Medical Update Group in collaboration with The Department of Medicine, University of Mauritius

Trends in the Diagnosis and Management of Haematological Malignancies

Dr Sajir G Mohamedbhai
Specialist Registrar, Haematology
University College Hospital, London

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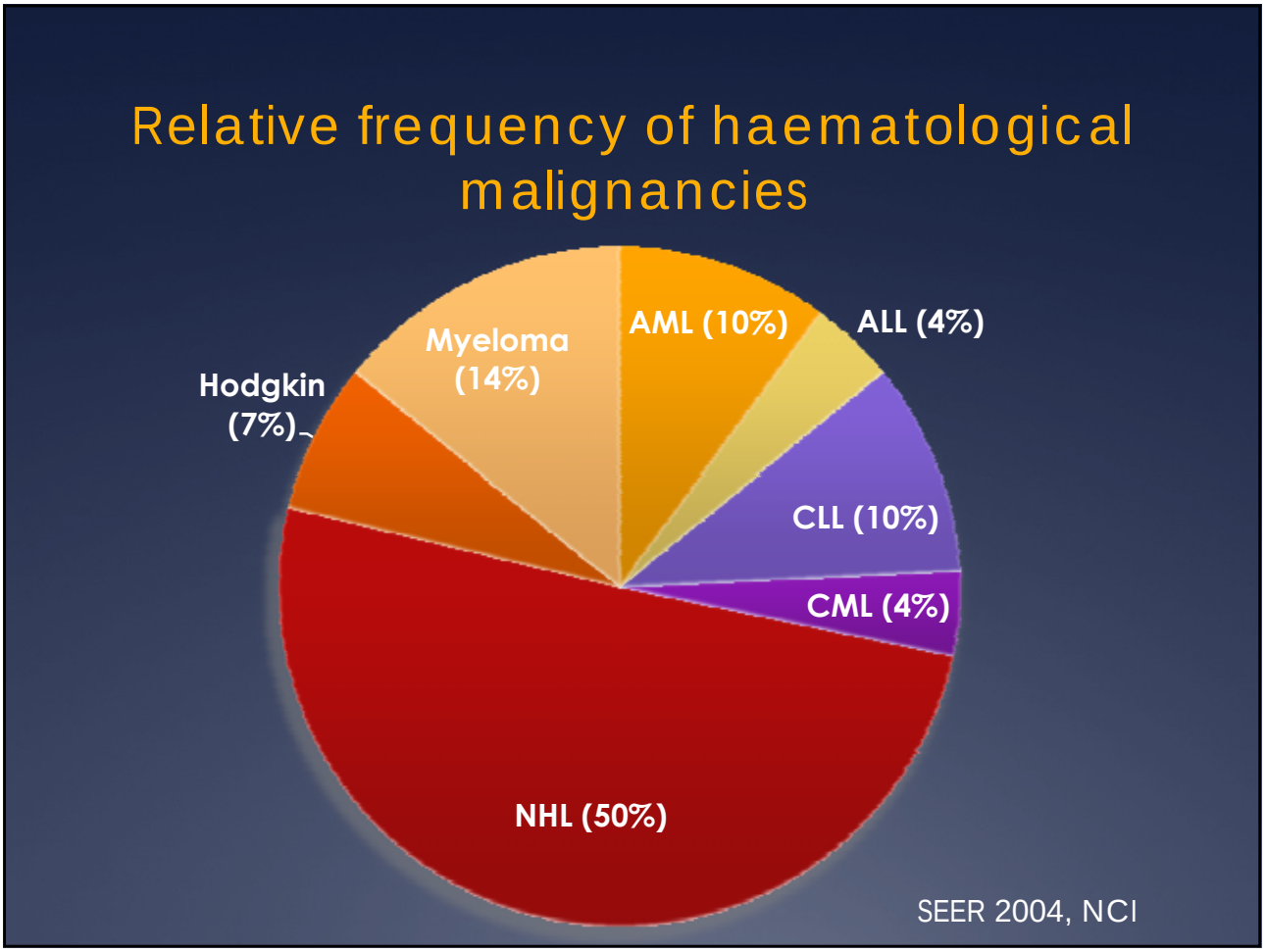
Aims & Objectives

- Highlight the importance of haematological cancers
- Discuss advances in diagnosis
- Discuss new approaches to treatment
- Go through case studies

Epidemiological importance

- 4th commonest cancer in men/3rd in women
- ALL is the commonest childhood cancer
- 1 in 20 individuals by age 75
- Increasing incidence worldwide


Relative frequency of haematological malignancies
AML (10%)
ALL (4%)
CLL (10%)
CML (4%)
NHL (50%)
Hodgkin (7%)
Myeloma (14%)
SEER 2004, NCI

Incidence in Mauritius 1997-2001

Diagnosis		Male	Female
Leukaemias and Myeloma	No. of cases	213	166
	% of total	7.3%	4.7%
Lymphomas	No. of cases	156	94
	% of total	5.3%	2.6%

124 cases/year
10 per 100000/year

Source: Manraj SS et al. Cancer incidence in the Republic of Mauritius- 5 Years Review 1997 to 2001.

Disease	Percentage surviving ≥ 5 years		
	1974-1976	1996-2003	2010
AML	6	21	30
ALL	38	65	>80% children 30% adults
CLL	68	75	80
CML	23	44	95
NHL	47	60	60
Hodgkin	71	86	80-90
Myeloma	24	34	40

5-year survival rates for hematological malignancies (1996-2003 compared with 1974-1976); SEER data

What has led to these improvements?

