Management of Acute and Chronic Leukemia PG-CME 2017

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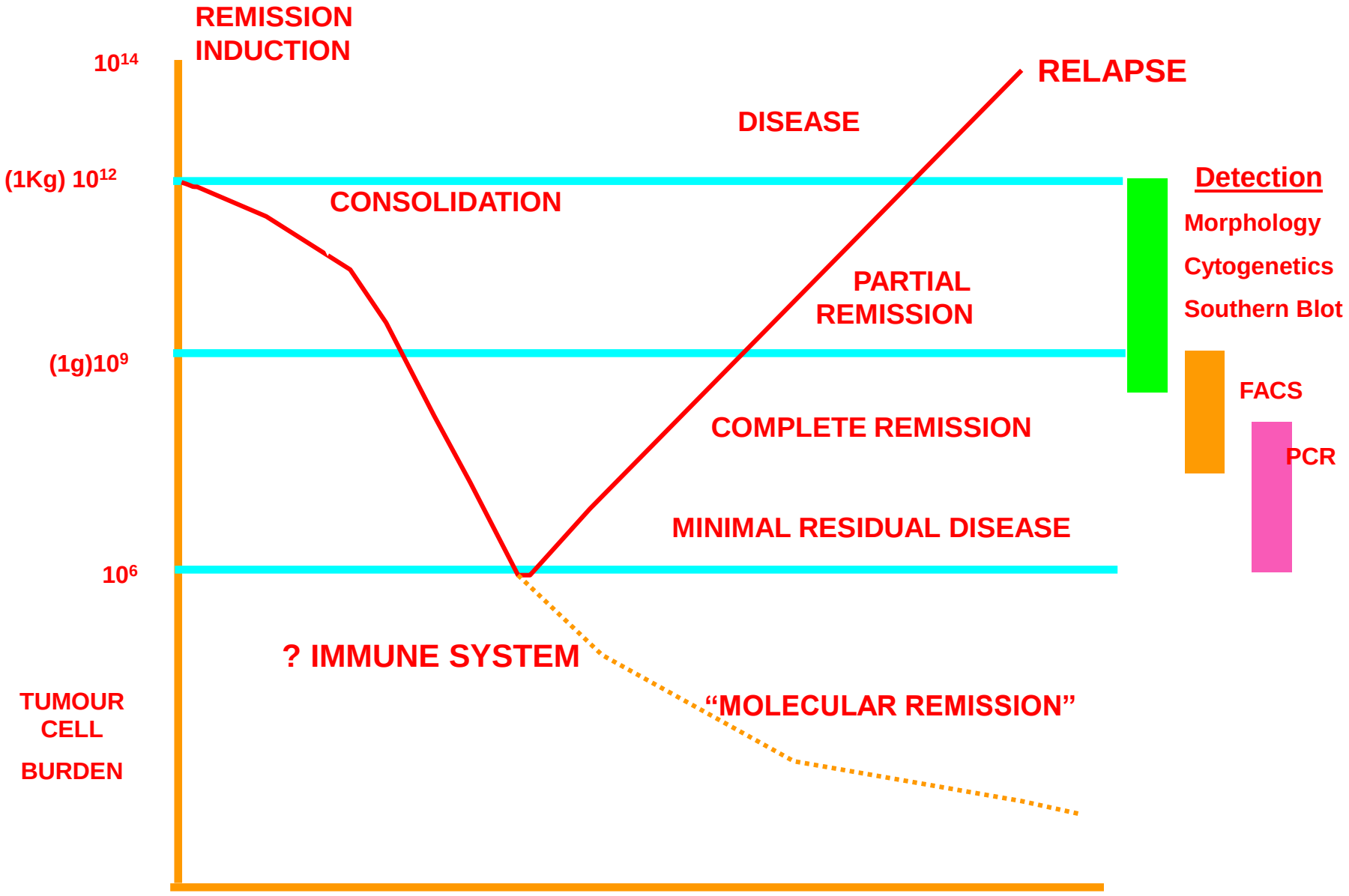
- **ACUTE MYELOID LEUKEMIA**
- **ACUTE PROMYELOCYTIC LEUKEMIA**
- **ACUTE LYMPHOBLASTIC LEUKEMIA**

  - **Principle of Treatment**
  - **Overview of treatment schedule**
  - **Rationale for existing schedules**
  - **Risk stratification**
  - **Cost of treatment**
  - **Anticipated clinical outcomes**
  - **Recent advances**

Principle of treatment



Acute Lymphoblastic Leukemia

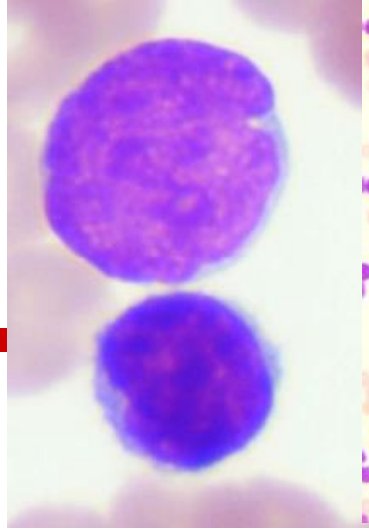
- **Pediatric :**
  - **Good prognosis**
  - **Commonest leukemia**
  -
- **Adult**
  - **Intermediate prognosis**
  - **Less common than AML**

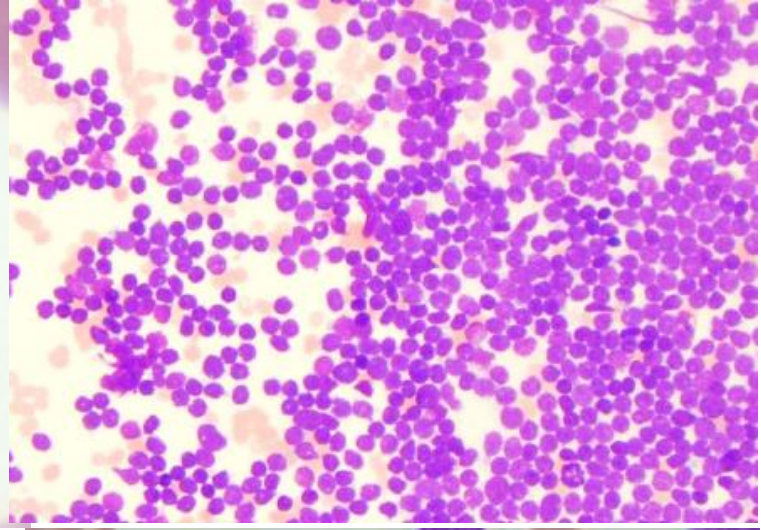
Epidemiology

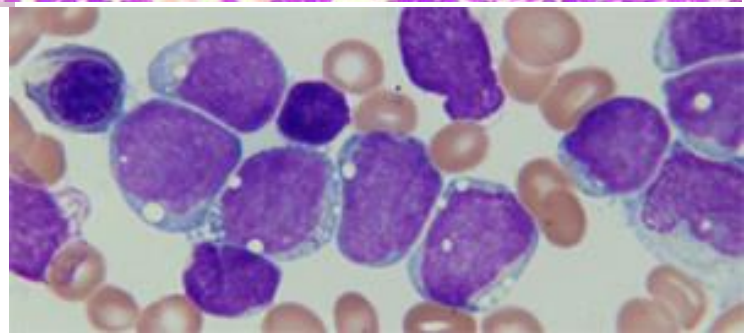
- Most common malignancy of childhood
- Annual incidence ~1 - 4 / 100,000 <15 years
- 25% of all childhood cancers
- 80% of acute leukemia's in children. Slight male preponderance
- Peak incidence approximately 2-5 years
- Affluent countries increased incidence
- In the USA higher incidence in whites than in blacks

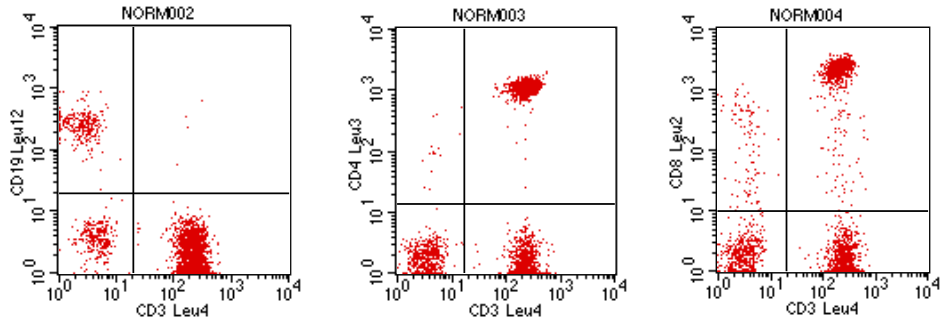
Diagnosis:

- Cytomorphological
- Cytochemical
- Immunophenotype
- Cytogenetics / molecular
- ?Expression profile









Lymphoblastic leukemias

WHO Classification:

- B lymphoblastic leukemia (NOS)
- B lymphoblastic leukemia with recurrent genetic abnormalities:
  - t(9;22) BCR-ABL1
  - 11q23 rearrangement
  - t(12;21) TEL-AML1
  - with hyperdiploidy (>50 <66)
  - with hypodiploidy (<46 ?<45)
  - t(5;14) IL3-IGH
  - t(1;19) E2A-PBX
- T lymphoblastic leukemia / lymphoma
  - (ETP – not in classification at present)

Early T cell precursor phenotype: CD1a^{-}, CD5 dim, cytoCD3+, CD3-CD13+, CD33+ - VERY POOR PROGNOSIS

Prognostic Factors and Risk Stratification

Table 2. Important Prognostic Factors and Their Approximate Incidences in Childhood ALL

Factor	Favorable Prognostic Factors and Their Approximate Incidence (%)	Unfavorable or Less Favorable Prognostic Factors and Their Approximate Incidence (%)
Age at diagnosis	≥1 and <10 years (77%)	<1 year (3%) or ≥10 years (20%)
Gender	Female (45%)	Male (55%)
White blood cell count at diagnosis	<50,000/μL (80%)	≥50,000/μL (20%)
Immunophenotype	$CD10^+$ precursor B-cell ALL (83%)	$CD10^-$ precursor B-cell ALL (4%), T-ALL (13%)
CNS disease*	CNS 1 (80%)	CNS 3 (3%), TLP+ (7%)
Genetic features†	Hyperdiploidy (20%), TEL/AML1 positivity (20%)	Hypodiploidy (1%), t(9;22) or BCR/ABL positivity (2%), t(4;11) or MLL/AF4 positivity (2%)
Prednisone response‡	<1,000/μL blood blasts (90%)	≥1,000/μL blood blasts (10%)
Early bone marrow response	<5% blasts (M1) on day 15 of induction treatment (60%)	≥25% blasts (M3) on day 15 of induction treatment (15%)
Remission status after induction therapy in the bone marrow (morphologically assessed)	<5% blasts (M1) after 4 to 5 weeks of induction treatment (98%)	≥5% blasts (M2 or M3) after 4 to 5 weeks of induction therapy (2%)
Minimal residual disease§ in the bone marrow (molecularly assessed)	$<10^{-4}$ blasts after 5 weeks of induction treatment (40%)	$\geq 10^{-3}$ blasts after 12 weeks of treatment (induction and consolidation) (10%)

Schrappe. Semin Hematol 2009

Prognostic Factors and Risk Stratification

Rome Risk criteria (1985)

Risk Group	Definition	% B cell	% T cell
Standard	WC < 50 x 10^9/l and Age 1-9 yrs	75	25
High	WC > 50 x 10^9/l or Age > 9 yrs	25	75

Acute Lymphoblastic Leukemia

Risk Stratification: Pediatric

Standard Risk

Age > 1 yr, < 10 yrs
WBC ≤ 20,000/cmm
Pre B, CALLA immunophenotype
(no T immunophenotype, no aberrant markers)
No CNS disease
No translocation t(9;22) , t(4;11), t(1;19)
Prednisolone good response
Post induction marrow in remission.

Intermediate risk

Age <1 and ≥10
WBC >20,00cmm
T cell immunophenotype (any aberrant markers)
t(1 ;19)
CNS disease / Suspicious CNS disease
Testicular disease at diagnosis
(+prednisolone good response + marrow in remission)

Acute Lymphoblastic Leukemia

- Risk Stratification: Pediatric

High Risk

t(9;22)
t(4;11)
Poor prednisolone response
with any — **T cell**, **Pro B cell** (**WBC >1,00,000/cmm**)
Post induction marrow not in remission

Acute Lymphoblastic Leukemia

Table 64-2 Differential Diagnosis of ALL

Nonmalignant Disorders

- Aplastic Anemia
- Myelodysplastic syndrome[a]
- Myelofibrosis[a]
- Autoimmune diseases (e.g., systemic lupus erythematosus)[a]
- Infectious mononucleosis
- Juvenile rheumatoid arthritis[c]
- Idiopathic thrombocytopenia purpura[c]
- Leukemoid reactions secondary to infection

Malignant Disorders

- Other leukemias
- Hodgkin's and Non-Hodgkin's lymphoma
- Bone marrow metastases from solid tumors (e.g., neuroblastoma)[c]
- Multiple myeloma[a]

Where indicated, symbols denote disorders that are to be particularly considered in the differential diagnosis of children (c) or of adults (a).

