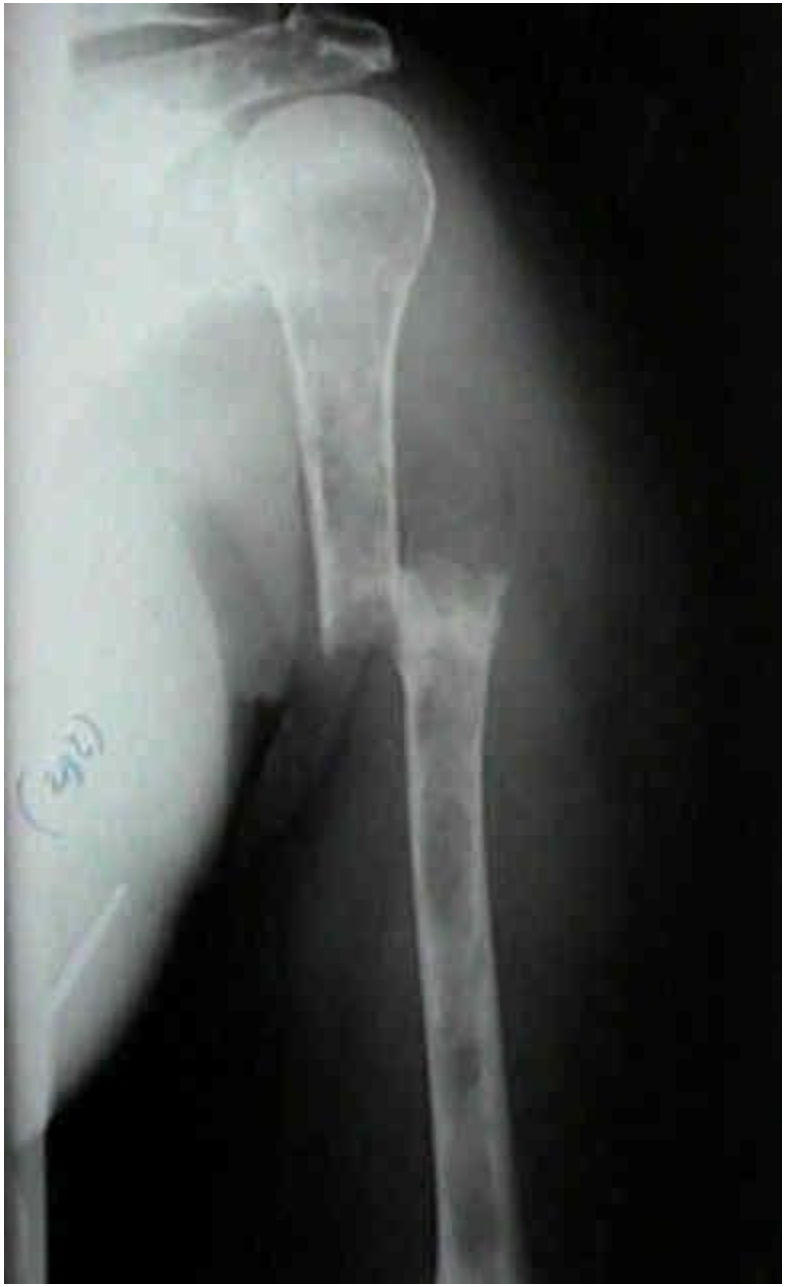
Clinical manifestations are related to malignant behavior of plasma cells and abnormalities produced by M protein

- plasma cell proliferation:
  - multiple osteolytic bone lesions
  - hypercalcemia
  - bone marrow suppression ( pancytopenia )