Better Diagnosis

Conventional diagnostic tools

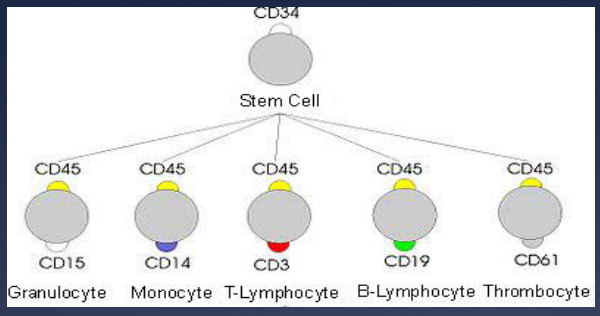
- FBC
- Biochemistry
- Morphology
- Histology (H&E)
- Imaging

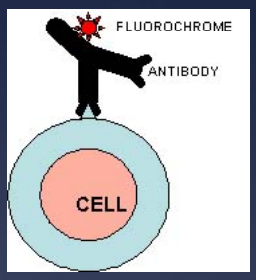
- Sensitivity low
- Not specific
- Inter-reporter error high
- Do not give biological/genetic information about the disease

Novel diagnostic tools complement conventional methods

- Immunophenotyping
- Immunohistochemistry
- Cytogenetics
- Molecular methods- FISH, PCR

Immunophenotyping



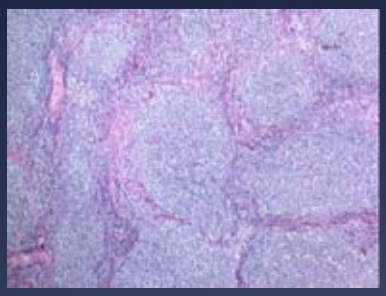


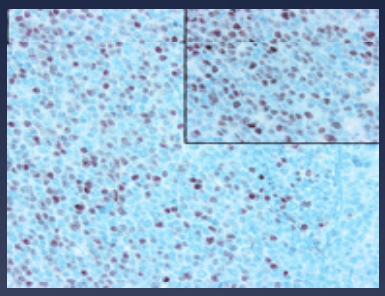
- Identifies specific antigens on cells in suspension
- Monoclonal antibody labelled cells are processed in a flow cytometer, a laser-based instrument capable of analyzing thousands of cells per second
- Specific cell marker profile helps make diagnosis

Immunohistochemistry

Lymph node

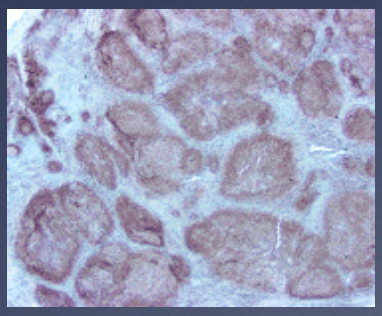
H & E

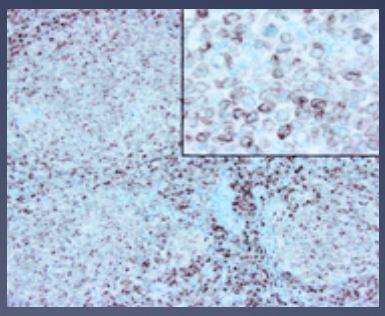




Bcl6

CD20

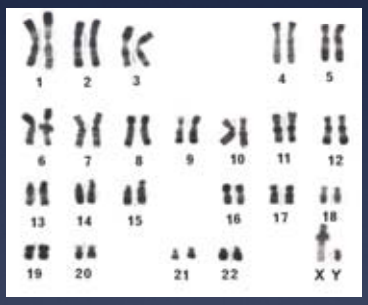




Bcl2

FOLLICULAR LYMPHOMA

Cytogenetics

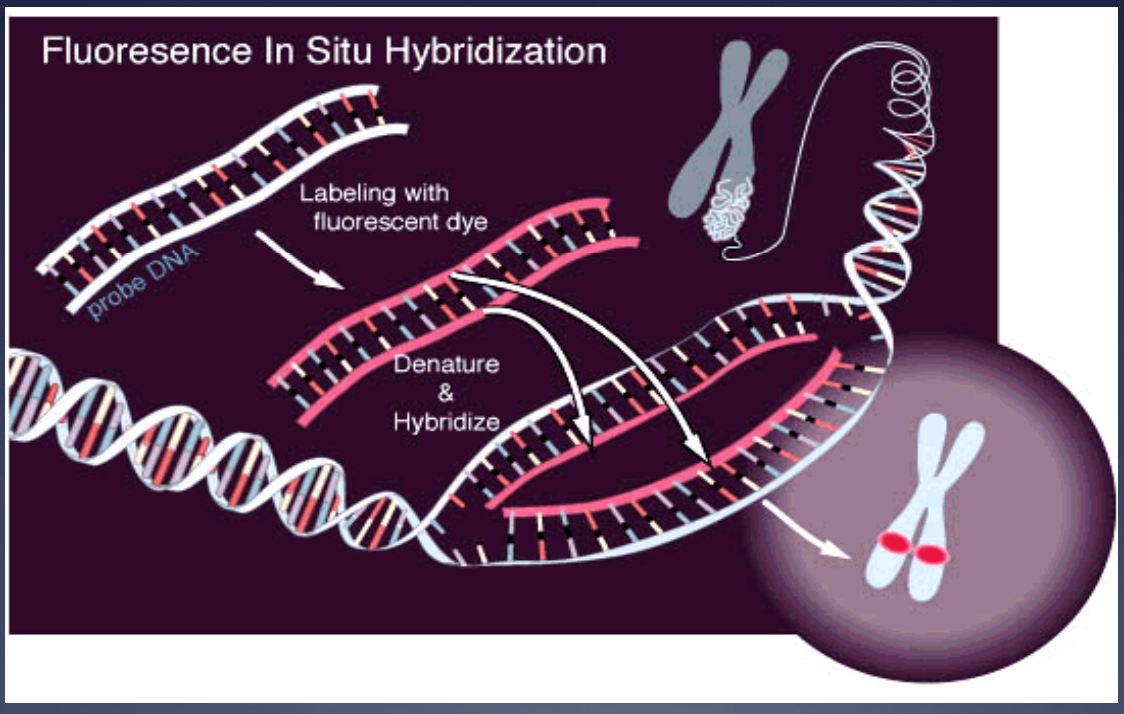


-Recurrent acquired abnormalities (structural/ numerical) are common in haematological cancers