Clinical Features:

Musculoskeletal pain

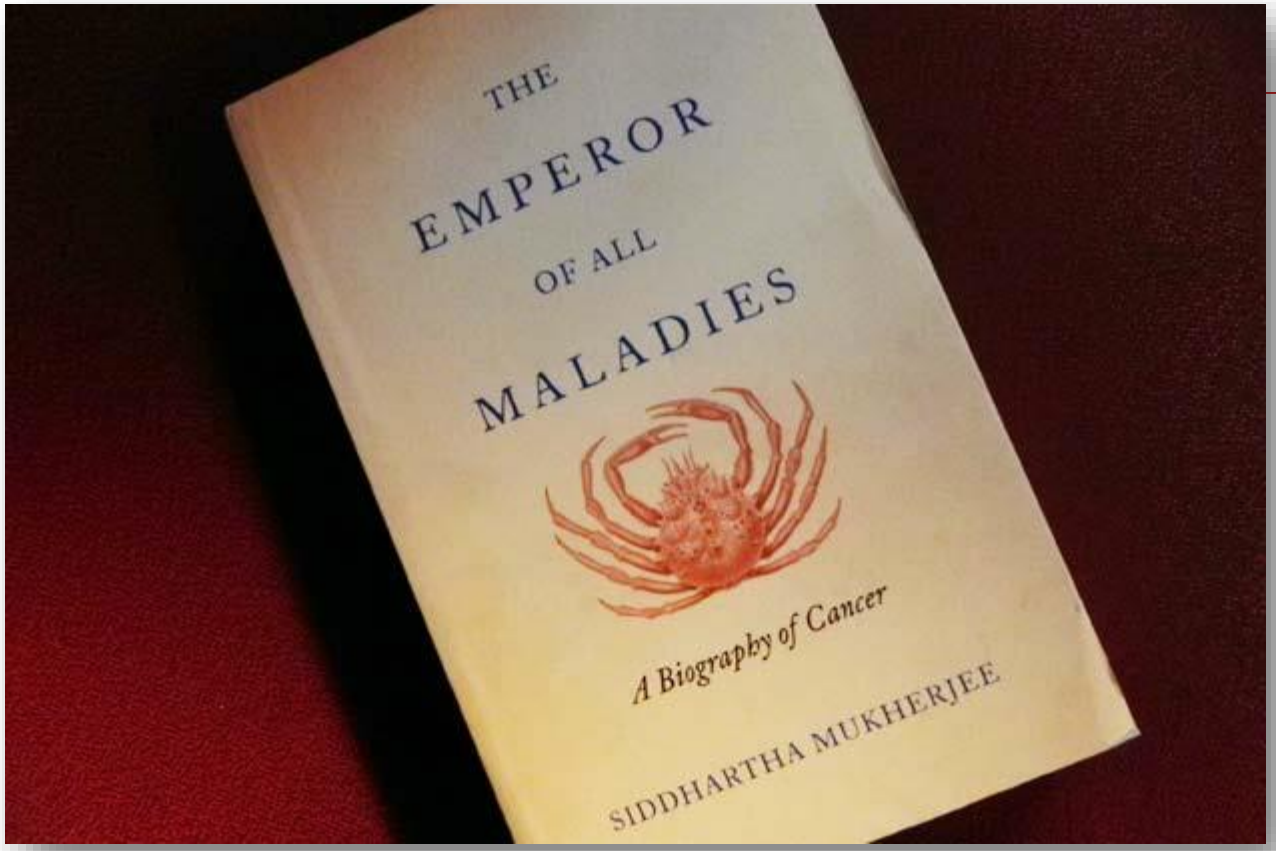
JRA/JIA	Acute Leukemia
Morning stiffness	Nocturnal pain
Rash	Nonarticular bony pain
LAD	LAD
HSM	HSM

Acute Lymphoblastic Leukemia

Table 65–1 Chemotherapy of Childhood ALL: Historical Perspective

	Frequency of Complete remission (%)
Single agents	
Prednisone	57
Vincristine	55
6-Mercaptopurine	27
Methotrexate	21
Cyclophosphamide	18
Combination agents	
Prednisone + vincristine	85
Prednisone + 6-mercaptopurine	81
Methotrexate + 6-mercaptopurine	45
Vincristine + prednisone + methotrexate + 6-mercaptopurine	94

From Freireich EJ, Frei E Jr: Recent advances in acute leukemia. Prog Hematol 4:187, 1964, with permission.


THE
EMPEROR
OF ALL
MALADIES
A Biography of Cancer
SIDDHARTHA MUKHERJEE

Acute Lymphoblastic Leukemia

- Elements in Treatment:
  - Pre-induction
  - Induction
  - CNS prophylaxis
  - Consolidation
  - Re-Induction
  - Maintenance

Acute Lymphoblastic Leukemia

PREINDUCTION(1 week)

1. Dexamethasone 6 mg/ m2 iv Days 1 & 2
2. Prednisolone 60 mg/ m2 p/o daily Days 3 - 7
3. Inj Methotrexate IT stat Day 1

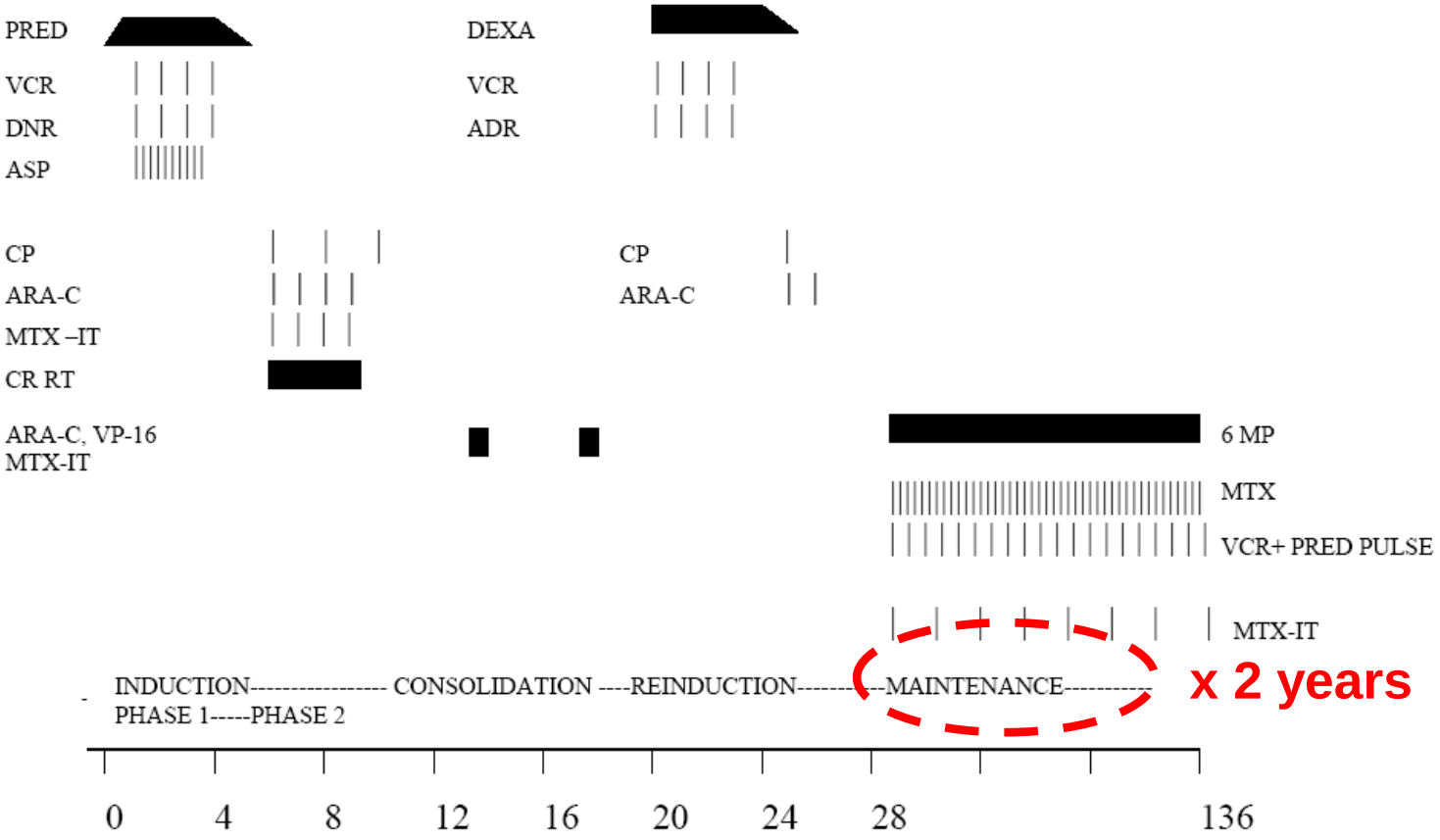
INDUCTION

Phase I: 2 - 5 wks

1. Vincristine 1.5 mg/ m2 iv weekly x 4 (Day 8,15,22,29)
2. Daunorubicin 30 mg/ m2 iv weekly x 2 (Day 8,15)
3. L'Asparaginase 5,000 U/ m2/day IV every third day X 8 doses (days12,15,18,21,24,27,30,33) (minimum number of doses=8)
4. Prednisolone 60 mg/ m2 p/o daily x 3 weeks and then taper over 10 days
5. Inj Methotrexate IT stat day 15

1 week after completion of Phase I, BM and CSF to assess remission status

Figure 1 – TREATMENT PROTOCOL 1994-2003



PRED Prednidolone 60mg/m^2 ARA-C 75mg/m^2 x 5 days
VCR Vincristine 1.4mg/m^2 VP-16 50mg/m^2 x 5 days
DNR Daunorubicin 30 mg/C
ASP- L Asparaginase 70,000U mg/m^2 .
CP Cyclophosphamide 650mg/m^2
ARA-C Cytosine arabinoside 75mg/ m^2 x 4 days
MTX-IT 12.5 mg
CR-RT Cranial radiotherapy 2400 cGY

DEXA Dexamethasone 10mg/m^2 6MP Mercaptopurine 60mg/m^2
ADR Doxorubicin 25 mg/m^2 MTX Methotrexate 20mg/ m^2 once a week
VCR Vincristine 1.4mg/m DEXA Dexamethasone 6mg/m^2 x 5 days a month
CP Cyclophosphamide 650mg/m^2 VCR Vincristine 1.4 mg/m^2 once a month
ARA-C Cytosine arabinoside 75mg/ m^2 x 4 days

Current Treatment

Tumor Lysis Syndrome

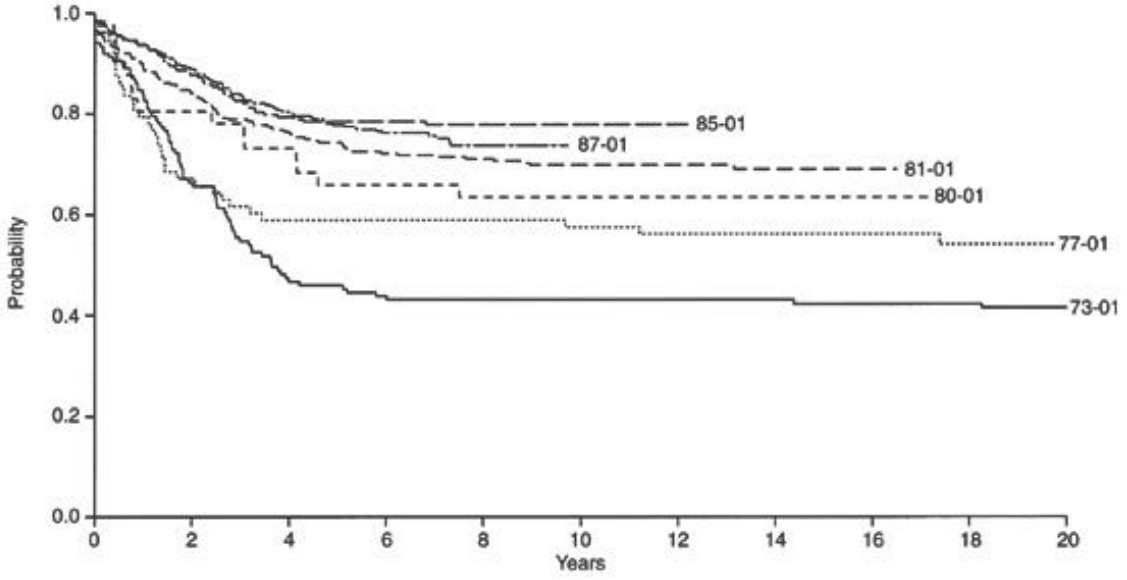
Characteristics

- Release of intracellular uric acid, potassium, and phosphate from rapid turnover of malignant cells
- Usually precipitated by chemotherapy, but can occur before
- Most often with high tumor burden or T-cell **leukemia**
- Components of tumor lysis:
  - -Hyperuricemia
    - -Renal precipitation can progress to **acute** renal failure
  - -Hyperkalemia
    - -Can progress to fatal arrhythmia
  - -Hyperphosphatemia/Hypocalcemia
    - -Increased phosphate can cause hypocalcemia and renal precipitation → renal failure

