DIAGNOSIS AND TREATMENT OF BLOOD CANCERS IN PRIMARY HEALTHCARE

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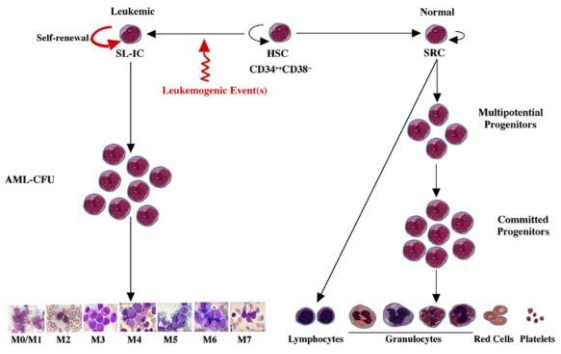
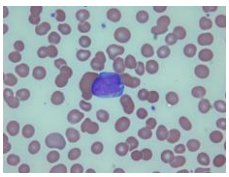
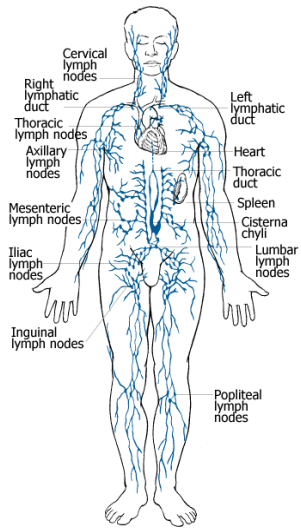
Haemato-oncology



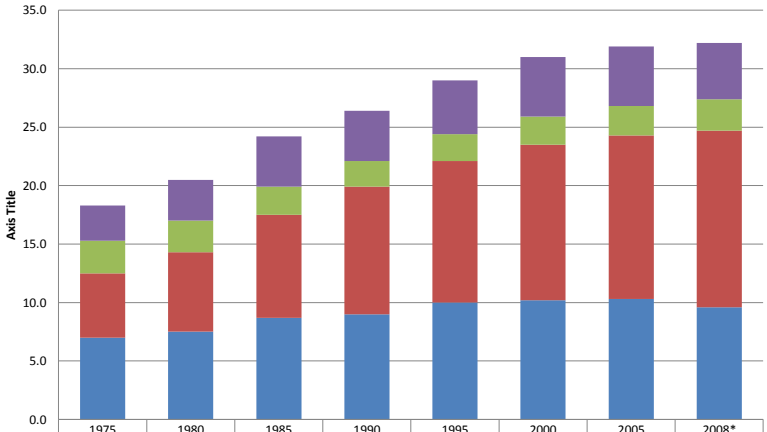




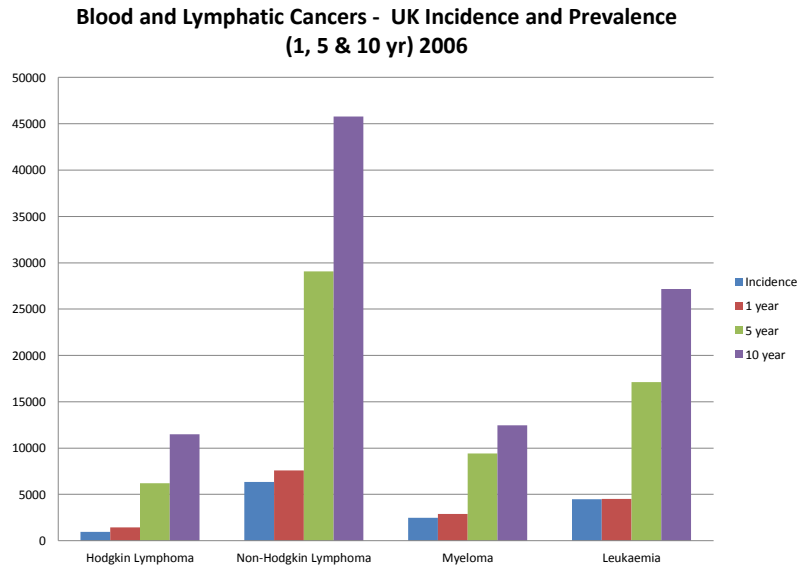
Haem-Onc Stats (LLRF)

- 5% of all cancers are cancers of the blood
- In the UK approximately 60 people every day are diagnosed with a cancer of the blood.
- Blood cancers are the most common cancers in men and women aged 15-24.
- They are the main cause of cancer death in people aged 1-34 years
- One in 45 of the UK population will die of leukaemia, lymphoma or myeloma

Age-standardised rates of Haematological Cancers per 100,000 Persons, Great Britain



	1975	1980	1985	1990	1995	2000	2005	2008*
MYEL	3.0	3.5	4.3	4.3	4.6	5.1	5.1	4.8
HD	2.8	2.7	2.4	2.2	2.3	2.4	2.5	2.7
NHL	5.5	6.8	8.8	10.9	12.1	13.3	14.0	15.1
LEUK	7.0	7.5	8.7	9.0	10.0	10.2	10.3	9.6