-Usually lead to alterations in oncogenes and tumour suppressor genes

-Correlate with distinct subtypes

FISH


Fluoresence In Situ Hybridization
Labeling with
fluorescent dye
probe DNA
Denature
&
Hybridize

Polymerase Chain Reaction

- Synthetic complementary oligonucleotide sequence (cDNA probe) specific only to target DNA sequence
- Amplification steps makes it highly sensitive
- Q-PCR: method allowing semiquantitative assessment of mutation load

Uses of novel techniques

- In conjunction with conventional methods
- At Diagnosis:

  - Rapidly and reliably confirm diagnosis

  - Prognostic information
- During treatment: Monitoring of response and residual disease
- After treatment: Detection of relapse

Advances in Therapy

Conventional Therapy

- Radiotherapy
- Steroids
- Chemotherapy
- Combination therapy (additive/synergistic/dose intensity/cycling)
- Non-targeted
- Significant toxicity
- Resistance
- Except for Hodgkin's disease and childhood ALL, cure rates low

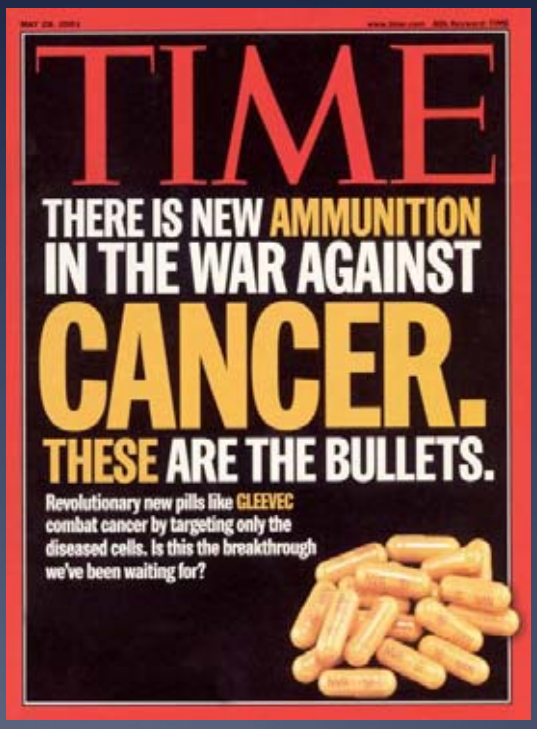
Bone marrow transplantation

- High dose therapy for patients with higher risk disease
- Matched donor stem cells salvage recipient from marrow aplasia
- Donor immune cells

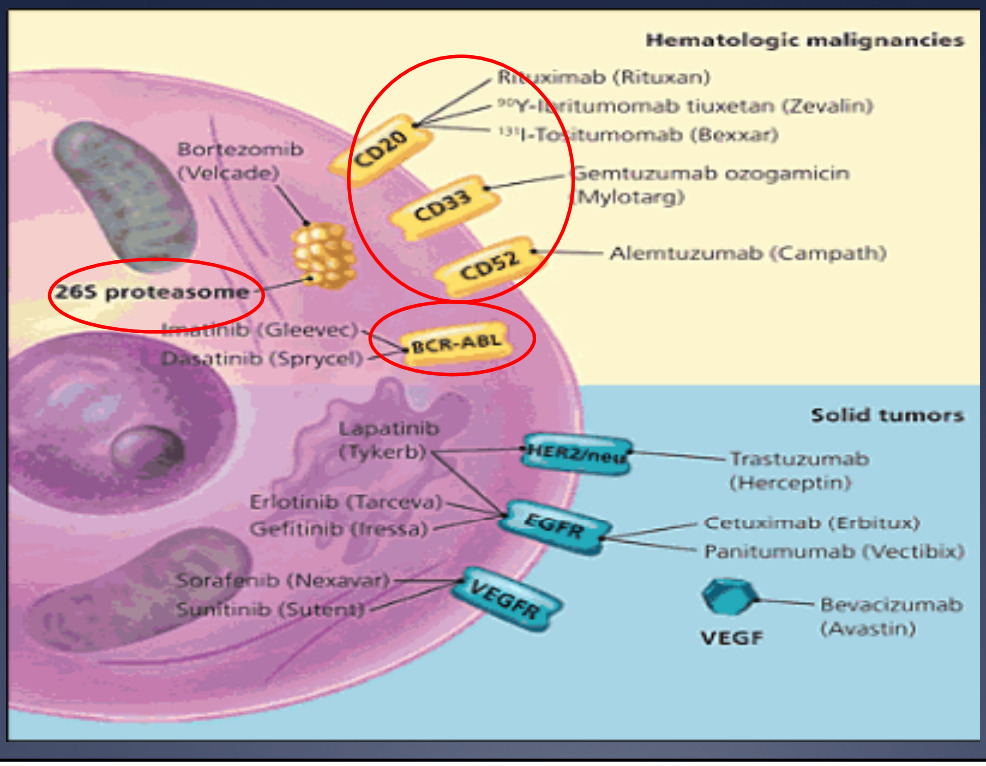
  - mediate graft versus host disease

  - BUT have an important graft versus tumour effect
- Cure is the goal but there is a price to pay