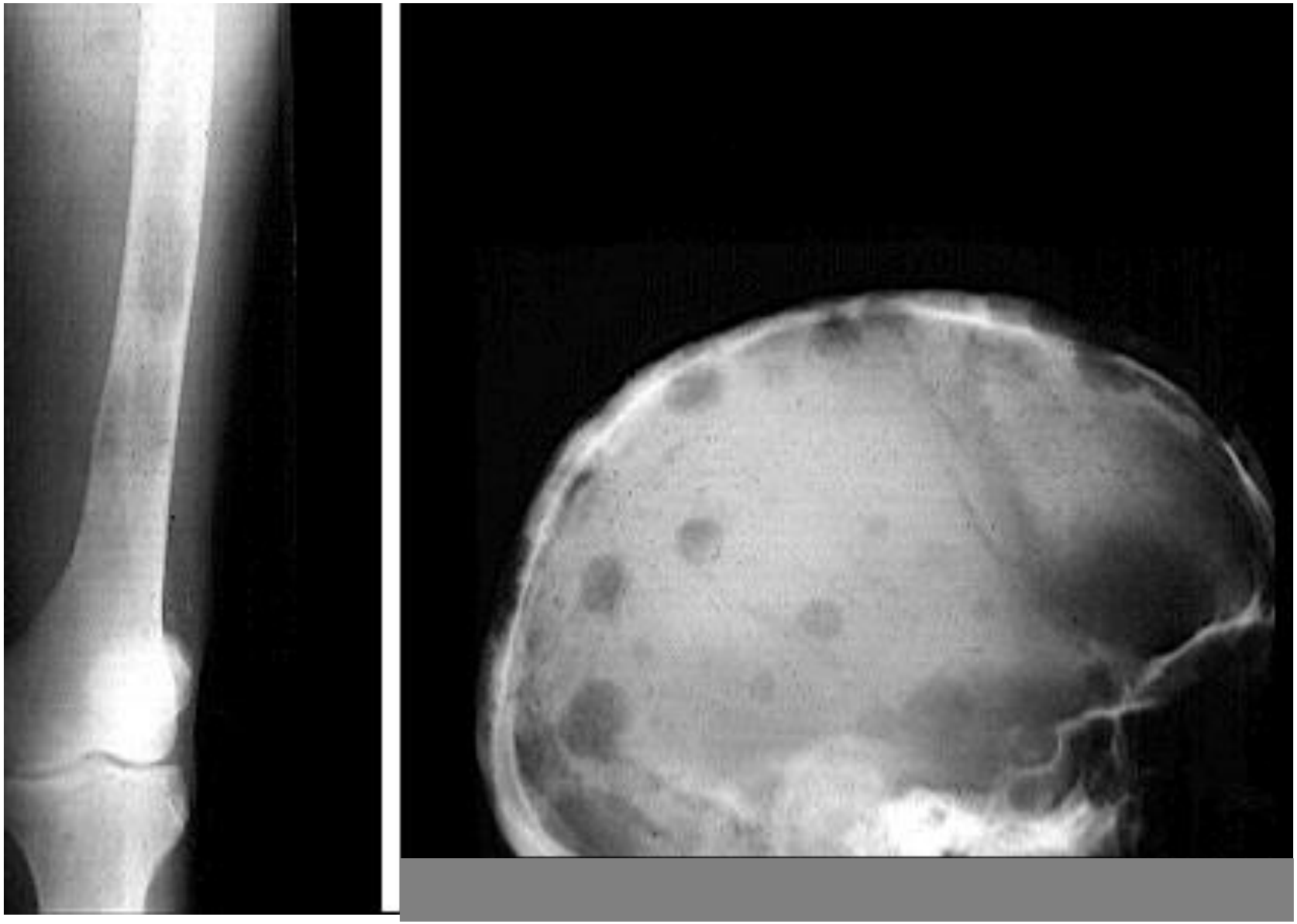
- monoclonal M protein
  - decreased level of normal immunoglobulins
  - hyperviscosity

Clinical symptoms:

- bone pains,
- pathologic fractures
- weakness and fatigue
- serious infection
- renal failure
- bleeding diathesis



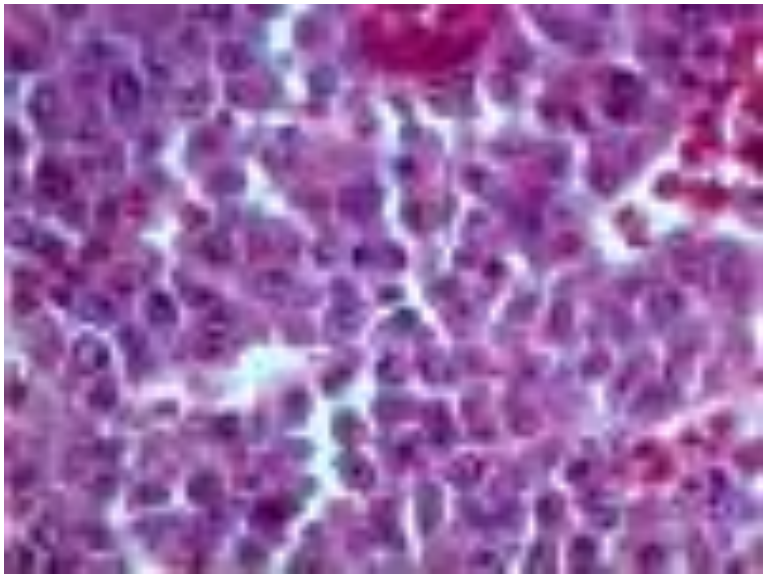
Pathological fracture of the bone due to plasmocytoma



Bones (especialy skull) demonstrates characteristic rouned ‘’pounched out’’ lesions of multiple myeloma.