Basic questions: What to do with…

- Low blood counts
- High blood counts
- Patients on treatment
- Patients finished treatment

Classification

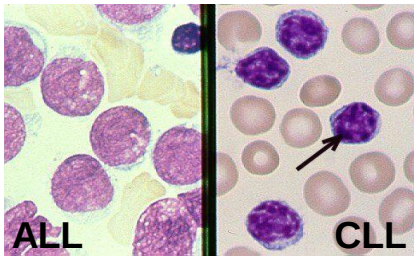
Acute vs Chronic

Acute - rapid onset and progression
Chronic - slow onset and progression

Lymphoid vs Myeloid

Lymphoid - affecting lymphocytes
Myeloid - affecting any other type of white cell

- Acute myeloid
- Acute lymphoblastic
- Chronic myeloid
- Chronic lymphocytic



Daily Requirements

Every day:

~~200 Billion Red Cells~~

~~10 Billion White cells~~

~~400 Billion Platelets~~

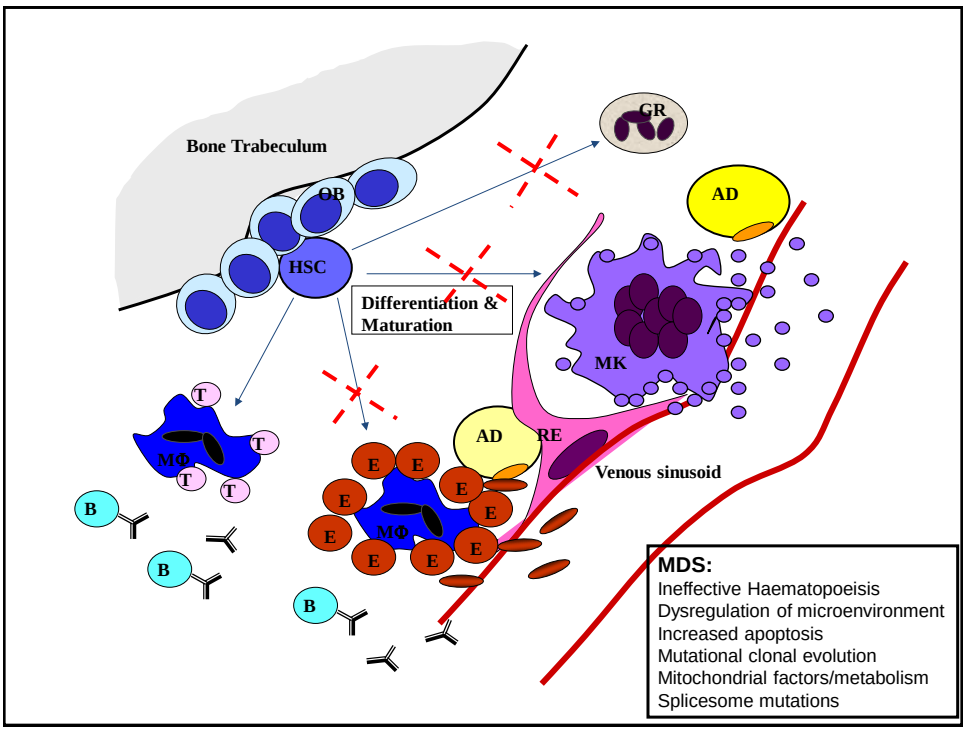
Types of BM Failure

- Aplasia
- Infiltration
- 1° BM malignancy

Clinical Solutions:

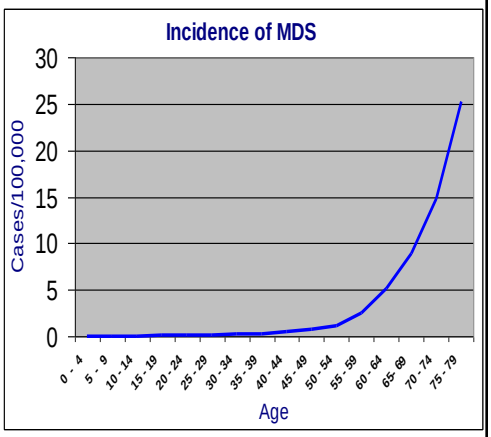
•Supportive care (transfusions, etc)

•Treat cause (chemotherapy)



Myelodysplastic syndromes (MDS)

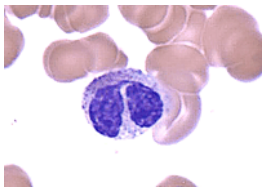
- **This is a group of conditions in which blood cell production is severely disrupted.**
- **Majority of cases occur in later life.**
- **Small proportion of patients may develop secondary AML.**
- **Only potentially curable treatment is a stem cell transplant.**



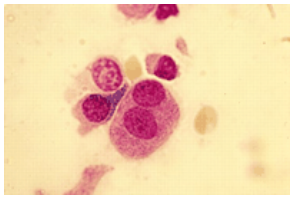
MDS Diagnosis for Primary Care Physician