Targeted Therapy



Novel therapeutic targets



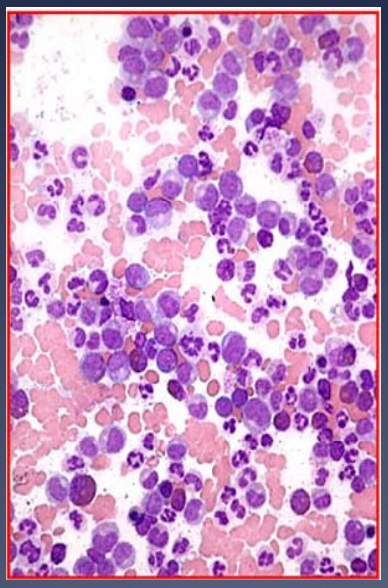
Cases

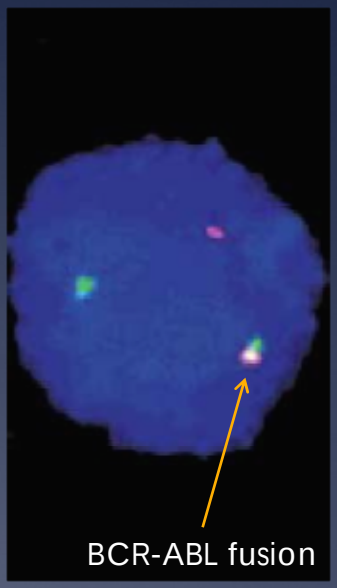
Case 1

- 45 year old male
- Lethargy, weight loss, LUQ discomfort
- Headaches, blurred vision
- Hepatosplenomegaly
- Fundal haemorrhages

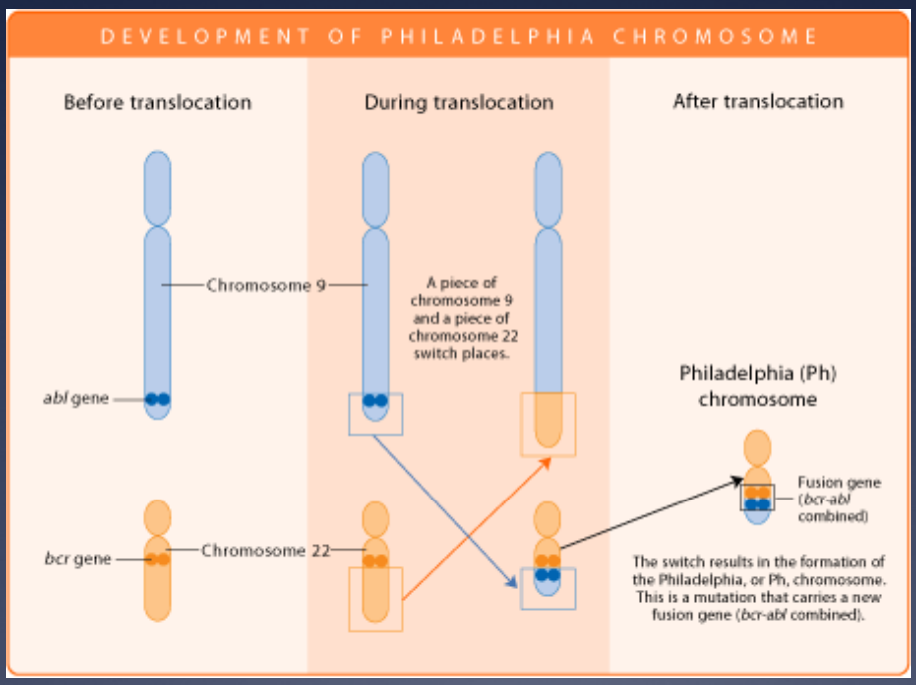
Case 1

FBC





Philadelphia chromosome in CML



Case 1- Treatment & Outcome

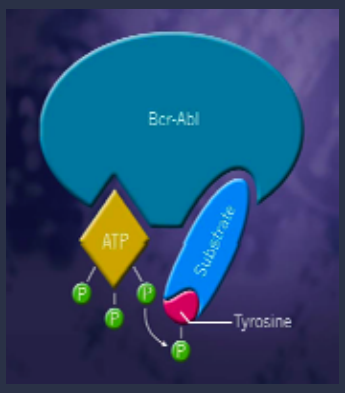
Treatment

- Rapid cytoreduction- hydroxycarbamide + leucocytopheresis
- Allopurinol
- Imatinib (Glivec™) 400mg PO OD

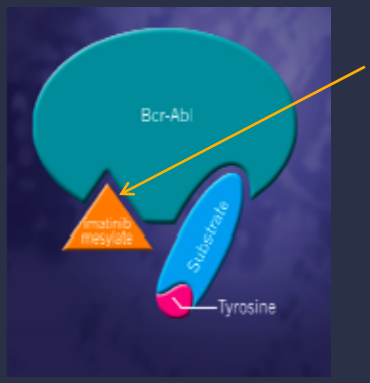
Outcome

- FBC normalised by 3 months
- Bone marrow normal with no detectable Ph chromosome by FISH at 6 months