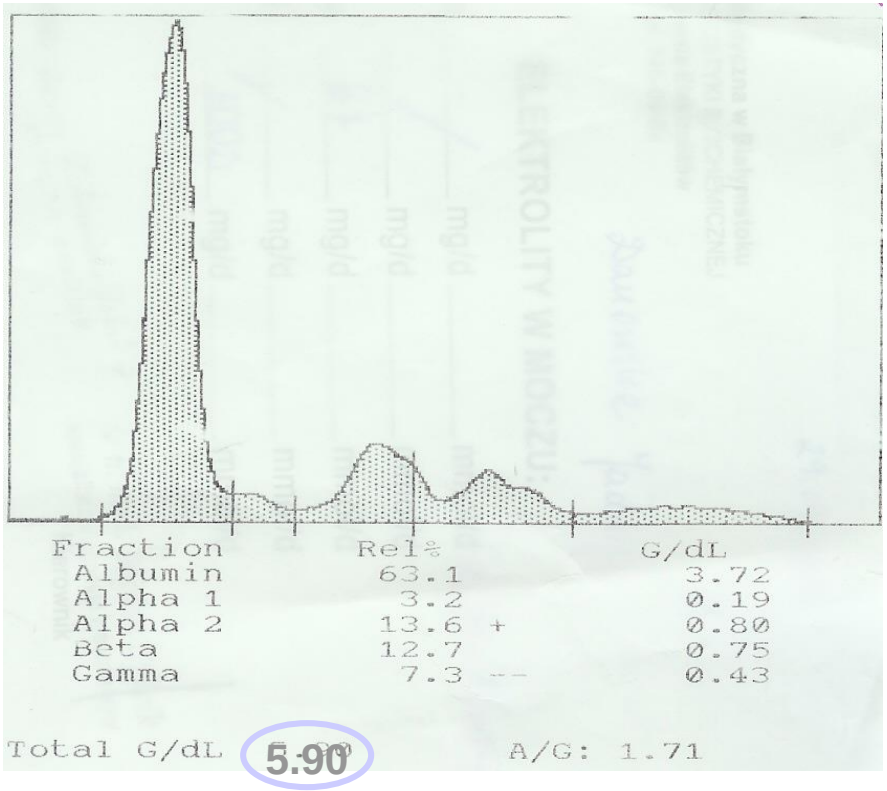
# Laboratory tests:

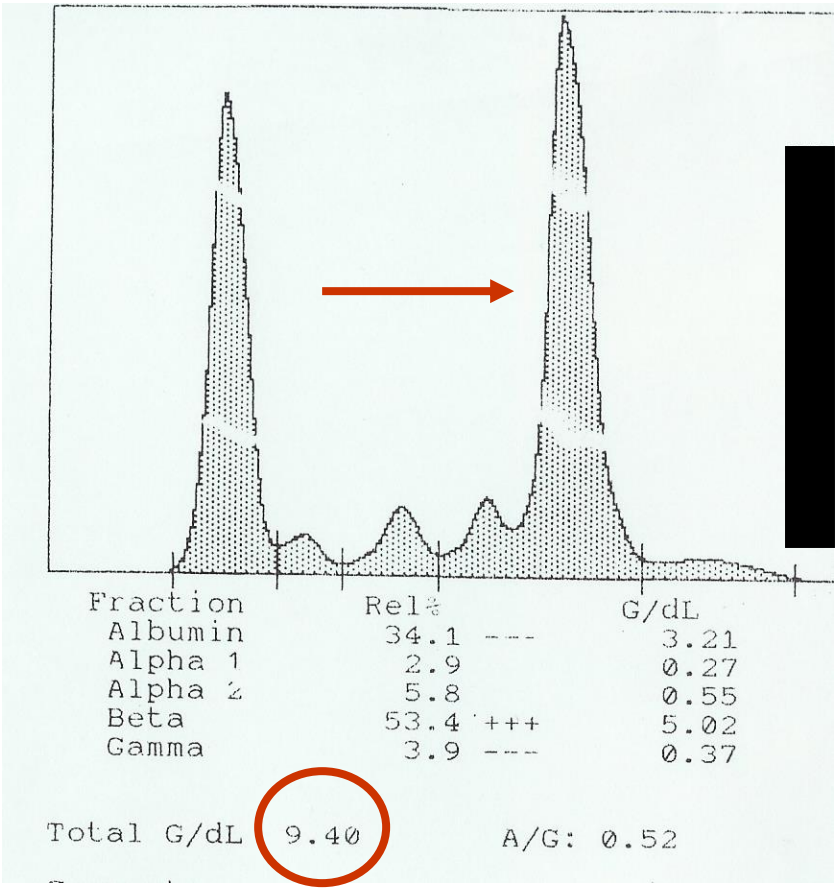
- ESR > 100
- anaemia, thrombocytopenia
- rouleaux in peripheral blood smears
- marrow plasmacytosis > 10 -15%
- hyperproteinemia
- hypercalcemia
- proteinuria
- azotemia