Mangement

- Provide hydration and diuresis, avoid supplemental potassium
- Treat hyperkalemia emergently, if necessary
- Decrease uric acid with allopurinol or urate oxidase
- Consider oral phosphate binders
- Initiate dialysis for **acute** renal failure

Acute Lymphoblastic Leukemia



Protocol	Total	CCR	Relapse	Other event	Median F/U (years)
73-01	137	57	67	13	21.8
77-01	73	40	27	6	18.0
80-01	41	26	7	8	16.3
81-01	289	202	58	29	12.7
85-01	220	172	37	11	9.7
87-01	369	278	71	20	7.1

(Adapted from Sallan SE, Gelber RD, Kimball V, et al: More is better! Update of Dana-Farber Cancer Institute/Children's Hospital childhood acute lymphoblastic leukemia trials. Haematol Bluttransfus 33:459, 1990, with permission.)

Associated Clinical Outcomes in ALL

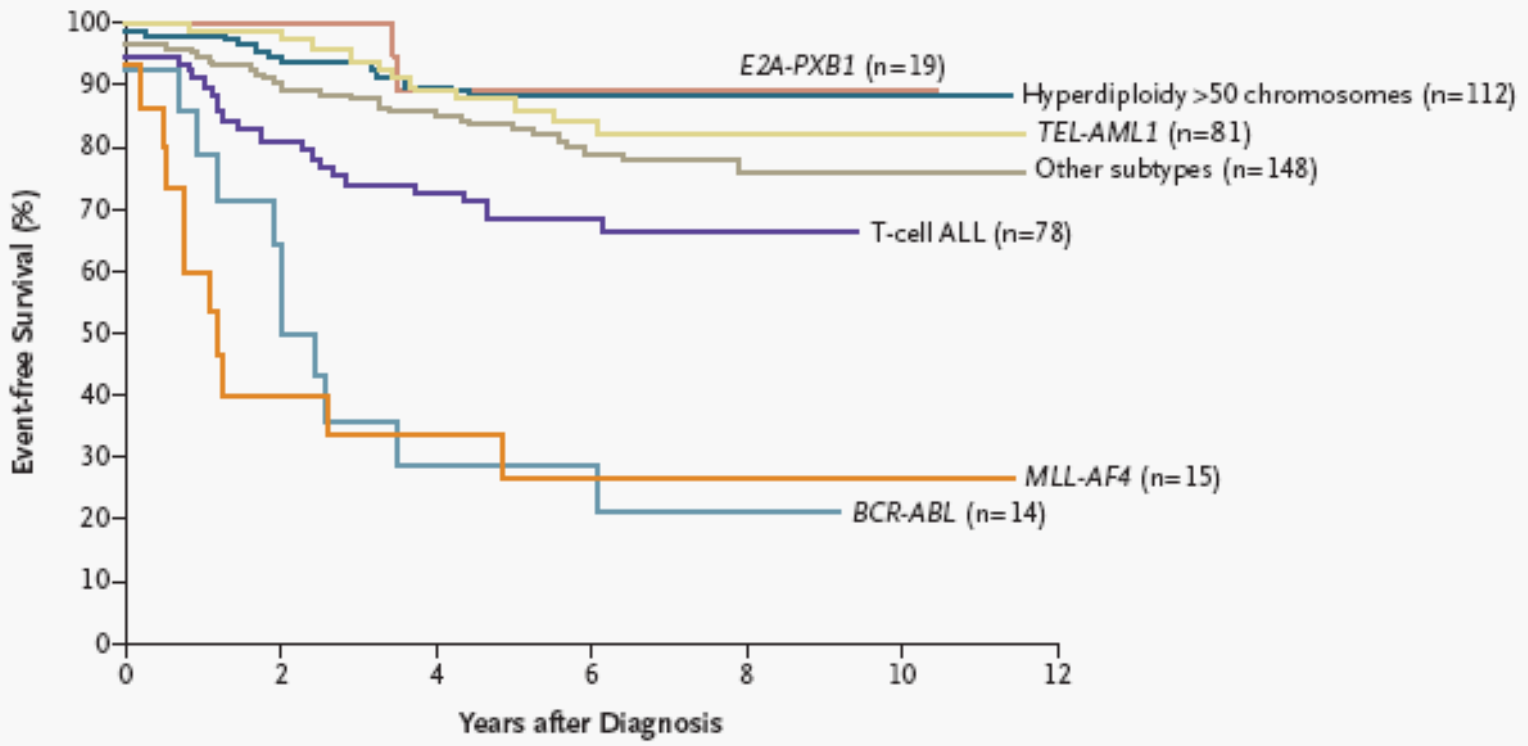


Figure 5. Kaplan–Meier Analysis of Event-free Survival According to the Subtype of Leukemia in 467 Children with ALL Who Were Enrolled in Three Consecutive Treatment Protocols at St. Jude Children's Research Hospital from 1991 to 1999.

Patients with t(1;19) leading to *E2A-PBX1* fusion, hyperdiploidy involving more than 50 chromosomes, or *TEL-AML1* fusion have a favorable treatment outcome, with mean (±SE) five-year event-free survival rates of 89.5±7.3 percent, 88.3±3.3 percent, and 87.5±4.0 percent, respectively, whereas those with t(4;11) leading to *MLL-AF4* fusion and t(9;22) leading to *BCR-ABL* fusion have a dismal prognosis, with five-year event-free survival rates of 26.7±11.4 percent and 28.6±10.8 percent, respectively. The prognosis is intermediate for patients with other B-cell–lineage ALL (83.6±3.3 percent) and T-cell ALL (68.6±5.9 percent).

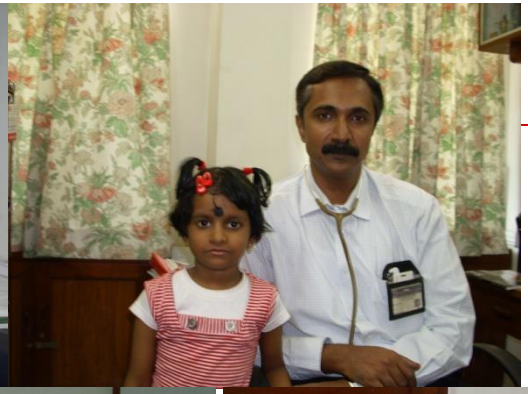
Ching Hon-Pui et al. NEJM 2004

Impact on Treatment Algorithms in ALL

Low risk	**Hyperdiploid** ***TEL-AML1***	**Conventional antimetabolites**
Intermediate risk	**No other adverse features standard risk**	**Intensified antimetabolites**
High risk	**High risk features**	**Intensive chemotherapy**
Very high risk	***MLL*** ***BCR-ABL*** **Induction failure**	**Allogeneic SCT**

Special children

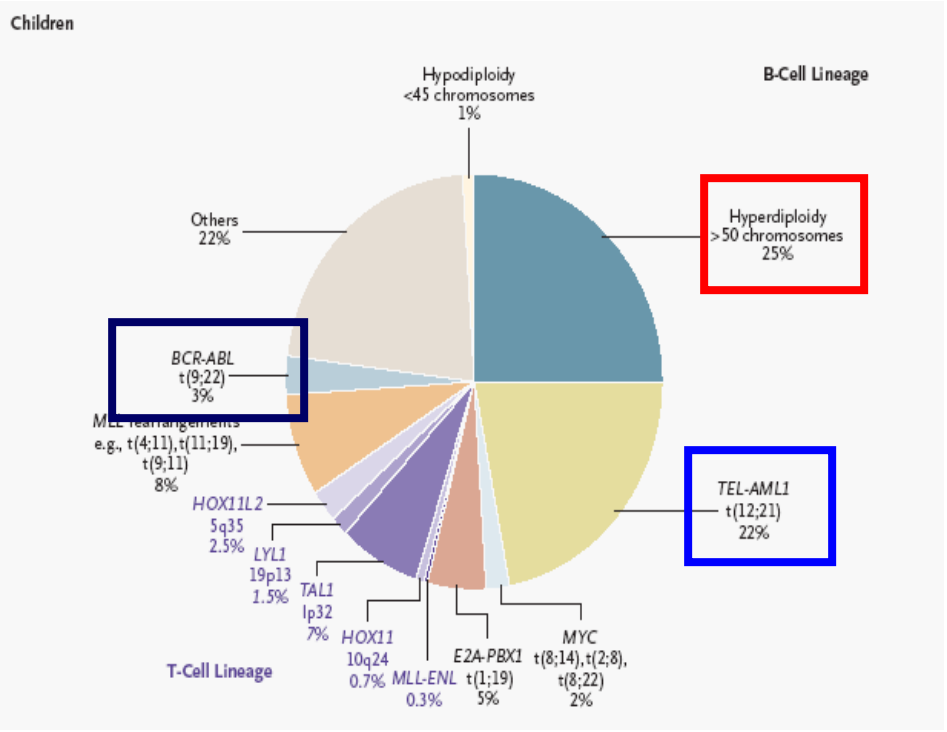


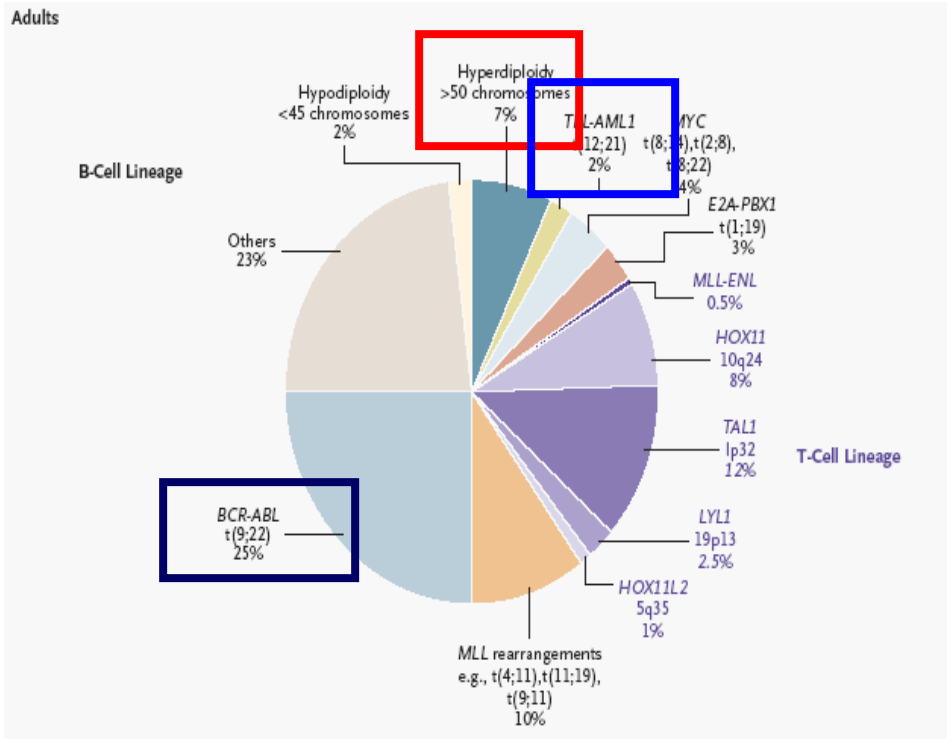



Childhood ALL represents the success story of modern oncology

Why has it not been possible to achieve similar results with adult ALL?