- Fatigue
- Bruising / Bleeding
- Recurrent Infections
- Weight loss
- Night sweats

MDS Diagnosis for Primary Care Physician



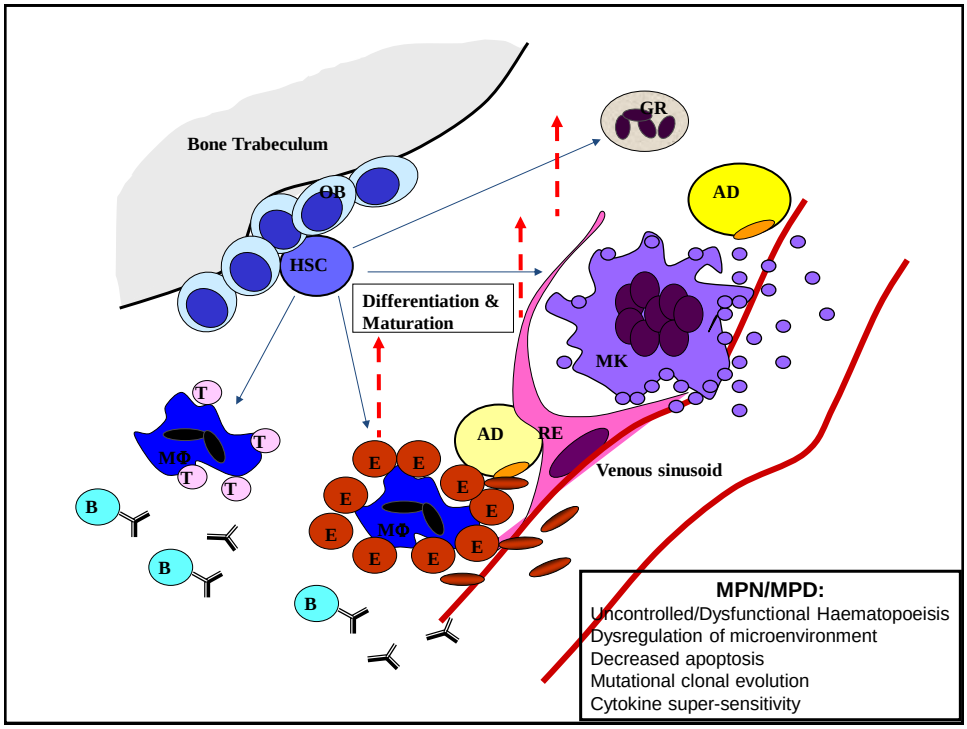
Persistent (>6 months):



- Low Hb
- Low plts
- Low ANC
- High MCV
- Normal iron studies, Vit B12, Folate, TSH
- No Medical cause (e.g. infection)
- No Iatrogenic cause (e.g. medicines)

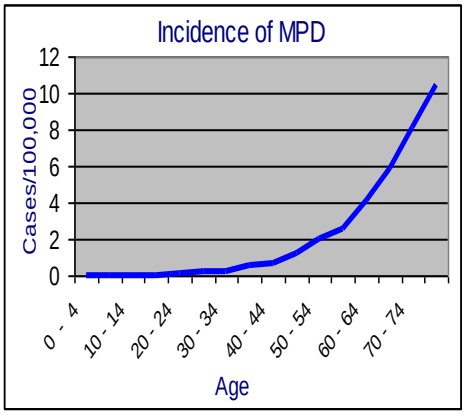
MDS-Treatment Strategies

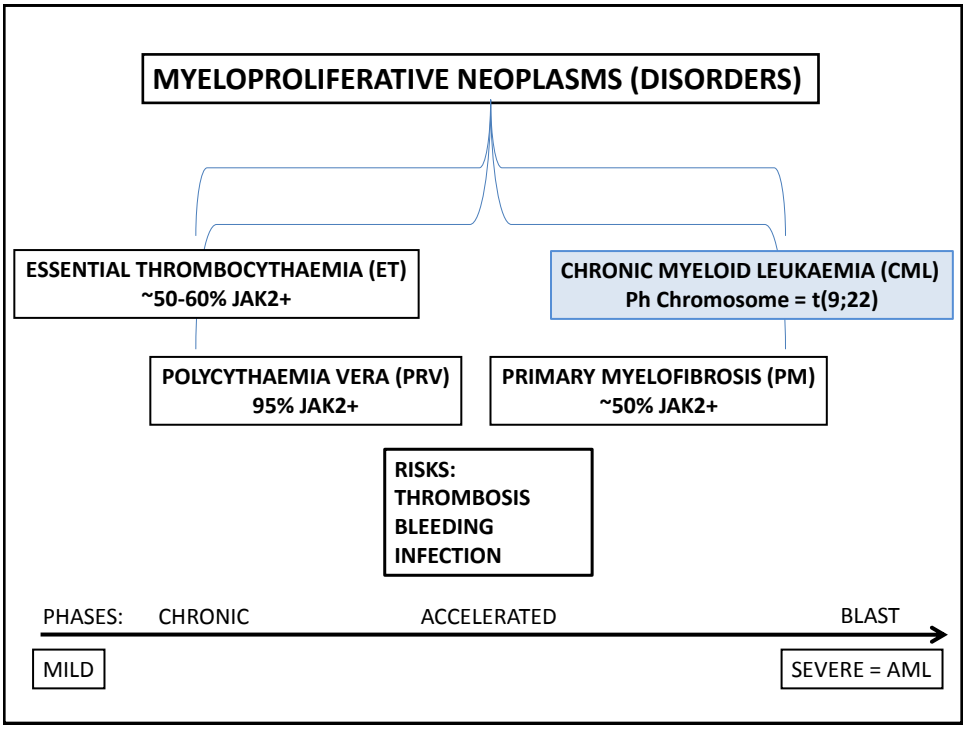
- Supportive care
- Epo/G-CSF
- Chemotherapy (a la AML Rx)
- Demethylating/Hypomethylating agents (Azacytidine/Dacitadine)
- Allogeneic Stem Cell Transplantation