Bone marrow: the plasma cells of multiple myeloma. Usually, the plasma cells are differentiated enough to retain the function of immunoglobulin production.

| Test | Wynik | Jedn. | Uwagi | Zakres | Min | Max | Rozc. |
|---|---|---|---|---|---|---|---|
| IgA | 4477 | mg/dl | R | (---)* | 69 | 382 | 1+50.0 |
| IgG | 1399 | mg/dl | R | (---*) | 723 | 1685 | 1+50.0 |
| IgM | 325 | mg/dl | R | (---)* | 63 | 277 | 1+100.0 |




Patients with multiple myeloma show a "spike" in the β or γ regions of the serum protein electrophoresis. The abnormal antibody protein appears as a tall spike, because the molecules of M proteins are identical in size and therefore all sort out at exactly the same point. Urine electrophoresis can detect Bence Jones proteins.

**Table 2:** Diagnostic Criteria for MGUS, Asymptomatic Myeloma and Symptomatic Myeloma (International Myeloma Working Group, 2003)

| **MGUS** | **Asymptomatic myeloma** | **Symptomatic myeloma*** ** |
|---|---|---|
| M-protein in serum <30 g/L | M-protein in serum >30 g/l *and/or* Bone marrow clonal plasma cells >10% | M-protein in serum and or urine** |
| Bone marrow clonal plasma cells <10% and low level of plasma cell infiltration in a trephine biopsy (if done) | | Bone marrow (clonal) plasma cells |
| No myeloma-related organ or tissue impairment (including bone lesions or symptoms<br>No evidence of other B-cell lymphoproliferative disorder or light chain associated amyloidosis or other light chain, heavy chain or immunoglobulin-associated tissue damage* | No myeloma-related organ or tissue impairment (including bone lesions or symptoms | Myeloma-related organ or tissue impairment (including bone lesions or symptoms |

# Treatment of Multiple Myeloma

- Patients < 65 years
  - high-dose therapy with autologous stem cell transplantation
  - allogeneic stem cell transplantation

    ( conventional and „mini”)

- Patients > 65 years
  - conventional chemotherapy
  - non-myeloablative therapy with allogeneic transplantation („mini”)

- Autologous transplantation
  - patients < 65-70 years
  - treatment related mortality 10-20%
  - response rate 80%
  - long term survival 40-50%

- Conventional allogeneic transplantation
  - patients < 45-50 years with HLA-identical donor
  - treatment related mortality 40-50%
  - long term survival 20-30%

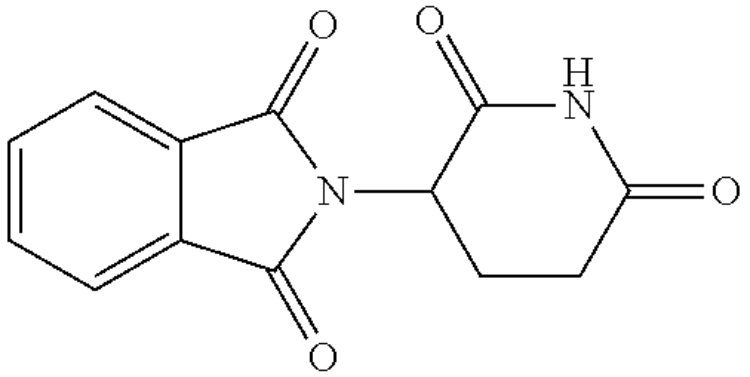
- Conventional chemotherapy
  - Melphalan +/- Prednisone
  - VAD (Vincristin, Adriamycin, Dexamethasone)