Cytogenetics and Molecular Pathogenesis of ALL





Ching Hon-Pui et al. NEJM 2004

Response profile

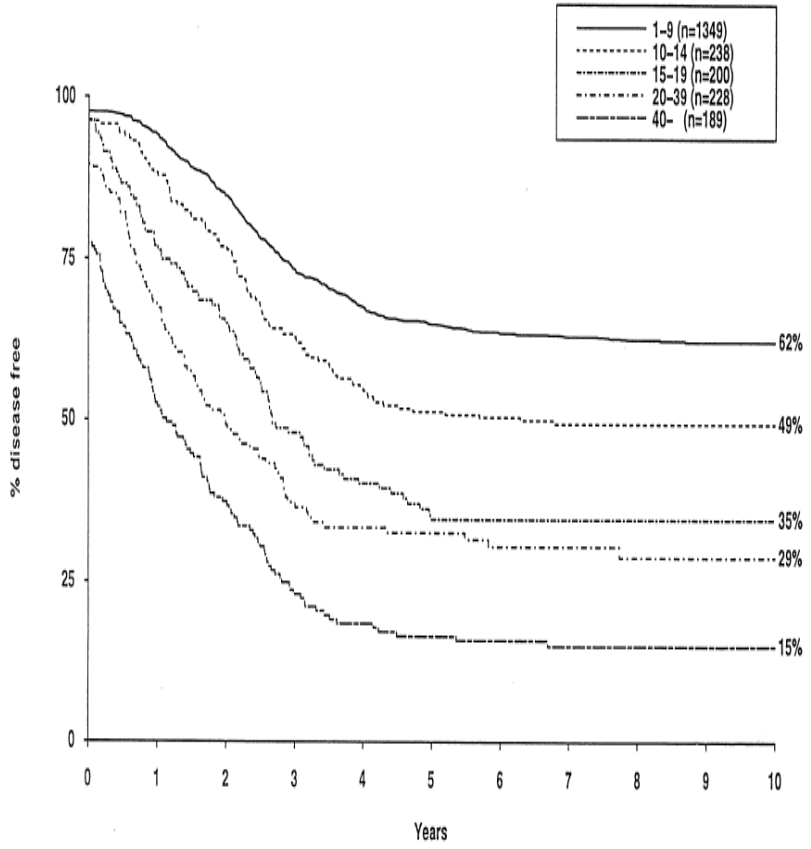


Figure 3 Disease-free survival by age in patients entered in UKALL X and XA. The starting point on the curve indicates remission rate. Patient under 1 year are excluded and all patients are censored at bone marrow transplant.

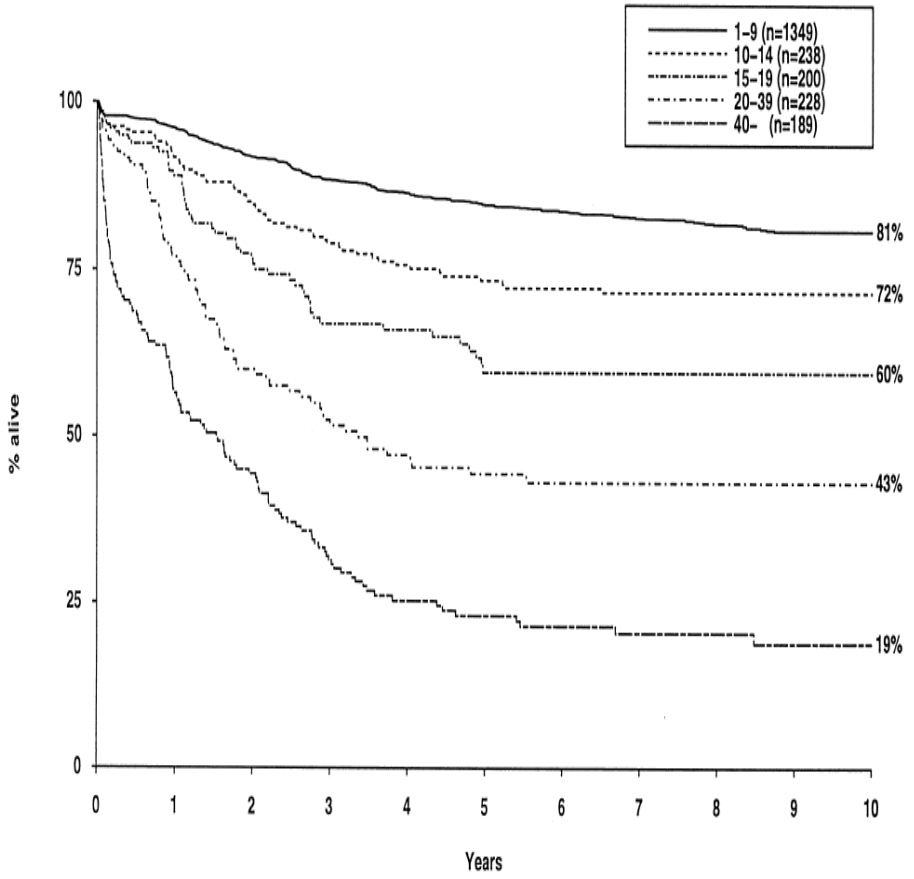
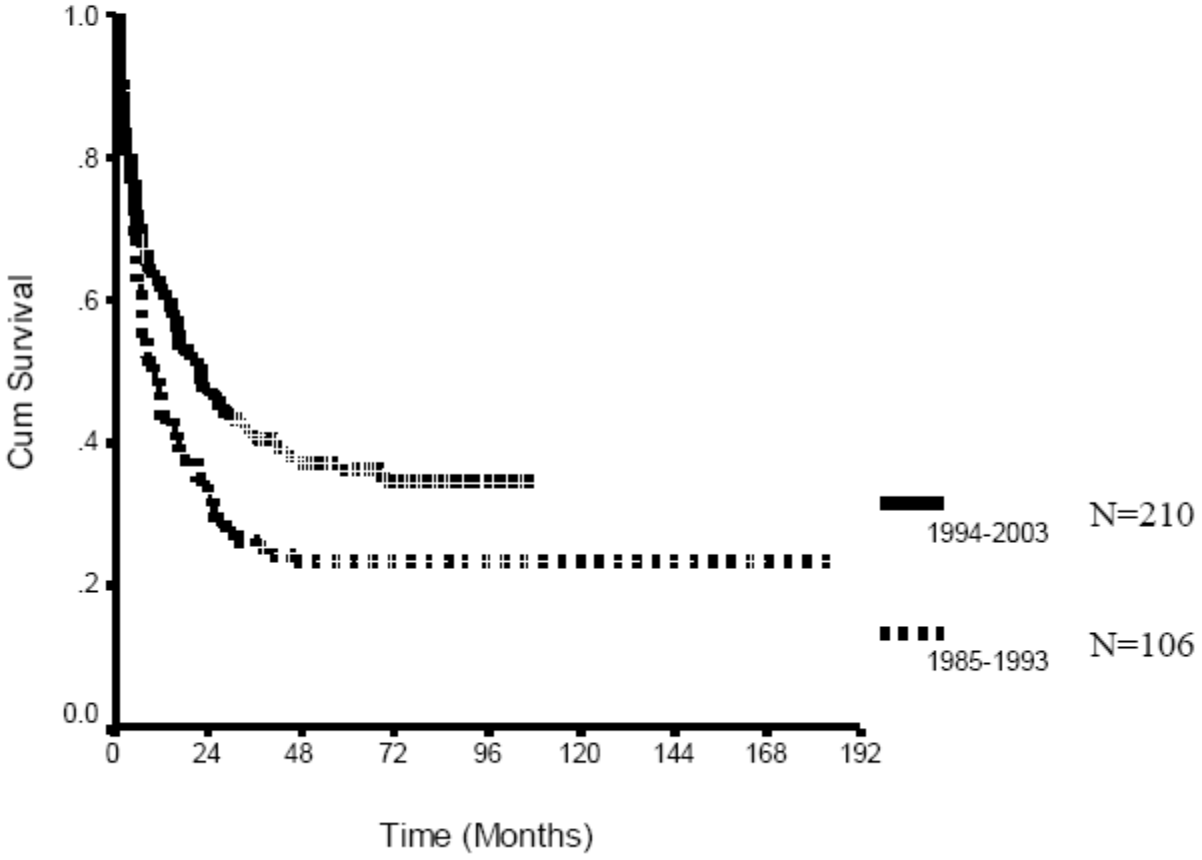


Figure 4 Survival by age in UKALL X and XA. Patients under 1 year are excluded and all patients are censored at bone marrow transplant.

Leukemia (1998) 12, 463–473The impact of age on outcome in lymphoblastic leukaemia; MRC UKALL X and XAcompared: a report from the MRC Paediatric and Adult Working PartiesJM Chessells et al.

CMC-Vellore: Adult ALL

Fig 3 – Kaplan Meier estimate of event free survival of patients treated between 1994-2003 and 1985-1993



ALL

- Principle of Treatment :

  combination chemotherapy

- Overview of treatment schedule:

  Remission Induction followed by consolidation, CNS prophylaxis re-induction and maintenance

- Rationale for existing schedules

  Multiple course of multi agent chemotherapy with maintenance chemotherapy

- Risk stratification

  As illustrated – combination of parameters

- Cost of treatment

  Rs 2.5 – 3.5 lakhs. Ph+ve Rs 10 – 12 lakhs

- Anticipated clinical outcomes

  ~ 70 – 80% cured (ped) ~40-50% cured (adult)

- Recent advances

  Use of Nelarabine in T cell ALL

  Use of Imatinib in Ph+ve ALL

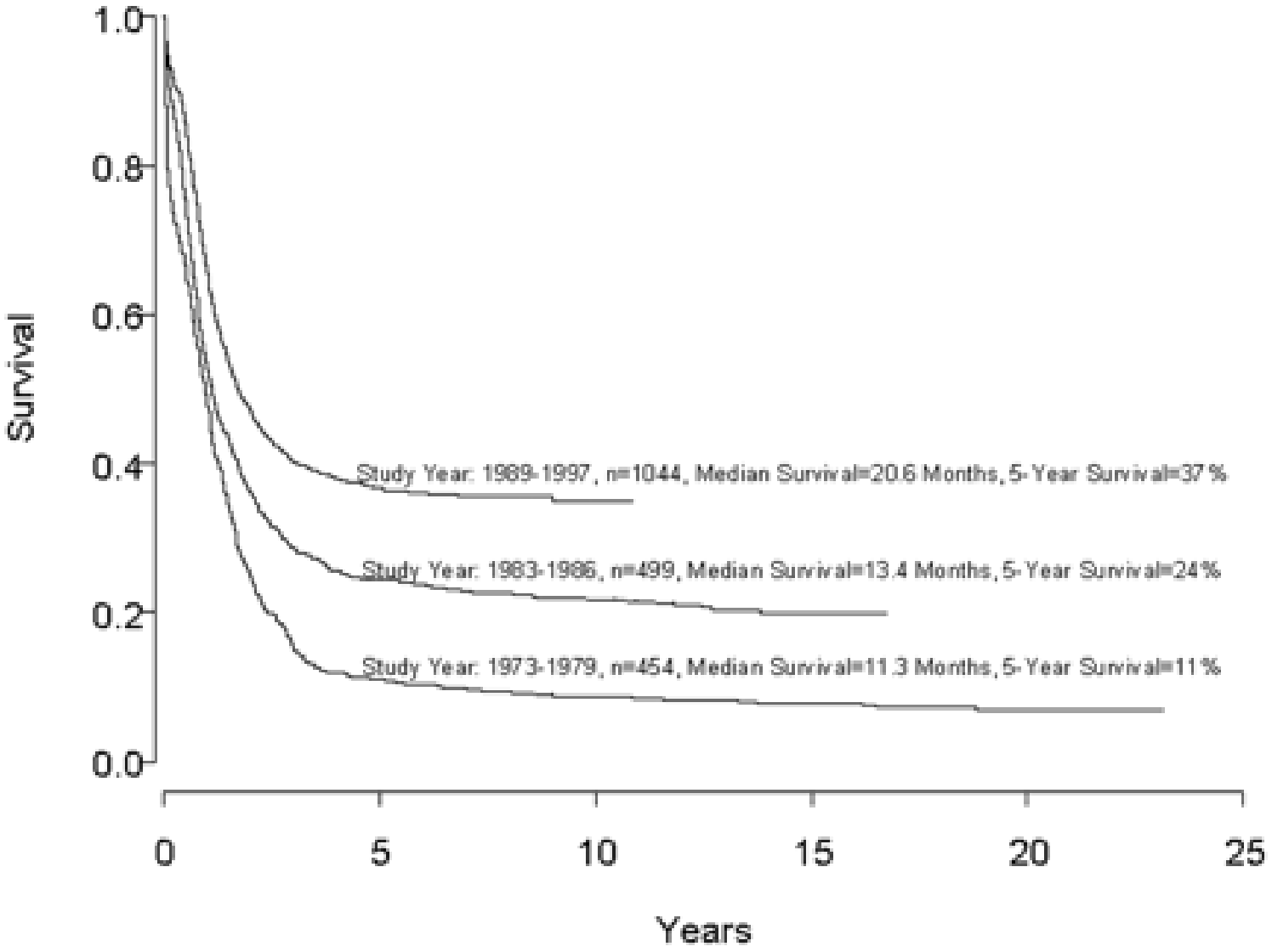
  Use of allogeneic SCT in CR1

Acute myeloid leukemia:

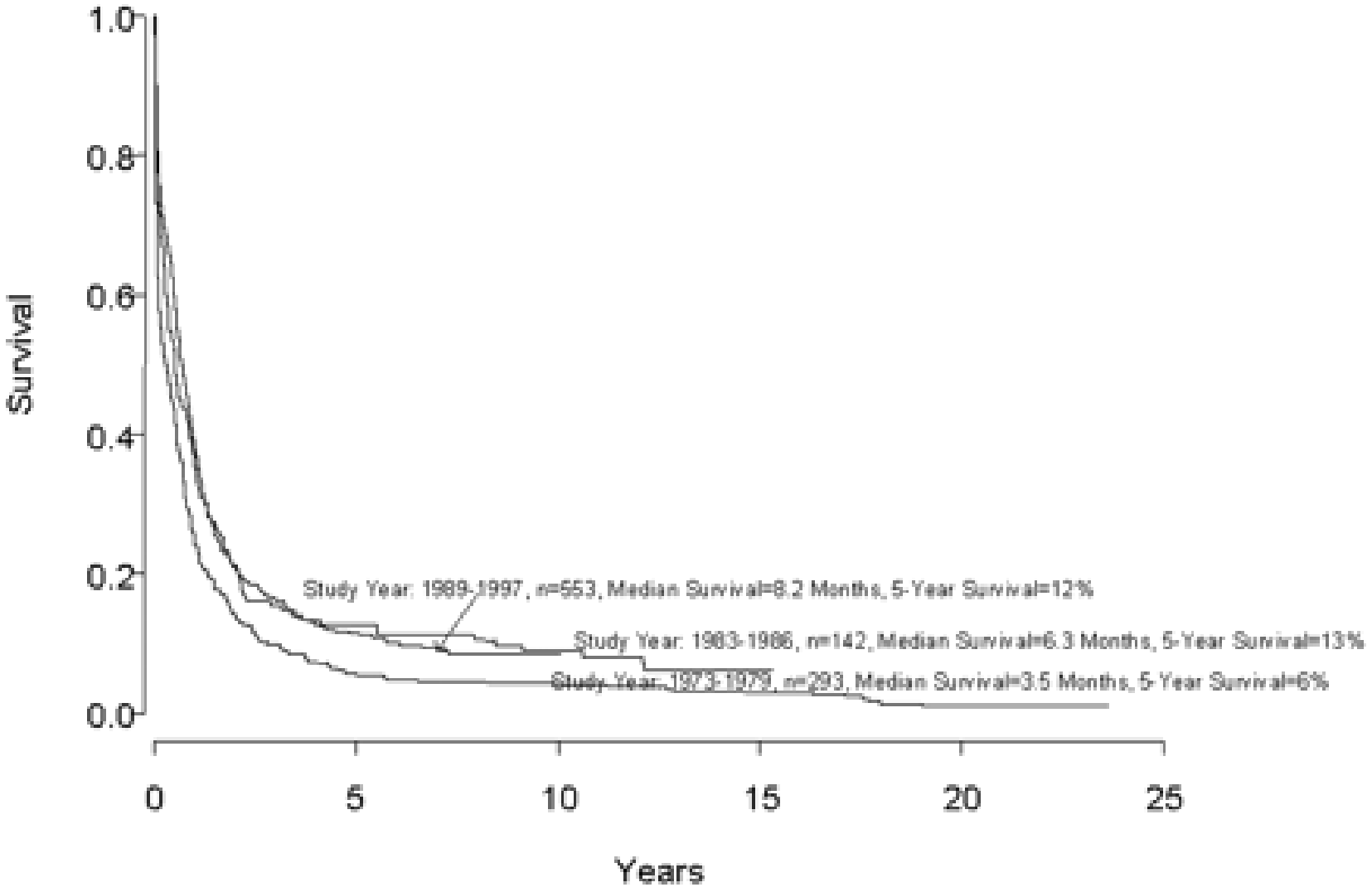
WHO classification of AML:

- AML with recurrent genetic abnormalities
  - AML with t(8;21) (*AML1/ETO*)
  - AML with inv(16) or t(16;16)(*CBF /MYH11*)
  - APL t(15;17)(*PML/RAR*) and variants (5 -15%)
  - AML 11q23 (*MLL*) abnormalities
- AML with multilineage dysplasia
- AML and MDS therapy related
- AML not otherwise categorized
  - AML minimally differentiated
  - AML without maturation
  - AML with maturation
  - AML myelomonocytic leukemia
  - AML monoblastic / monocytic leukemia
  - Acute erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
  - Myeloid sarcoma

Patients <55 years with newly diagnosed acute myeloid leukemia (AML) treated on ECOG protocols since 1973.



Appelbaum et al. Hematology 2001



Patients > 55 years with newly diagnosed AML treated on ECOG protocols since 1973.

Appelbaum et al. Hematology 2001

Risk group definition: US intergroup

Good:	**t(15;17)**
(10-15%)	**t(8;21)**
	inv16, t(16;16)
Standard:	**+8**
(Intermediate)	**-y**
(65-75%)	**del 12 p**
	Normal karyotype
Poor:	**-5/del 5q**
(15-20%)	**-7/del7q**
	inv3q
	11q23
	20q
	21q
	t(9;22)
	complex cytogenetics

Success rates of karyotyping varies from 73 – 98%.

Giles et al. Hematology 2002

Acute Myeloid Leukemia

- Remission Induction 7/3

  Cytosine arabinoside 100 – 200mg/m2 CI x 7 days

  Anthracycline (Daounorubicin 45-60mg/m2/day) x 3 days

- Consolidation Therapy
  - Chemotherapy
  - Autologous Stem Cell Transplant
  - Allogeneic Stem Cell Transplant

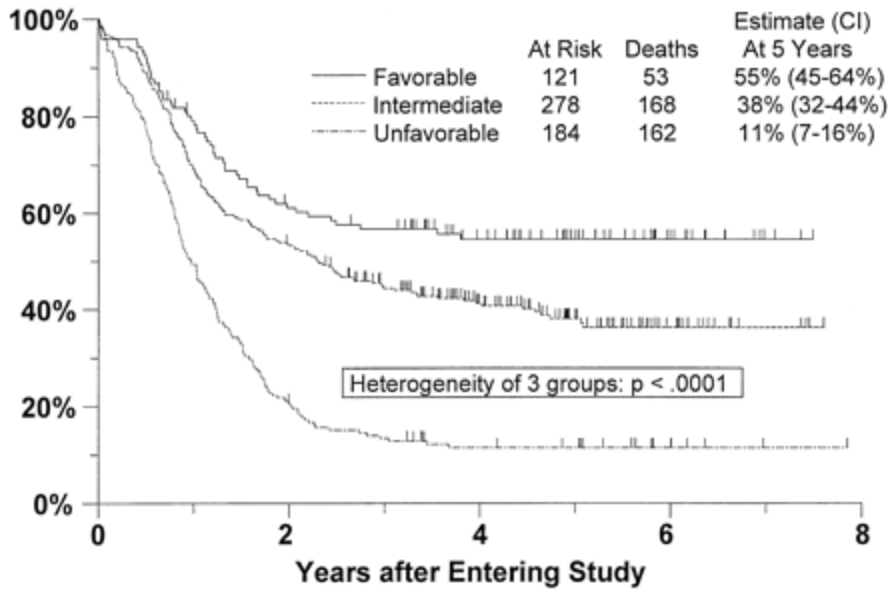
No role for maintenance chemotherapy

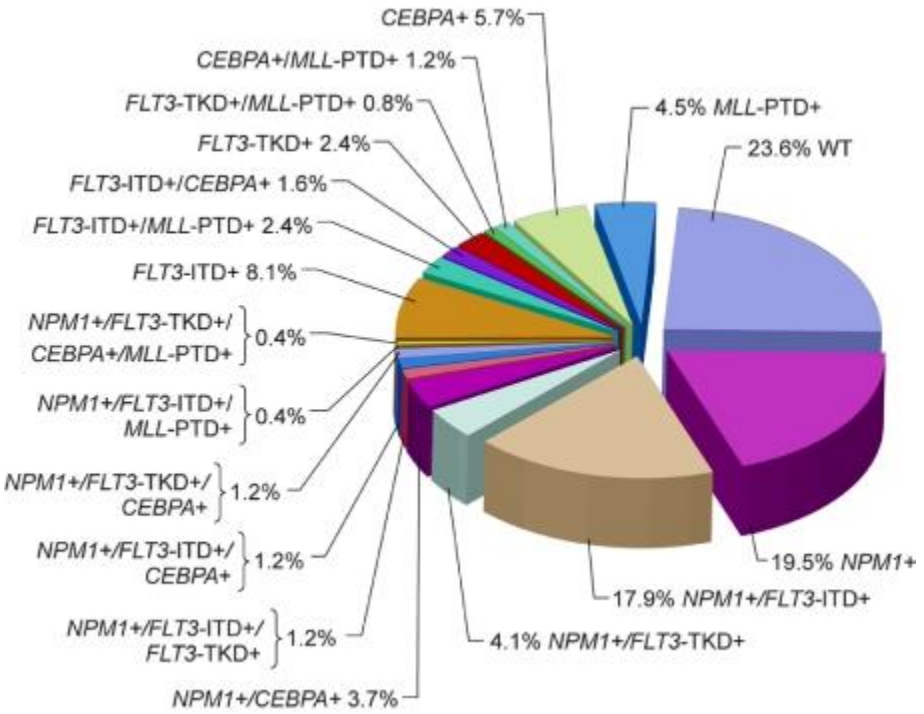
Consolidation:

	TRM	Relapse
- Intensive chemotherapy (High Dose Cytosine) x 2-4 cycles Cytosine arabinoside 3gm/m2 q12h day 1,3,5	+	+++
- Autologous stem cell transplantation	+	++
- Allogeneic stem cell transplantation	+++	+

AML outcome based on cytogenetic risk groups

Overall survival by AML cytogenetic risk group





Mrozek and Bloomfield, Blood 2007

Ref: Slovak ML et al Blood 2000: 96: 4075-83

Risk group definition:
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	11q
	20q
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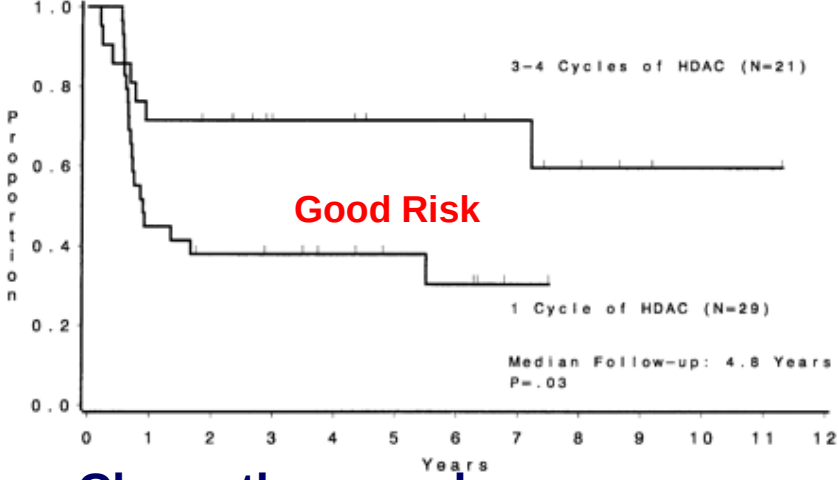
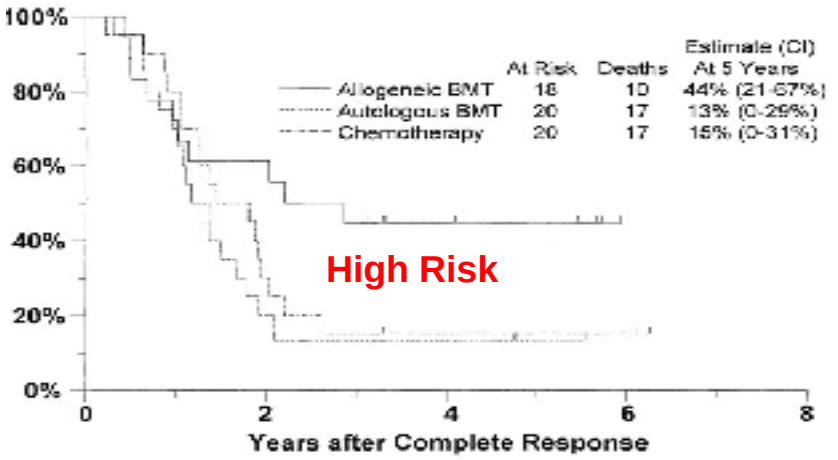