Imatinib targets the cause of CML

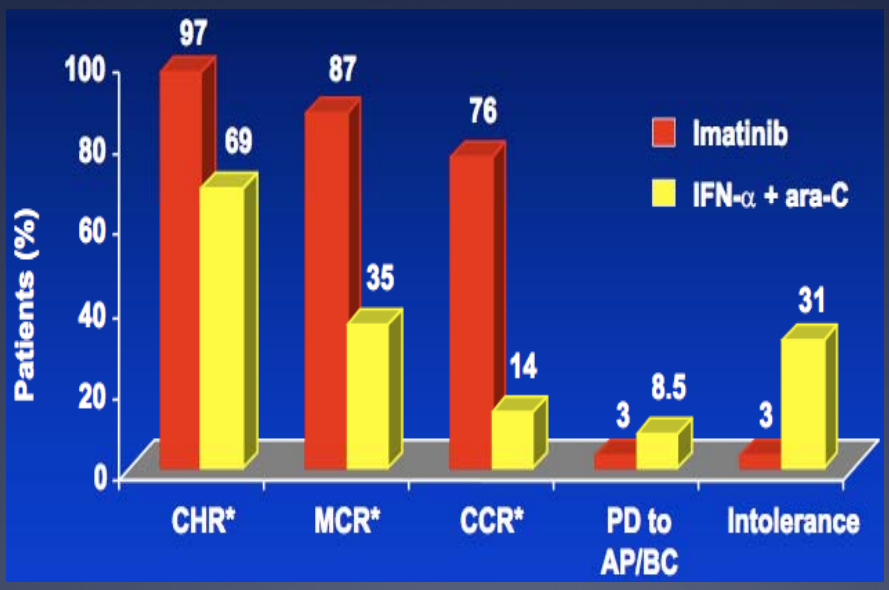


Cell Proliferation



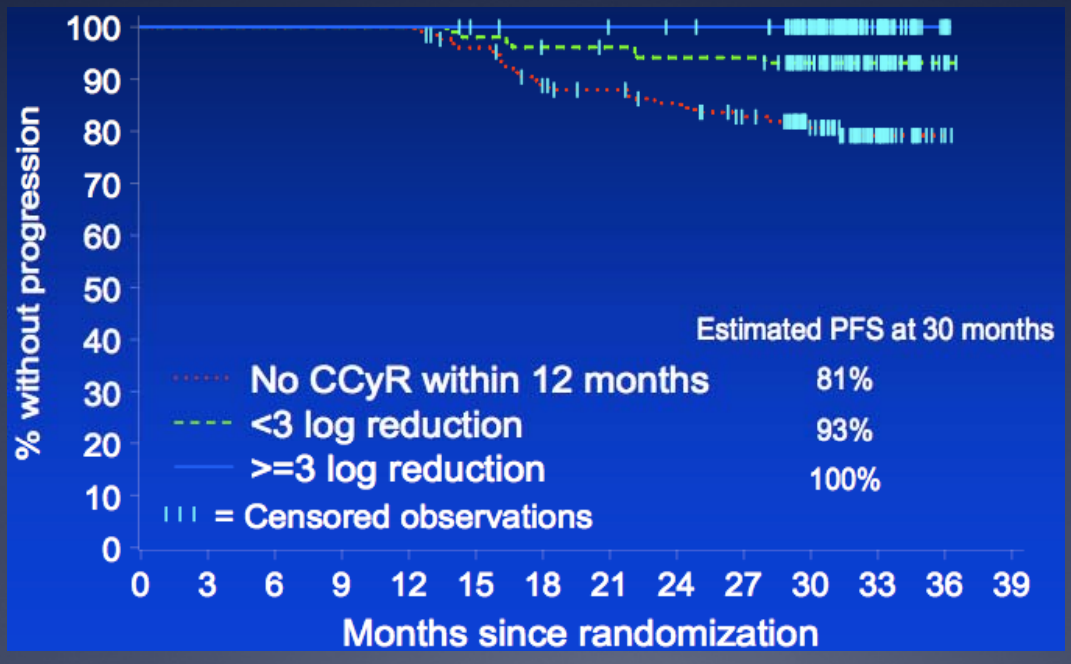
Cell cycle arrest and cell death

IRIS study: 18 month follow-up

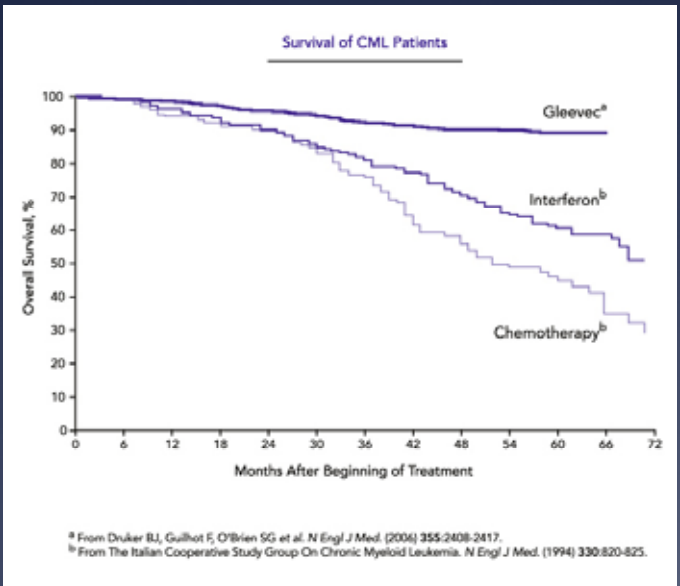


CHR= complete haematological response
MCR=major cytogenetic response
CCR=Complete cytogenetic response
PD=progressive disease
AP=accelerated phase
BC=blast crisis

IRIS study- BCR-ABL load at 12 months with imatinib predicts progression risk



Imatinib has changed the treatment of CML in the last 10 years



[a] From Druker BJ, Guilhot F, O'Brien SG et al. *N Engl J Med.* (2006) **355**:2408-2417.
[b] From The Italian Cooperative Study Group On Chronic Myeloid Leukemia. *N Engl J Med.* (1994) **330**:820-825.

- >90% survival at 5 years
- compared to 20% in 1975

- Imatinib failures do still occur and monitoring bcr-abl on treatment is essential

- Second-line treatments available for Imatinib failures

- Imatinib needs to be continously taken- cost!

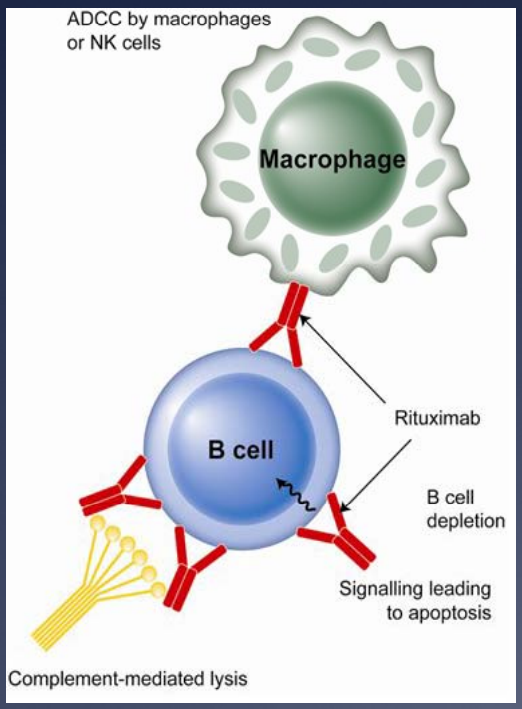
Case 2

- 60 year old male
- Weight loss, sweats
- CT- mesenteric mass and paraaortic adenopathy
- USS-guided biopsy
- Histology and immunohistochemistry shows diffuse large B cell lymphoma
- Stage 2 B
- What treatment?