- New method
  - non-myeloablative therapy and allogeneic transplantation
  - Thalidomid, Lenalidomide
  - Bortezomib (Valcade)

- Supportive treatment
  - biphosphonates, calcitonin
  - recombinant erythropoietin
  - immunoglobulins
  - plasma exchange
  - radiation therapy

# THALIDOMIDE

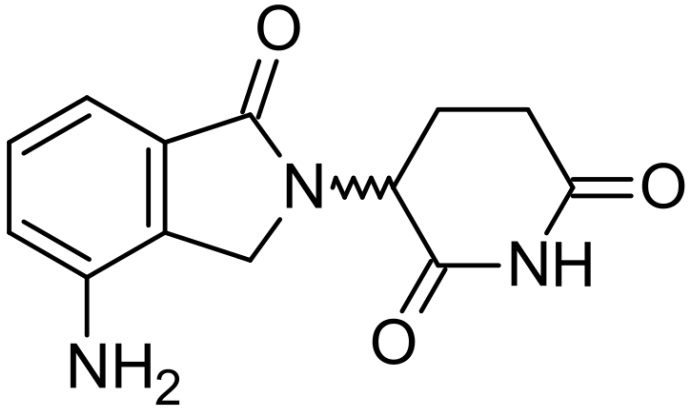
- Immunomodulatory drug
- Mechanism of action:
  - induce growth arrest associated with apoptosis in MM cells
  - inhibit adhesion of MM cells to bone marrow stromal cells (BMSCs)
  - reduce expression of IL-6 and TNF-α
  - Antiangiogenic effect (VEGF, bFGF)
  - Induce T-cell stimulation and proliferation, with release of IL-2 and INF-γ
- Teratogenic effects- „birth defects crisis”




Thalidomide

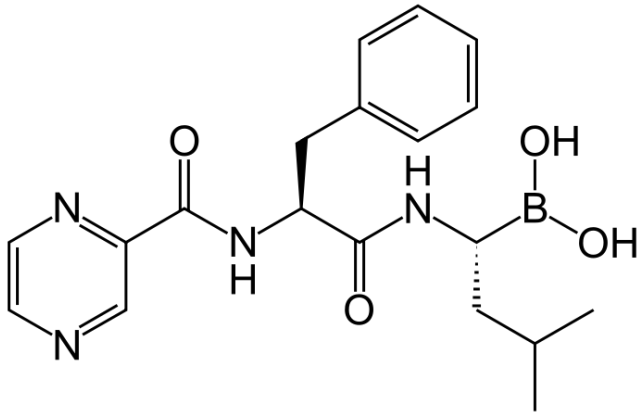
# LENALIDOMIDE

- Structural thalidomide analogues
- Like thalidomide inhibits tumour angiogenesis, secrete cytokines and tumour proliferation through the induction of apoptosis
- Substantially more powerful and has fewer side effects — except for greater myelosuppression



# BORTEZOMIB

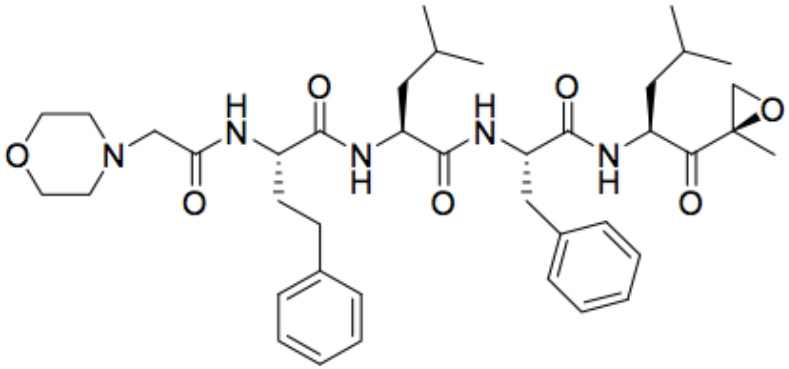
- First therapeutic proteasome inhibitor approved by FDA (2003)




- Mechanism of action:
  - induction apoptosis myeloma cells
  - inhibit proliferation of plasma cells
  - antiangiogenic effect
  - disrupts the interaction between bone marrow strome cells (BMSC) and MM cells, through the downregulation of adhesion molecules and reduced NF-kB-dependent secretion of cytokines from BMSC
- increases the activity of other drugs, i.e.. melphalan, doxorubicin
- the most common side effect is peripheral neuropathy- 30-50% of patients receiving the drug