Chemotherapy alone. JC0 1999

CR1

- **Chemotherapy alone**
- **Autologous SCT**
- **Allogeneic SCT**



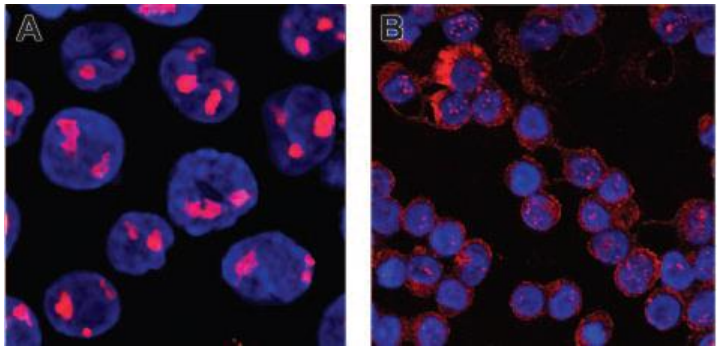
Blood 2000

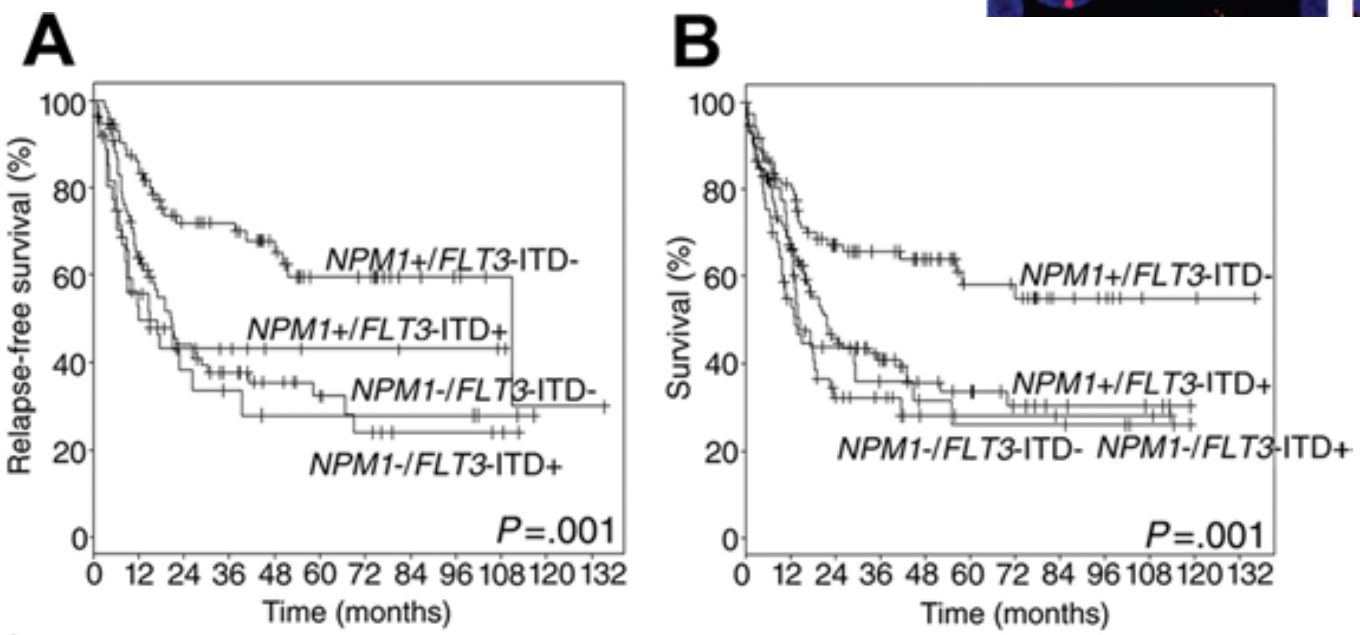
Giles et al. Hematology 2002

Intermediate / Standard Risk Group

- **Majority normal karyotype**
- **Heterogeneous group**
- **Identification of additional poor and good risk factors could potentially improve risk stratification and choice of therapy**

Nucleophosmin 1 gene mutations:





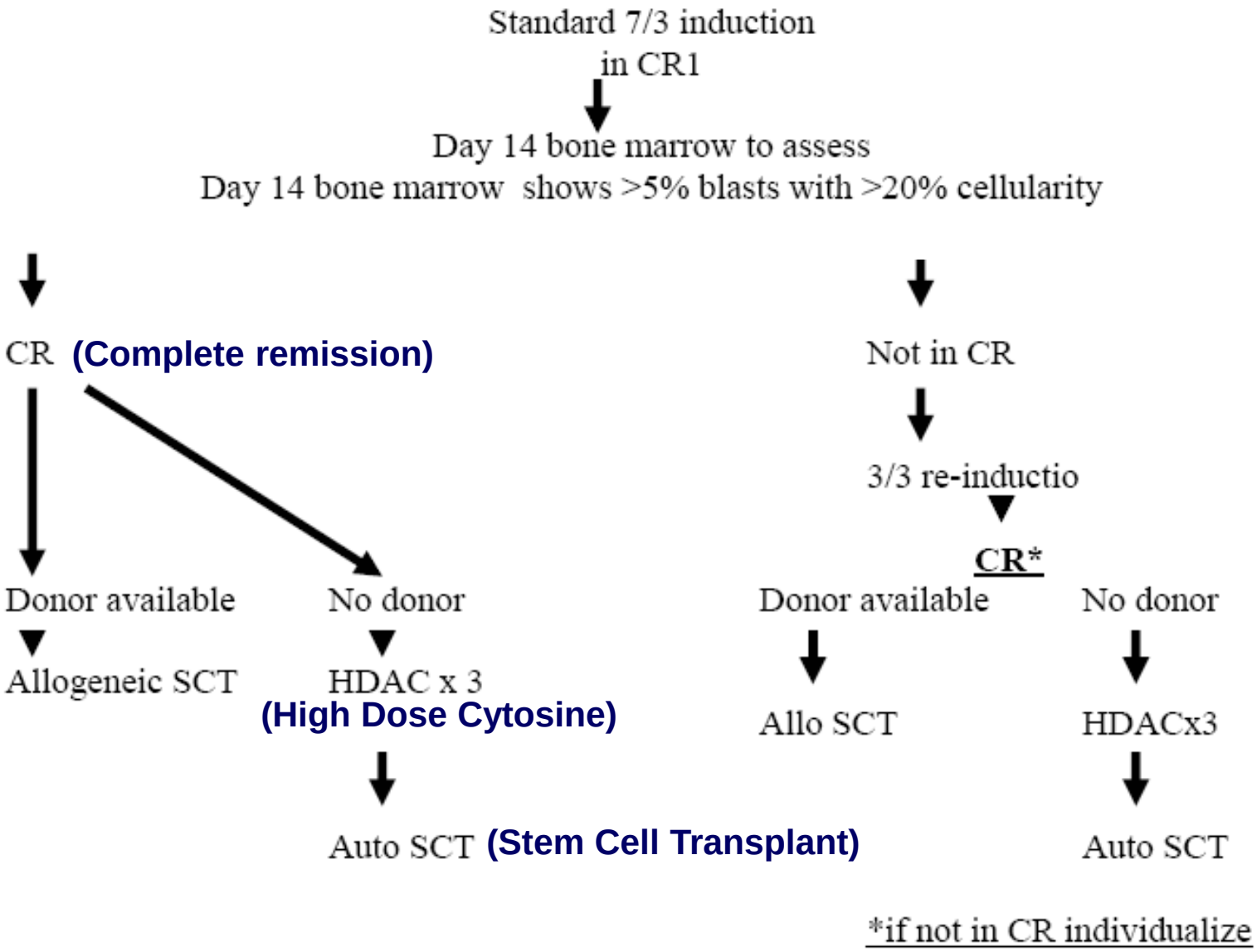
Number at risk:

NPM1+/FLT3-ITD-	74	58	40	36	26	15	13	6	4	2	1	1
NPM1-/FLT3-ITD-	78	47	28	20	14	9	6	3	3	2	0	0
NPM1+/FLT3-ITD+	37	16	10	8	4	3	3	2	2	1	0	0
NPM1-/FLT3-ITD+	28	15	8	6	4	4	4	4	4	2	0	0

	86	66	45	38	30	19	17	8	6	2	2	1
	117	71	42	29	18	14	8	5	4	3	0	0
	59	27	14	10	4	3	3	2	2	2	0	0
	38	24	11	8	6	5	5	5	4	2	0	0

Dohner et al. Blood 2005
Thiede et al. Blood 2006

Overview of approach – excluding Good Risk group:



- **Principle of Treatment :**

  high dose chemotherapy with graft versus leukemia effect with allogeneic SCT

- **Overview of treatment schedule:**

  Remission Induction followed by consolidation chemotherapy / auto SCT / allo SCT

- **Rationale for existing schedules**

  Short intensive therapy, no role for maintenance therapy

- **Risk stratification**

  Good, Standard/Intermediate and High Risk based on CTG

- **Cost of treatment**

  Rs 10 – 15 lakhs

- **Anticipated clinical outcomes**

  GR – 60-70%, SR – 40-50%, HR – 10-20%

- **Recent advances**

  Better understanding of risk stratification based on molecular markers

Acute promyelocytic leukemia

FAB: AML-M3

Distinctive

morphology
pancytopenia
clinical features - coagulopathy
younger age
response to retinoic acid
good prognosis

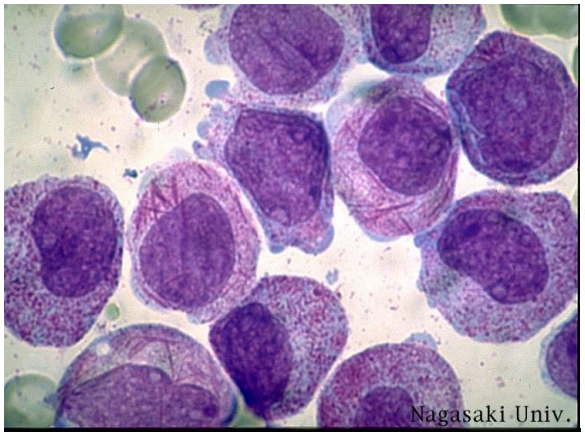
5 - 15% of all AML

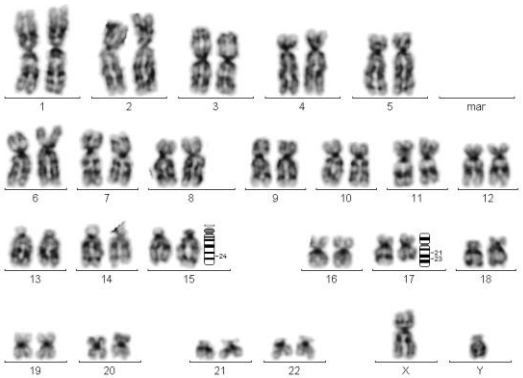
Estimated new cases of APL in the USA for 2003 = 900

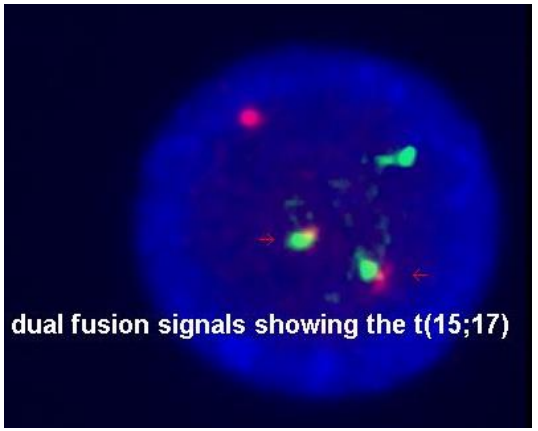
Jemal A et al. CA Cancer J Clin. 2003 Jan-Feb;53(1):5-26

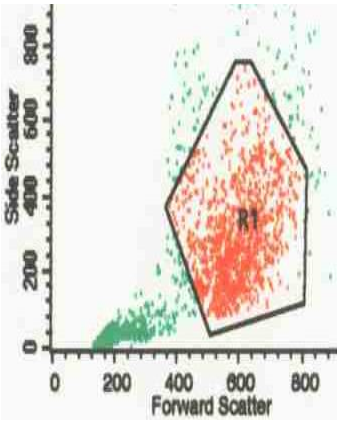
Projecting a similar incidence in India there should be approximately 4,000 – 5,000 new cases / year