Myeloproliferative disorders (MPD)

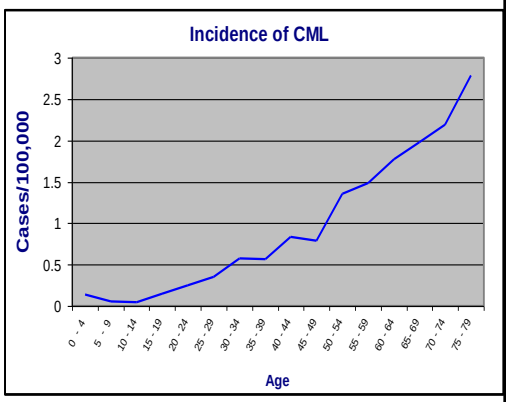
- This is a group of conditions in which there is excess production of one or more type of blood cell in the bone marrow.
- The MPDs are: polycythaemia vera, essential thrombocythaemia and myelofibrosis.
- Majority of cases occur in later life.
- Small proportion of patients may develop secondary AML.
- Treatment aimed at mainly controlling, but not curing disease.





Chronic myeloid leukaemia (CML)

- Occurs at all ages though rarely in children below the age of 15.
- Incidence increases with age.
- 95% of patients have the Philadelphia chromosome (t9;22).
- New drug Glivec has a significant impact by directly targeting the Philadelphia chromosome.

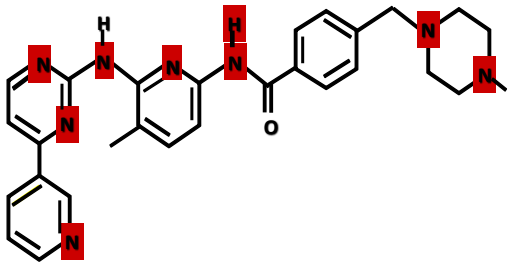


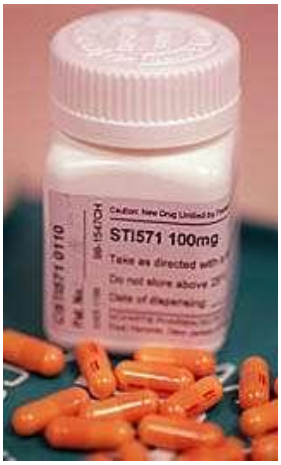
Presentation:

High WBC / Splenomegaly / Constitutional Sx

Imatinib mesylate (STI571 - Glivec®)

$(C_{30}H_{35}N_7SO_4)$





(From Novartis Pharma)

MYELOPROLIFERATIVE NEOPLASMS (DISORDERS)

ESSENTIAL THROMBOCYTHAEMIA (ET)
~50-60% JAK2+

CHRONIC MYELOID LEUKAEMIA (CML)
Ph Chromosome = t(9;22)

POLYCYTHAEMIA VERA (PRV)
95% JAK2+

PRIMARY MYELOFIBROSIS (PM)
~50% JAK2+

RISKS:
THROMBOSIS
BLEEDING
INFECTION

PHASES: CHRONIC → ACCELERATED → BLAST

MILD → SEVERE = AML

MPN Diagnosis for Primary Care Physician

- Fatigue / Lethargy / Headaches
- Bleeding / Bruising
- Pletho
- Ischae
- Erythr
- Blood nus Thrombosis, TIA
- Pruritus / Night Sweats
- Early satiety / Weight loss