CHOP chemotherapy

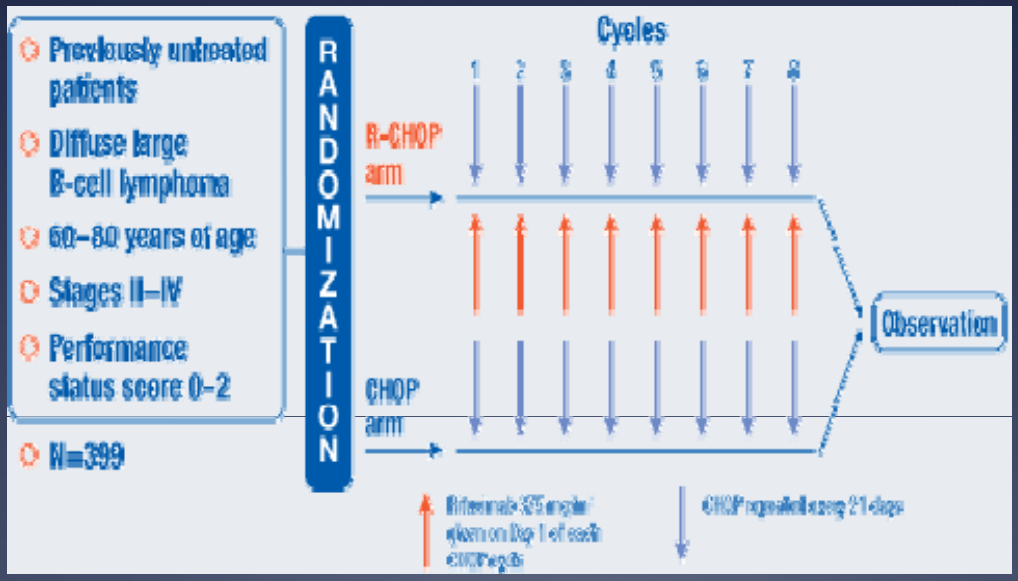
- DLBCL is the commonest NHL
- CHOP chemotherapy used since 1970s
- 3-weekly Cyclophosphamide/Doxorubicin/Vincristine/Prednisolone combination
- Outpatient treatment
- No other combination found to be superior
- Until the advent of Rituximab

Rituximab



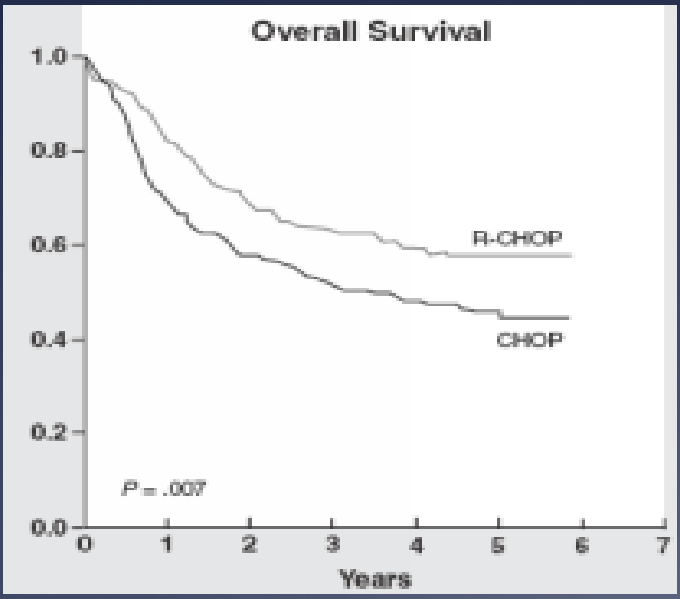
- Chimeric mouse/human monoclonal antibody (reduces allergic reactions)
- First Mab licensed in human cancer
- Used in a range of CD20-expressing B-cell lymphomas (DLBCL, FL CLL)

GELA study



GELA Coiffier et al 2002

Chemo-immunotherapy improves 5-year survival in DLBCL

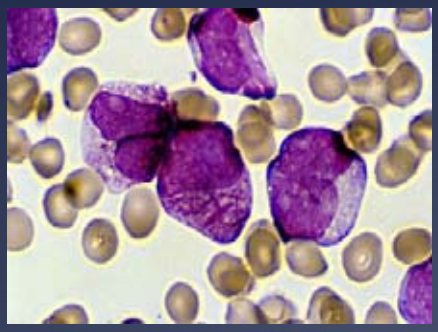


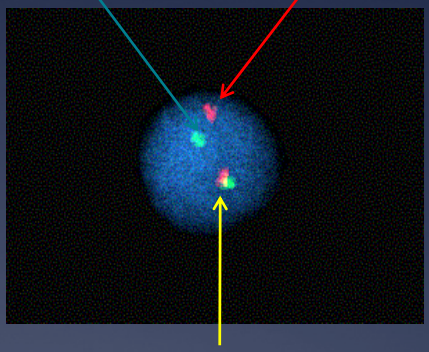
15% difference in OS at 5y

Case 3

- 55 yo female
- Tiredness, lethargy, excessive spontaneous bruising for 1 week + gum bleeding
- Unwell, febrile
- Hb 8.5 Platelets 15 WBC 25
- Fibrinogen <100 mg/dL
- PT 22s APTT 50s

Case 3





PML-RARA fusion arises from t(15;17)

ACUTE PROMYELOCYTIC LEUKAEMIA

Management

Supportive care:

* Antibiotics
* Keep platelets >50
* Cryoprecipitate to replace fibrinogen
* FFP to correct DIC

Definite treatment:

* Oral All-trans Retinoic Acid
* Anthracycline

Acute Promyelocytic Leukaemia

- Unique among acute myeloid leukaemias
- t(15;17) produces Pml-Rara fusion protein that blocks cell differentiation at promyelocyte stage
- Differentiation therapy with ATRA plus chemotherapy leads to >95% remission
- From one of the most fatal leukaemias to one of the most curable- 90% cure rates!
- Arsenic trioxide also active upfront and in relapse/refractory disease