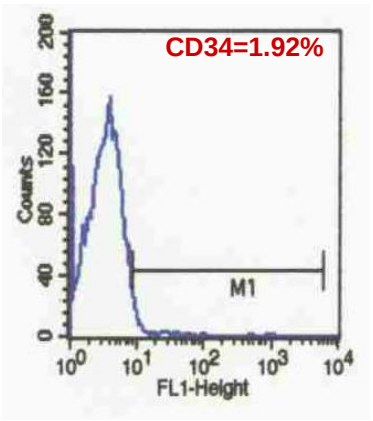
Acute promyelocytic leukemia

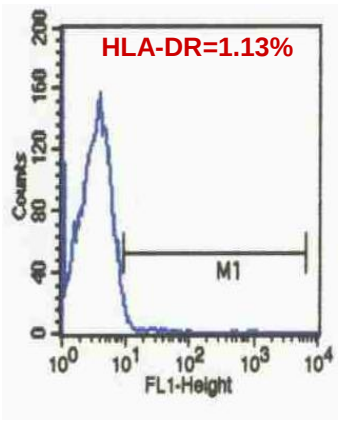


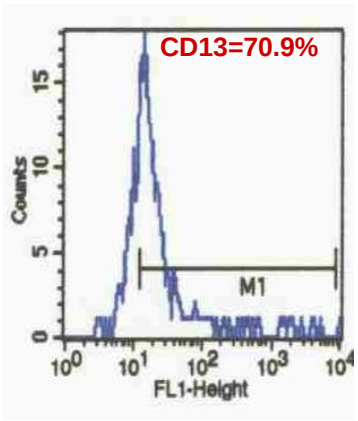


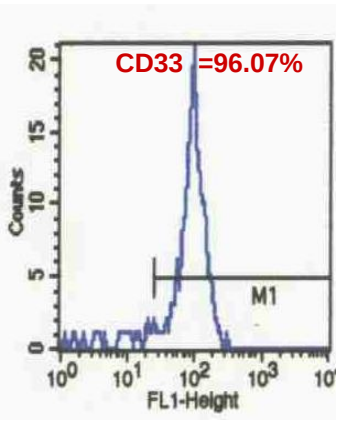




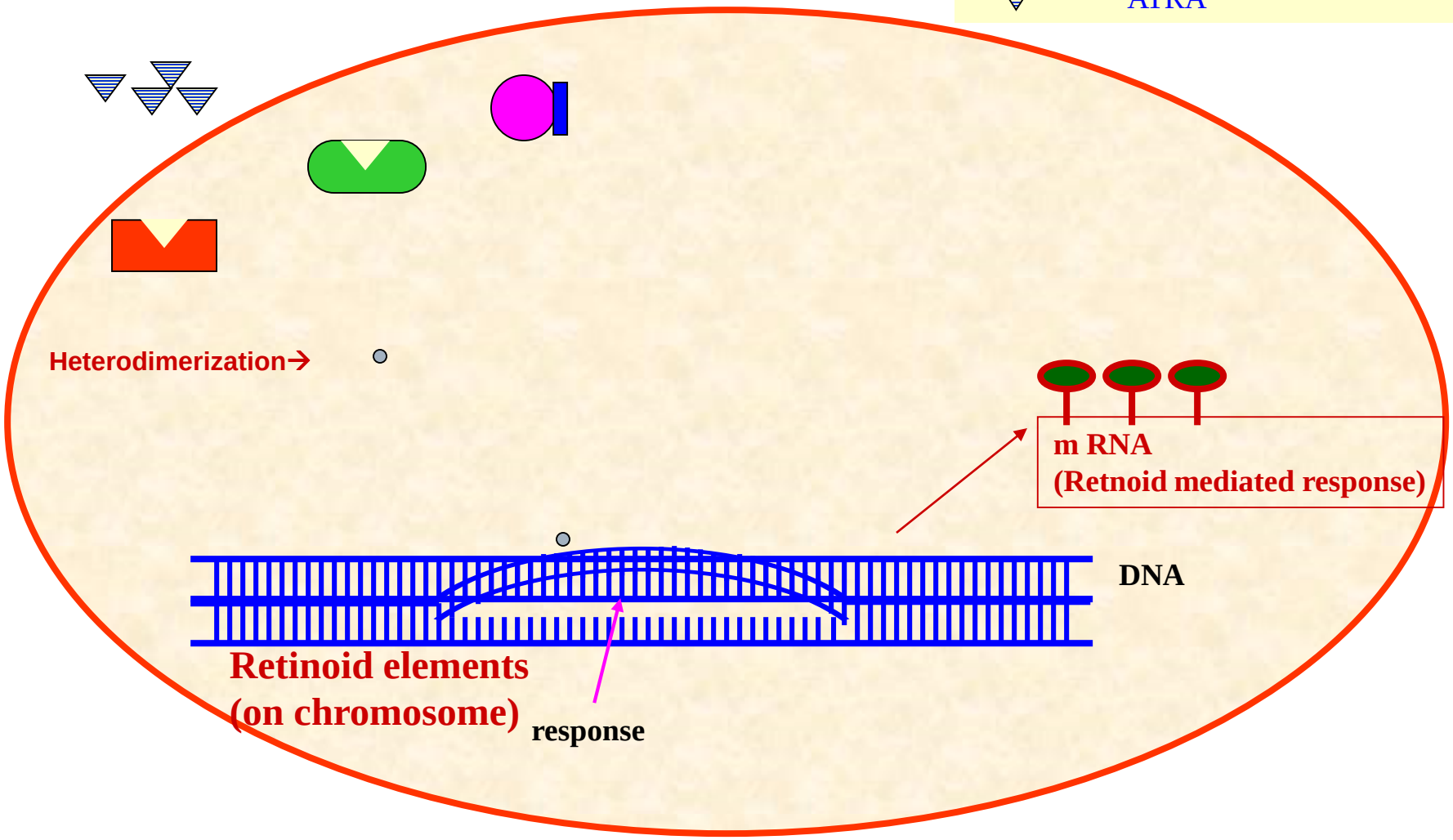








Molecular Pathogenesis

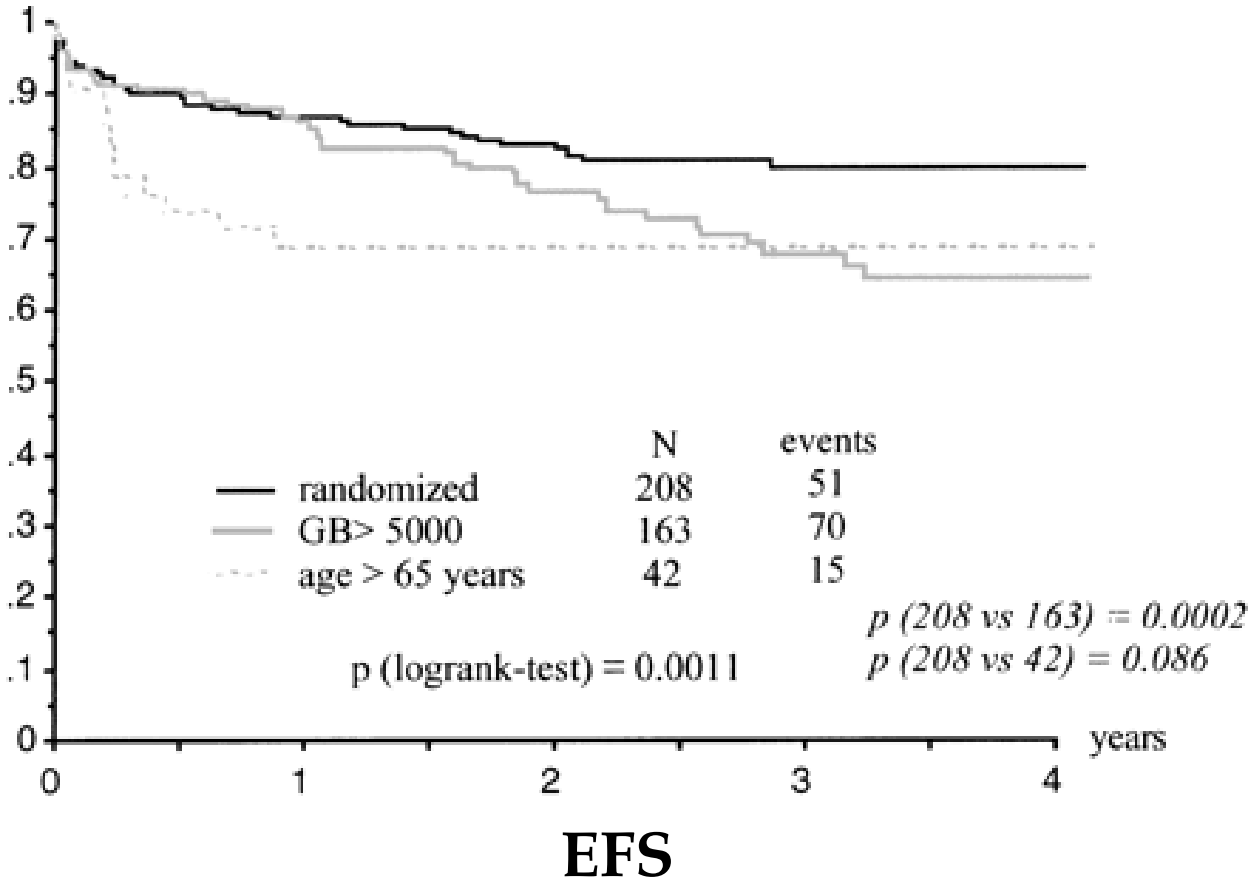


Treatment of APML

1970 - 1980's **chemotherapy** **5 yr CR 30 - 40%**
[myeloablative] early mortality 10 - 30%

Early 1990's **ATRA** **5 yr CR 70 - 80%**
[All-trans retinoic acid - differentiation] **early mortality 1 - 3%**

Treatment of APML



EFS

European APL 91 trial

EFS at 2 years 84±4%

Estimated 2 year survival 90% in those receiving maintaenance therapy

Established role of administration of ATRA with chemotherapy in induction.

Fenaux et al. Blood 1999

Risk Stratification

- WBC count > 10,000/mm3
- Platelet count < 40,000/mm3

  - High Risk
  - Intermediate
  - Low Risk

Sanz et al. Blood 2000

Treatment of APML

Conventional therapy:

- **expensive**
- **high incidence of grade III / IV neutropenia**
- **significant morbidity**
- **some mortality**

In the low risk group and other subsets associated with increased morbidity could potentially avoid

Treatment of APML

Potential curability of newly diagnosed acute promyelocytic leukemia without use of chemotherapy: the example of liposomal all-*trans* retinoic acid

Estey et al. Blood 2005

All-trans retinoic acid/As_2O_3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia

PNAS 2004

Zhi-Xiang Shen*†, Zhan-Zhong Shi*†, Jing Fang*†, Bai-Wei Gu*, Jun-Min Li*, Yong-Mei Zhu*, Jing-Yi Shi*, Pei-Zheng Zhang*, Hua Yan*, Yuan-Fang Liu*, Yu Chen*, Yang Shen*, Wen Wu*, Wei Tang*, Samuel Waxman‡, Hugues de Thé§, Zhen-Yi Wang*, Sai-Juan Chen*¶, and Zhu Chen*¶

*Shanghai Institute of Hematology, State Key Lab of Medical Genomics, Rui Jin Hospital affiliated with Shanghai Second Medical University, 197 Rui Jin Road II, Shanghai 200025, China; †Centre National de la Recherche Scientifique, Unité Propre de Recherche 9051, Laboratoire Associé du Comité de Paris de la Ligue Contre le Cancer, Affilié à l'Université de Paris VII, Hôpital St. Louis, 1 Avenue C. Vellefaux, 75475 Paris Cedex 10, France; and ‡Division of Hematologic Diseases, Department of Medicine, Mount Sinai Medical Center, New York, NY 10029-6547

USE OF ALL-TRANS RETINOIC ACID + ARSENIC TRIOXIDE AS AN ALTERNATIVE TO CHEMOTHERAPY IN UNTREATED ACUTE PROMYELOCYTIC LEUKEMIA

Elihu Estey[1], Guillermo Garcia-Manero[1], Alessandra Ferrajoli[1], Stefan Faderl[1], Srdan Verstovsek[1], Dan Jones[2], Hagop Kantarjian[1]

Departments of Leukemia[1] and Hematopathology[2], University of Texas M.D. Anderson Cancer Center, 1515 Holcombe, Houston, Texas 77030