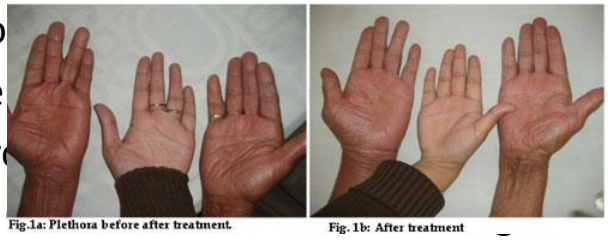
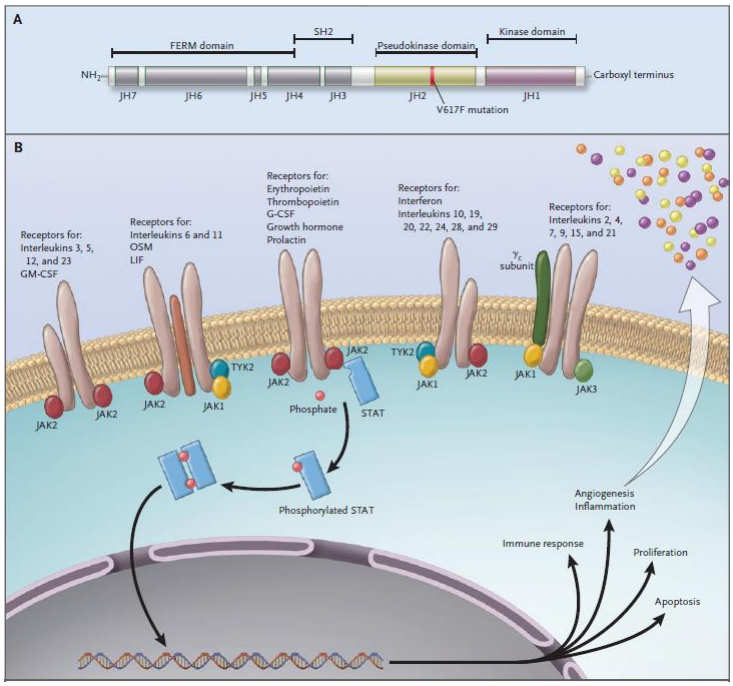


Fig.1a: Plethora before after treatment. Fig. 1b: After treatment

MPN Diagnosis for Primary Care Physician

- High platelets (exclude iron deficiency)
- High Hb (esp. with iron deficiency = PV)
- High WBC
- Exclude other causes
  - Hypoxia / COPD
  - iron deficiency
  - Inflammation
  - infection



Cytokine signalling via JAK1/JAK2

A. Vannucchi, NEJM, Sept 2010

RISK STRATIFICATION OF PV AND ET PATIENTS

POLYCYTHAEMIA

High risk PV ANY ONE of the following:

- **Age >60** years
- Previous documented **thrombosis, erythromelagia** (if refractory to aspirin)
- **Platelets > 1000** x 10^9/L
- Diabetes or hypertension requiring pharmacological therapy*
- Significant (i.e. > 5cm below costal margin on palpation) or symptomatic (pain, early satiety) splenomegaly. NB this may be an indication for treatment rather than a risk factor *per se*

Low risk PV – patients not having any of the above risk factors.

ESSENTIAL THROMBOCYTHAEMIA

High risk ET ANY ONE of the following factors:

- **Age > 60** years
- **Platelet count > 1500** x 10^9/L
- Previous **thrombosis, erythromelagia** (if refractory to aspirin)
- Previous **hemorrhage related to ET**
- Diabetes or hypertension requiring pharmacological therapy*

Low risk ET* patients <40yrs lacking any of the above markers of high risk disease

Intermediate risk ET* patients 40-60 yrs lacking any of the above markers of high risk disease

Claire Harrison, Hematology, 2010

RECOMMENDATIONS FOR THERAPY IN ET AND PV PATIENTS

POLYCYTHEMIA VERA

- **ALL patients assess and manage cardiovascular risk factor; low dose aspirin** (unless contraindicated); venesection to target PCV 0.45.
- **HIGH RISK PATIENTS**

> 60 years Hydroxycarbamide; 2nd line IFN, if >75 yrs busulfan or 32P
<60 years IFN; 2nd line hydroxyurea, or anagrelide*

ESSENTIAL THROMBOCYTHEMIA

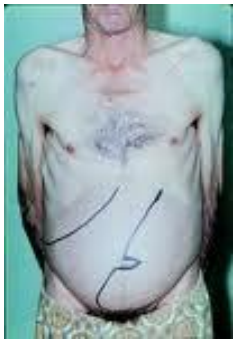
- **ALL patients assess and manage cardiovascular risk factor; low dose aspirin** (unless contraindicated).
- **HIGH RISK PATIENTS**

> 60 yrs Hydroxycarbamide; 2nd line IFN, anagrelide* alone or in combination; if >75 yrs busulfan or 32P
<60 yrs Hydroxycarbamide or IFN; 2nd line IFN, anagrelide* alone or in combination

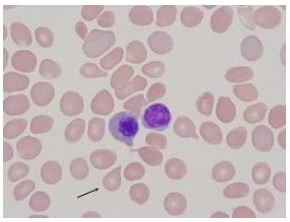
*Current British Guidelines recommend regular monitoring of patients treated with anagrelide for the development of fibrosis.