Other new concepts

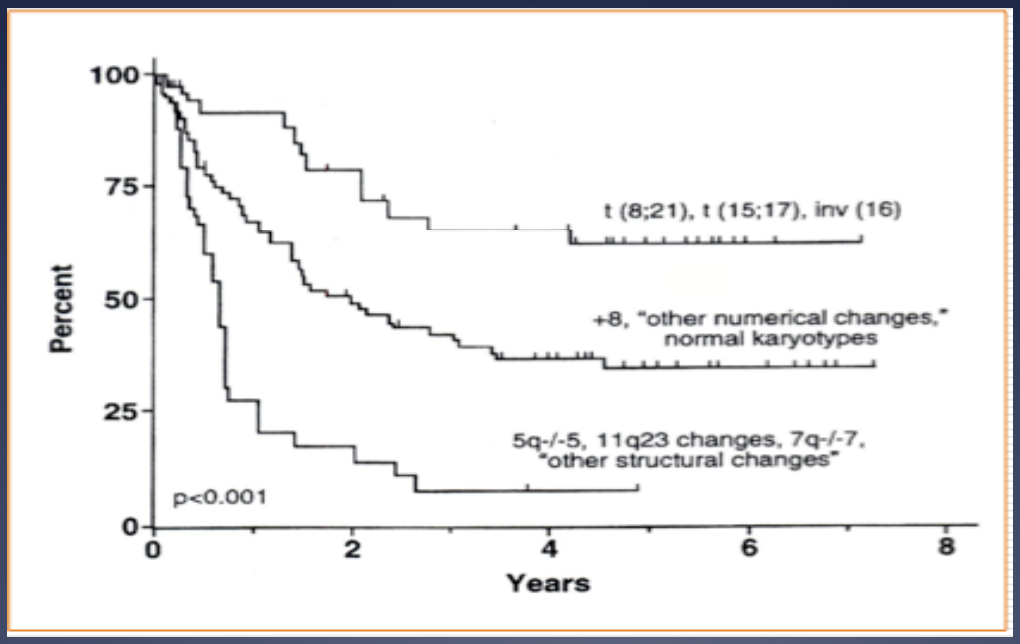
Myeloma- new kids on the block

- Thalidomide based induction therapies (Melphalan/Prednisone, Cyclophosphamde/Dexamethasone)
- Bone marrow autograft improves survival
- Newer agents like Lenalidomide and bortezomib active upfront and in relapse/refractory setting
- No cure yet, but myeloma patients live longer
- Median survival now 5 years

AML- cytogenetics predicts outcome

- Cytogenetic abnormalities in 40% at diagnosis
- Large collaborative studies have shown three groups, favorable, intermediate and poor, based on cytogenetic results at diagnosis.
- Important independent prognostic factors for achievement of remission, risk of relapse and survival

Cytogenetic risk group predicts survival after treatment



65 %

35 %

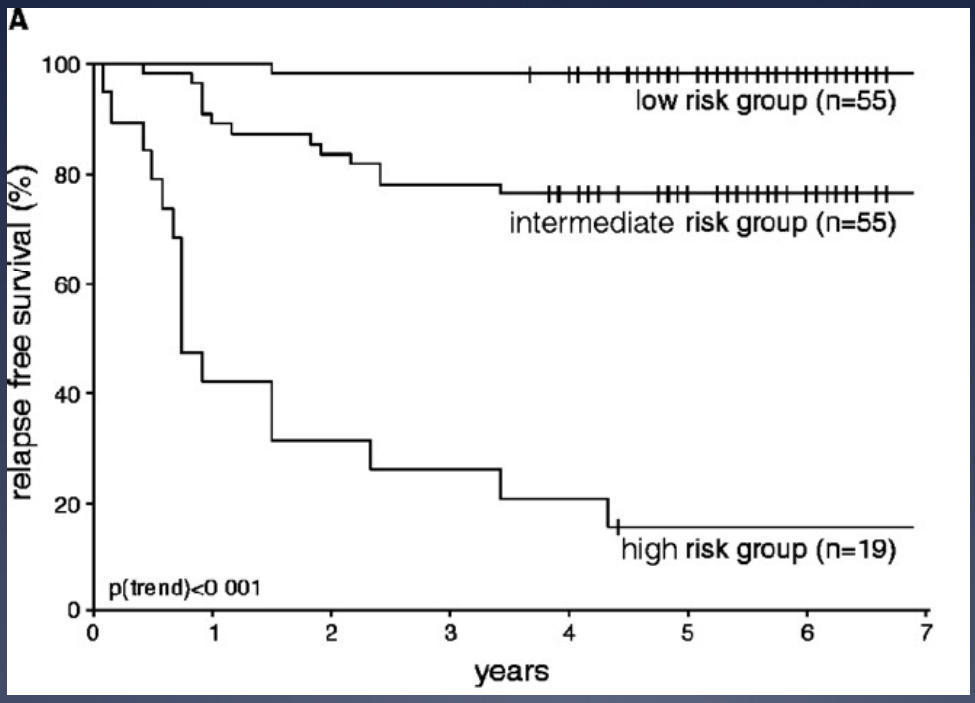
<10%

Dastague et al. Leukaemia 1995

ALL- Minimal residual disease predicts outcome

- >90% patients achieve CR at the end of induction (by bone marrow morphology), yet some still relapse
- Early fall in leukaemia cell burden during induction reflects sensitivity/resistance to chemotherapy used
- Immunophenotyping and PCR to assess MRD is more specific and sensitive than Day 15 or 28 bone marrow and has excellent prognostic value
- Identifies low-risk and high-risk patients, which may benefit from treatment reduction or escalation respectively