# CARFILZOMIB

- new drug next-generation proteasome inhibitor
- approved by FDA (2012)  as single-agent activity in patients with relapsed and refractory multiple myeloma
- selectively and irreversibly inhibits the chymotrypsin-like activities of proteasome
- In preclinical studies, carfilzomib showed greater selectivity than bortezomib for the proteasome without inhibiting off-target proteases, and had antiproliferative activity in cells resistant to bortezomib



# THE MOST COMMON SCHEME MM THERAPY

- CTD (cyclophosphamide, thalidomide, dexamethasone),
- VAD (vincristine, doxorubicin, dexamethasone)
- PAD (bortezomib, doxorubicin, dexamethasone)
- MPT (melphalan, prednisone, thalidomide)
- VMP (bortezomib, melphalan, prednisone)

# Myelodysplastic syndrome (MDS)

- It is a term for a heterogeneous collection of haemopoietic stem cell disorders affecting older adults.
- There is underlying ineffectiveness of haemopoiesis that results in dysplasia of bone marrow precursors and peripheral cytopenias.

- Moderate anaemia is the most common clinical problem in MDS patients, but complete myeloid bone marrow failure also occurs leading to death from bleeding or infection.
- Approximately half of the patients transform to AML.

# MDS background

- Pathobiology
  - The cardinal features of MDS are
    - Increased marrow proliferation
    - Failure of stem cells to differentiate
    - And increased marrow apoptosis.
  - The disease is of clonal origin
  - Chromosomal abnormalities are detectable in 30-70% of patients. The no. of chromosomal abn. may correlate with the risk of progression to AML.

# The most common chromosomal abnormalities in patients with MDS

- Deletion 5q
- Deletion 20q
- Lack of chromosome Y

„good” karyotype

- Trisomy chromosome 8

- Monosomy chromosome 7
- Complex chromosomal rearrangements (CCRs) (≥ 3)

„bad” karyotype

# WHO classification MDS

- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with excess blasts-1 (RAEB-1)- 5-9% blasts
- Refractory anemia with excess blasts-2 (RAEB-2)- 10-19% blasts
- Myelodysplastic syndrome – unclassified (MDS-U)
- MDS associated with isolated del(5q)
- Therapy-related MDS (t-MDS)

# International Prognostic Scoring System (IPSS)

- The most practical and validated MDS classification system currently available to clinicians is the IPSS which predicts both survival and risk of transformation to AML based on:
  - Marrow blast %
  - Cytogenetics
  - And number of cytopenias.

**Table 3.** International Prognostic Scoring System (IPSS) for MDS

| IPSS Score | Risk Group | % of Patients | When 25% Evolve to AML | Median Survival |
|---|---|---|---|---|
| 0 | Low risk | 31% | 9.4 years | 5.7 years |
| 0.5-1.0 | Int-1 risk | 39% | 3.3 years | 3.5 years |
| 1.5-2.0 | Int-2 risk | 22% | 1.1 years | 1.2 years |
| ≥2.5 | High risk | 8% | 0.2 years | 0.4 years |

Abbreviation: Int, intermediate.

# The scope of MDS

- MDS is primarily a disease of the elderly, with a median age at diagnosis of between 60-80 years.
- The incidence is approximately double that of AML.
- The recent increase in MDS incidence may be related to growing awareness, better diagnosis, and an aging population.

# Clinical signs and symptoms

- The common symptoms at presentation, fatigue or weakness, are attributable to cytopenia.
- Easy bruising, ecchymosis, epistaxis, gingival bleeding, and bacterial infections may also be encountered.
- 20-40 % or more of patients die of infections and/or haemorrhagic complications.

# Conventional therapies

- Supportive care:

-blood products with deferoxamine,

-haemopoietic growth factors (EPO and GM-CSF)

-antibiotics.

- Hormone suppressive therapy with danazol has been used to help resolve anaemia and reduce transfusion requirements.

- Low intensity chemotherapy

  with cytarabine induces response in approximately 30% of MDS patients. However, the relapse rate is high, and there is no improvement in overall survival.

- Bone marrow transplantation is currently the only potentially curative therapy for MDS patients

# Conclusion

- In the majority of patients with MDS who are not eligible for allogenic transplantation, the disease is fatal.
- Approximately 2/3 of patients die within 3-4 years of diagnosis.
- Patients with high risk MDS generally survive approximately one year.