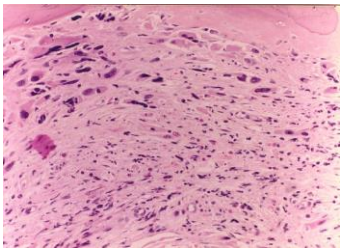
Claire Harrison, Hematology, 2010

PRIMARY MYELOFIBROSIS
(also SECONDARY FROM ET/PV)

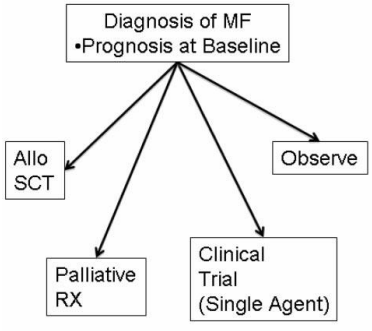


High WBC
Low plts / Hb
Fatigue / Bleeding / Bruising
Sweats
Urticaria / pruritus
Early satiety / Wt loss
Wasting
Leukoerythroblastic Blood Film



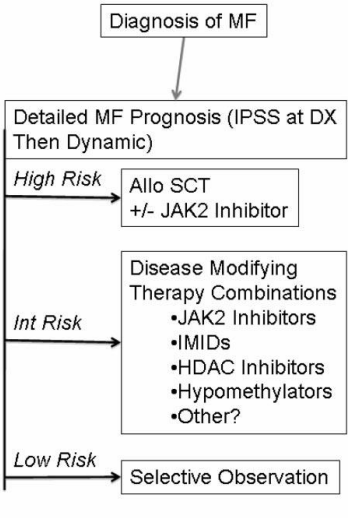


Managing MF 2010



MAYO CLINIC

Managing MF Future



Ruben Mesa, Hematology, 2010

MYELOPROLIFERATIVE NEOPLASMS (DISORDERS)

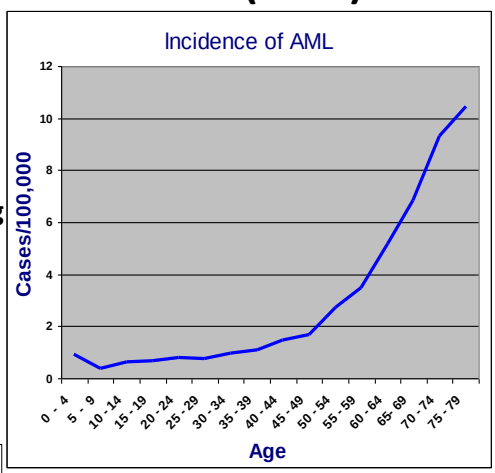
- **ESSENTIAL THROMBOCYTHAEMIA (ET)** ~50-60% JAK2+
  - **POLYCYTHAEMIA VERA (PRV)** 95% JAK2+
- **CHRONIC MYELOID LEUKAEMIA (CML)** Ph Chromosome = t(9;22)
  - **PRIMARY MYELOFIBROSIS (PM)** ~50% JAK2+

PHASES: CHRONIC → ACCELERATED → BLAST

MILD — SEVERE = AML

Acute Myeloid Leukaemia (AML)

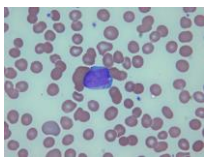
- Affects all ages, but is most common in later life.
- About 25% of cases occur in people under the age of 25.
- Treatable and in some cases curable with very aggressive drug treatment.
- Secondary AML may occur as a result of a previously diagnosed bone marrow condition.
- Secondary AML is usually not as responsive to treatment.



0.01-0.02% of the population

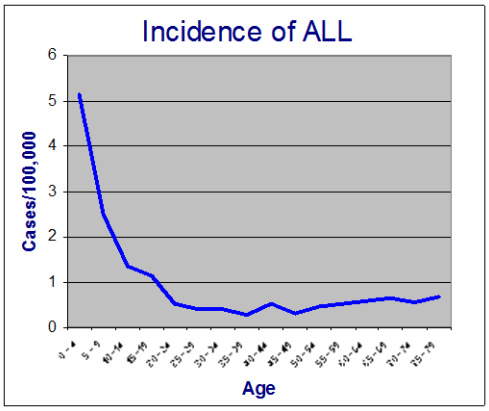
Without treatment, death within days to months