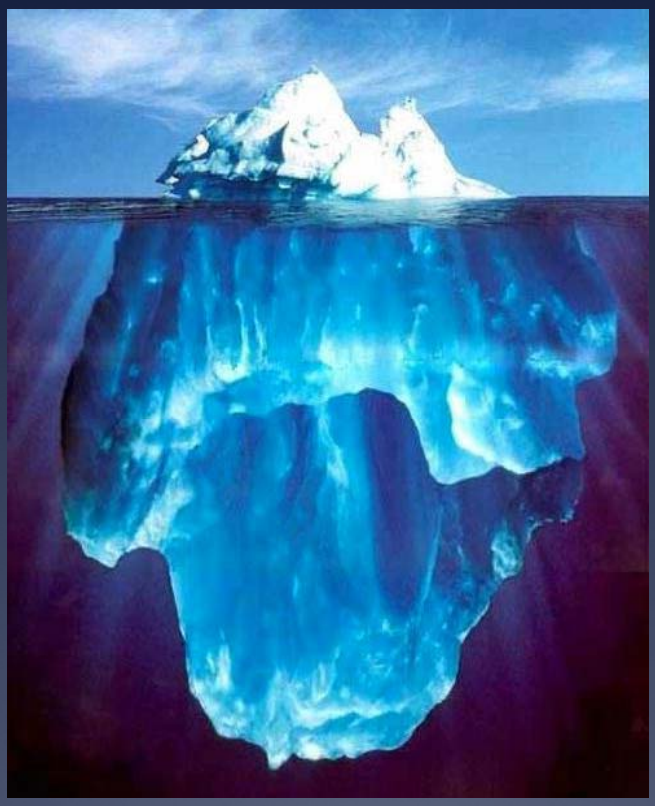
Relapse-free survival according to MRD-based risk groups of paediatric ALL- International BFM Study Group



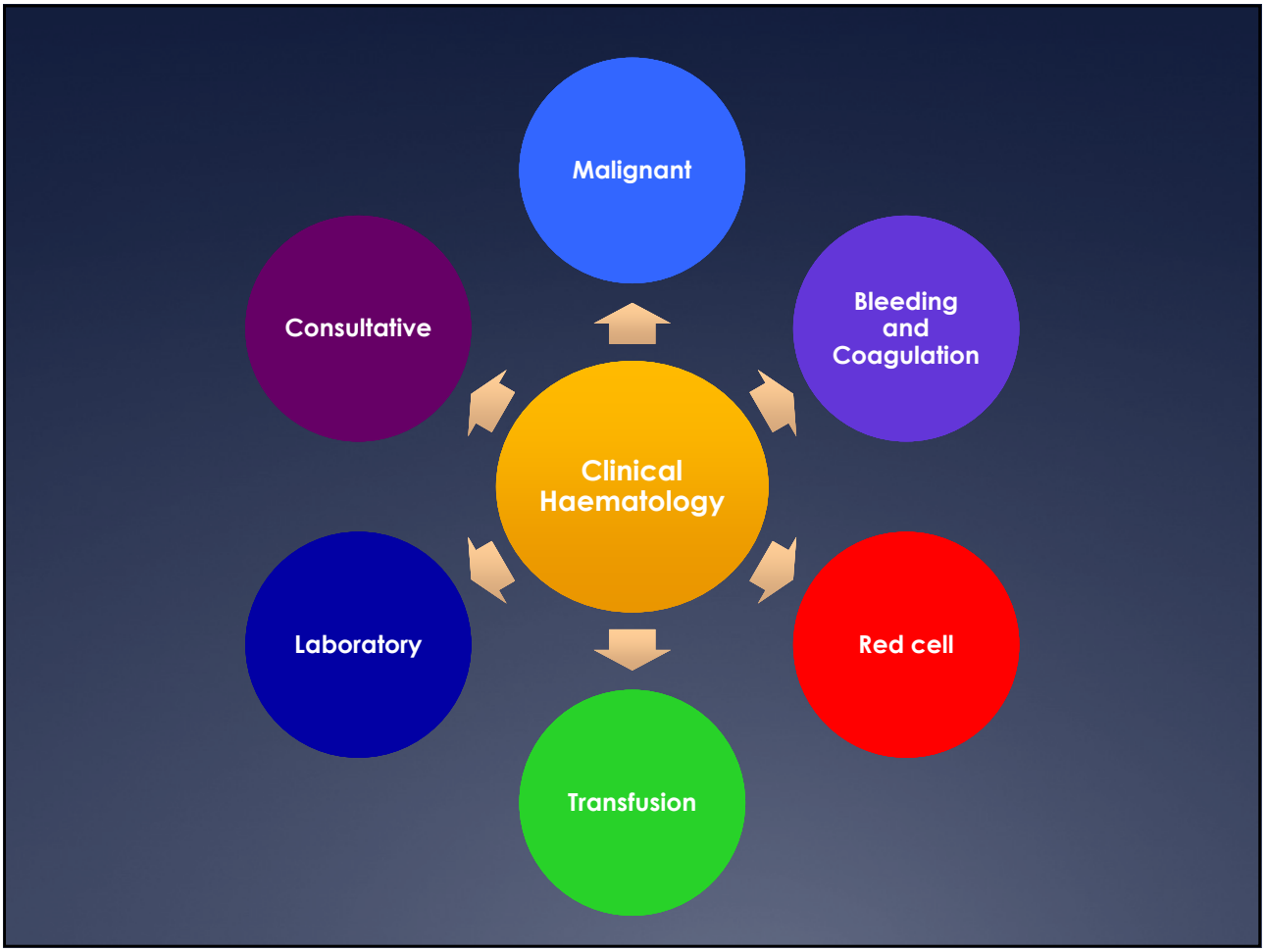
Hoelzer, D. et al. Hematology 2002;2002:162-192

Conclusion

- Dramatic changes have occurred in the field of haematological malignancies in the last 30 years
- New ways of classifying, diagnosing and treating haematological cancers
- Together, these strategies have improved outcomes
- There is probably not a single cure for cancer but many, reflecting the biological diversity of these tumours



Thank you


Malignant
Bleeding and Coagulation
Red cell
Transfusion
Laboratory
Consultative
Clinical Haematology