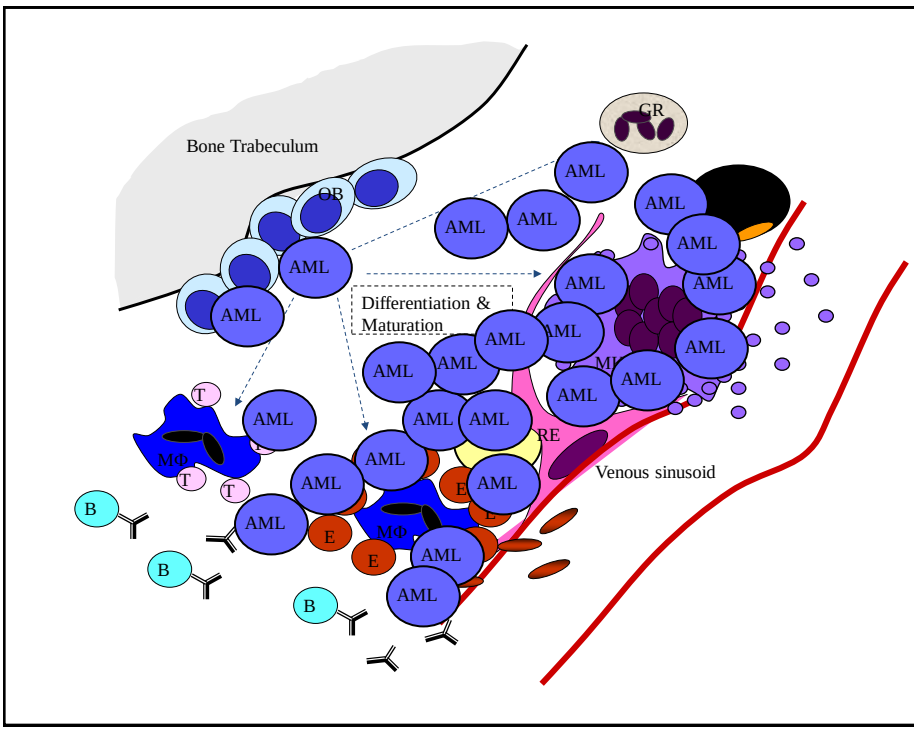
Clinical presentation….anything



Acute lymphoblastic leukaemia in adults

- Occurs most commonly between ages of 15-25 and over the age of 75.
- Treatable and in some cases curable with aggressive drug treatment.
- Ph+ve (t9;22) ALL is more frequent in adults than in children.
- No identifiable cause in most cases.

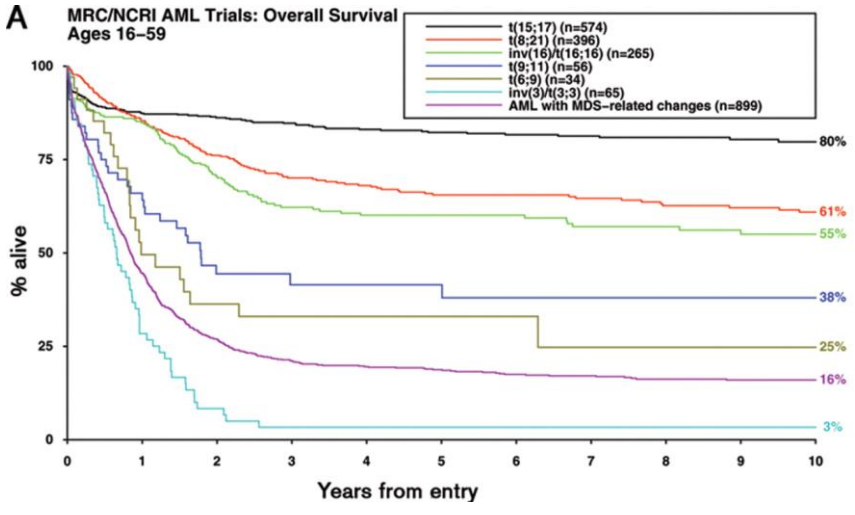




ACUTE LEUKEMIA TREATMENT PLAN

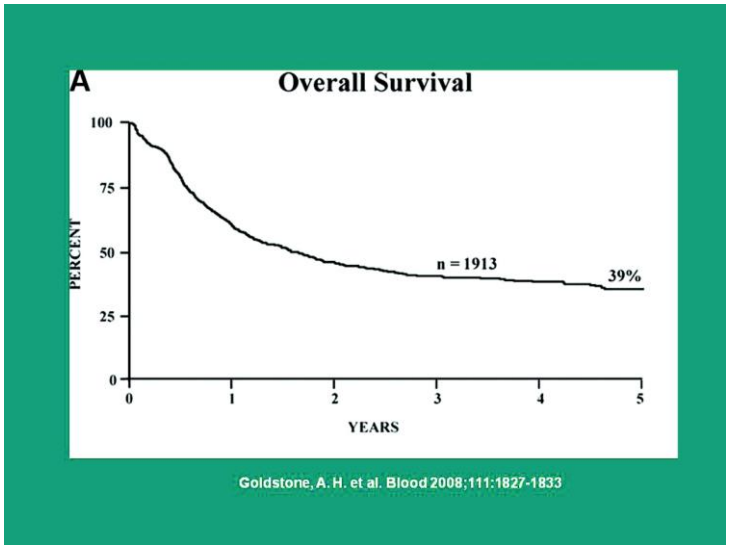
- INDUCTION
- INTENSIFICATION
- CONSOLIDATION
- MAINTENANCE vs. TRANSPLANT

Impact of karyotype on outcome in younger adults with AML



Grimwade, D. et al. Hematology 2009;2009:385-395

Overall survival of 1913 patients with ALL in UKALL XII/ECOG 2993



Marks, D. I. Hematology 2010;2010:13-20

TREATMENT FOR PATIENTS WITH BLOOD CANCERS

CHEMOTHERAPY

RADIOTHERAPY

IMIDS / SPECIFIC INHIBITORS

STEM CELL TRANSPLANTS

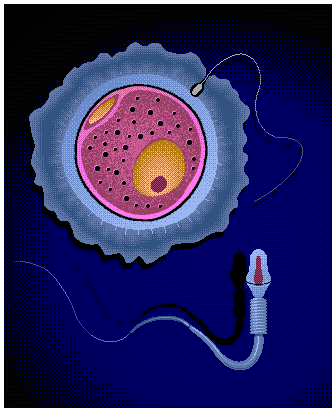
Late effects of treatment

Growth
CNS Rx in children impairs spine growth and ↓'s levels of growth hormone

Timing of puberty
girls: menarche earlier
boys: growth spurt in puberty ↓'ed

Fertility
possible infertility in both males and females

Obesity
common late problem in children Rx'ed for ALL

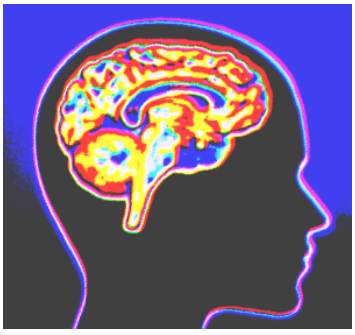


Late effects of treatment

IQ
CNS Rx in children may affect intellectual ability - IQ scores < untreated children

Cardiac Abnormality
drugs used in standard Rx for ALL/AML may cause cardiac abnormalities in children and adults

Secondary Cancers
One of the most devastating late effects is the possible development of a second cancer - 2° AML



LATE EFFECTS OF CHEMOTHERAPY
LONG-TERM / SURVIVORSHIP MONITORING

ANNUAL:

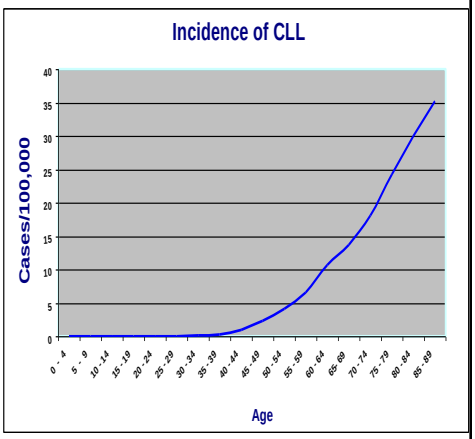
- Review of Systems & Physical Examination
- CVS risk-assessement: BMI / BP / HDL / LDL / TG lipids/ Fast glc / HbA1c
- U&Es / LFTs / Serum Ferritin
- AIS & ESR / Igs & SPEP
- TSH / FSH / LH / Testosterone / Sperm Counts at 1, 2 & 3 yrs post-Rx
- ECG / Dental review
- Lifestyle advice (smoking / EtOH / stress / fitness / protection against sun)
- Enhanced Cancer Screening: PSA / cervical and breast screening / Skin review / Screening according to symptoms (e.g. colonoscopy / CT)

EVERY 3-5 YEARS: DEXA / ECHO / Ophthalmology review for early cataracts

BREAST SCREENING BEGINS AT 30 YO OR 8 YRS POST TBI, WHICHEVER LATER

Chronic lymphocytic leukaemia (CLL)

- **Most common form of leukaemia in the West.**
- **Majority of cases occur in later life.**
- **Treatable but in most cases not curable.**
- **Significant morbidity and mortality.**
- **Increasing numbers of cases detected at routine screening of older population.**
- **New drugs are having a significant impact.**

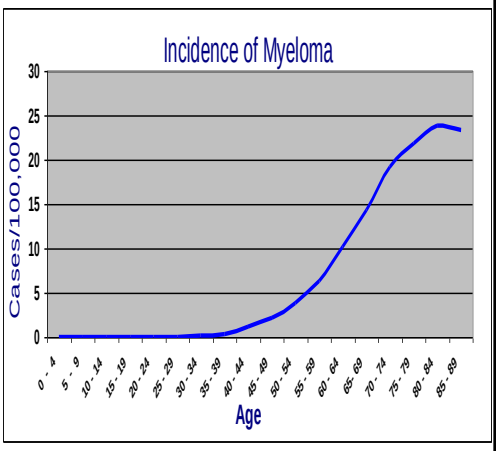


Key Points:

Increased risk of infections – use prophylactic antibiotics
Increased risk of other primary cancers - low threshold to screen
Familial component – significance of the family hx

Multiple myeloma

- **Malignant clonal proliferation of plasma cells and plasmablasts in BM**
- **Most cases produce monoclonal gammopathy, detected in serum or urine**
- **Majority of cases occur in later life.**
- **Treatable but, in most cases, not curable.**
- **Significant morbidity and mortality.**
- **New drug combinations are having a significant impact especially on the bone damage caused by the disease.**



Multiple Myeloma

Key Points:
Do a screen if - back pain, anaemia, high calcium , renal failure, lytic lesions/bone pain/fracture, recurrent infections.

For spine involvement – get patient into a back brace quickly to protect from paralysis/kyphosis & improve pain control + bisphosphonates for bone protection (dental review prior).