Blood 2005

ARSENIC

As

1910 Paul Erhlich used arsenic to treat syphilis

- Used as early as 2000BC as medicine as well as a poison
- Familiar to early physicians
  - Hippocrates (460-377 BC)
  - Aristotle (384-322 BC)
- Paracelsus (1493-1541 AD) “All substances are poisons, the right dose differentiates a poison from a remedy”
- Fowlers solution (1% potassium arsenite) popular for treatment of dermatological conditions
- Folkner and Scott (1931) used Fowlers solution in the treatment of CML
- More recently melarsoprasol (organic arsenical) used in the treatment of trypnosomiasis
- Used in the treatment of APML since 1970’s
  - Zhang TD et al. Chin J 1984 (Ai Ling No. 1)

Arsenic trioxide in APML

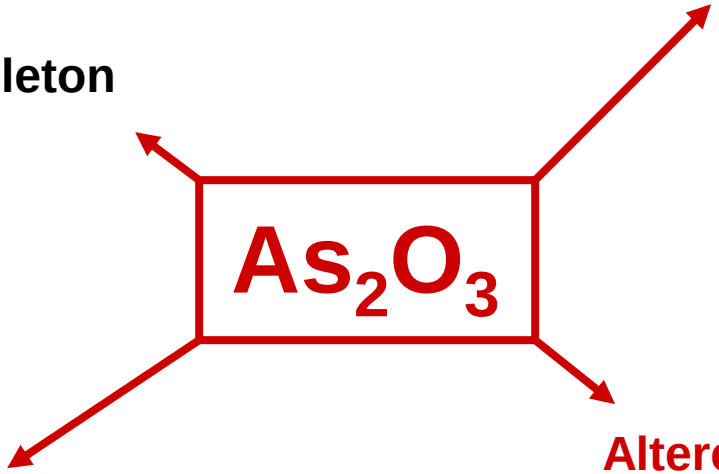
Mechanism of action

Induce apoptosis [0.5-1.0μM]

- downregulation of bcl2
- increased expression of caspases
- activation of jun kinases
- reorganize POD
- disruption of cytoskeleton
- inhibition of NFκB

Induce differentiation [<0.5μM]

- degradation of PML-RARα
- acetylation of histones 3, 4



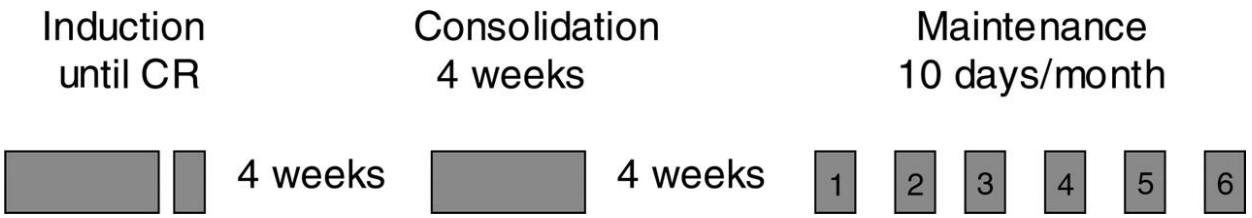
Inhibits angiogenesis

- HUVEC apoptosis
- down regulates VEGF

Altered cellular Redox status

- Reactive oxygen species (ROS generation
- bind sulfhydryl rich proteins/enzymes such as glutathione - reduce level

Figure 1. Regimen of single-agent arsenic trioxide



STUDY PROTOCOL:

Induction: As_2O_3 10mg/day till CR [max - 60 days]

4 weeks rest

Consolidation*: As_2O_3 10mg/day x 4 weeks

4 weeks rest

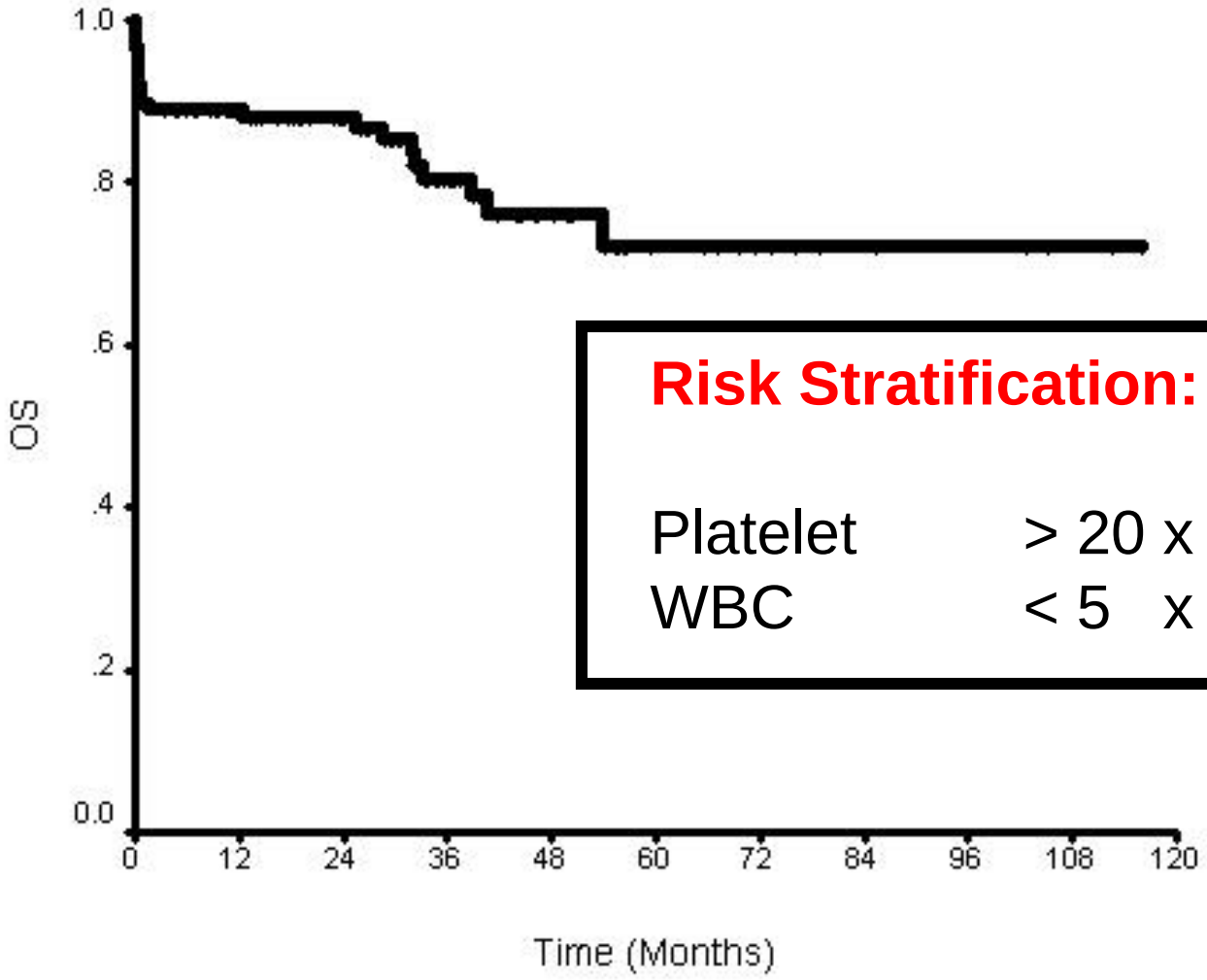
Maintenance*: As_2O_3 10mg/day x 10days, once a month x 6 months

*** Administered if in CR.**

n=129.

Mean follow up 35 months

5 year Kaplan-Meier estimate of OS = 72.11±6.13%



Risk Stratification:

Platelet	> 20 x 10e9/Lt
WBC	< 5 x 10e9/Lt

Arsenic trioxide in APML

Toxicity profile

- No infusional toxicities
- No alopecia
- No nausea / vomiting
- Post induction - no cytopenia
- No evidence of exacerbation of coagulopathy
- To date no case of secondary malignancy
- Most toxicities mild / no significant morbidity associated / resolve

APML

- **Principle of Treatment :**
  - differentiation + high dose chemotherapy
- **Overview of treatment schedule:**
  - Remission Induction followed by consolidation and maintenance
- **Rationale for existing schedules**
  - Short intensive therapy, no role for maintenance therapy
- **Risk stratification**
  - High and Low risk based on WBC count
- **Cost of treatment**
  - Rs 4 - 10 lakhs
- **Anticipated clinical outcomes**
  - ~ 70 – 80% cured
- **Recent advances**
  - ATO+ATRA+Anthracycline regimens

- **Chronic Myeloid Leukemia**
- **Chronic Lymphocytic Leukemia**

Chronic Myeloid Leukemia

1 – 2 cases per 100,000

15% of all leukemias in adults

Median age at presentation- 45 – 55 yrs

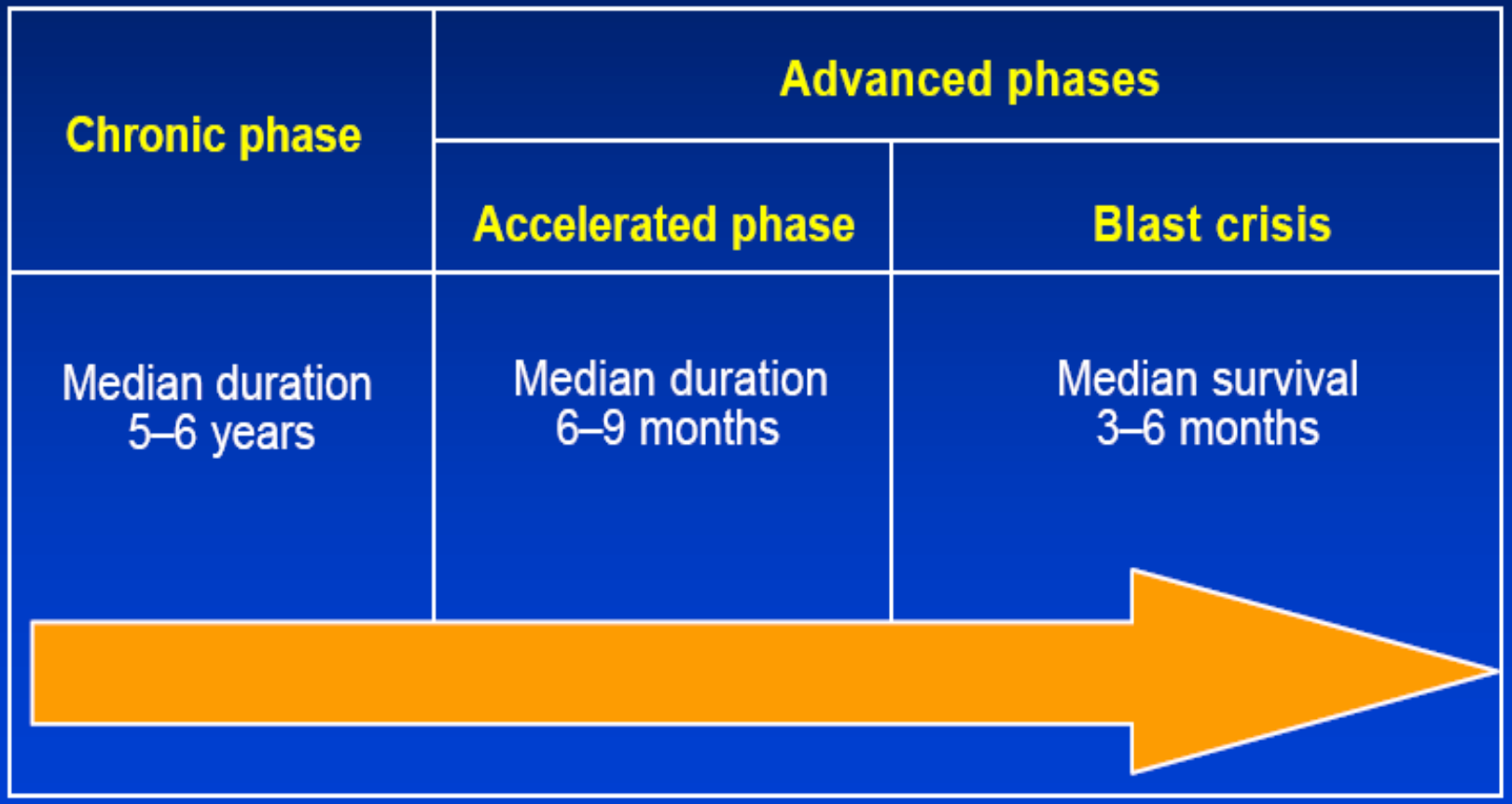
85% diagnosed in chronic phase and 50% are diagnosed on routine tests

In blast crisis 30% are lymphoid and 70% myeloid

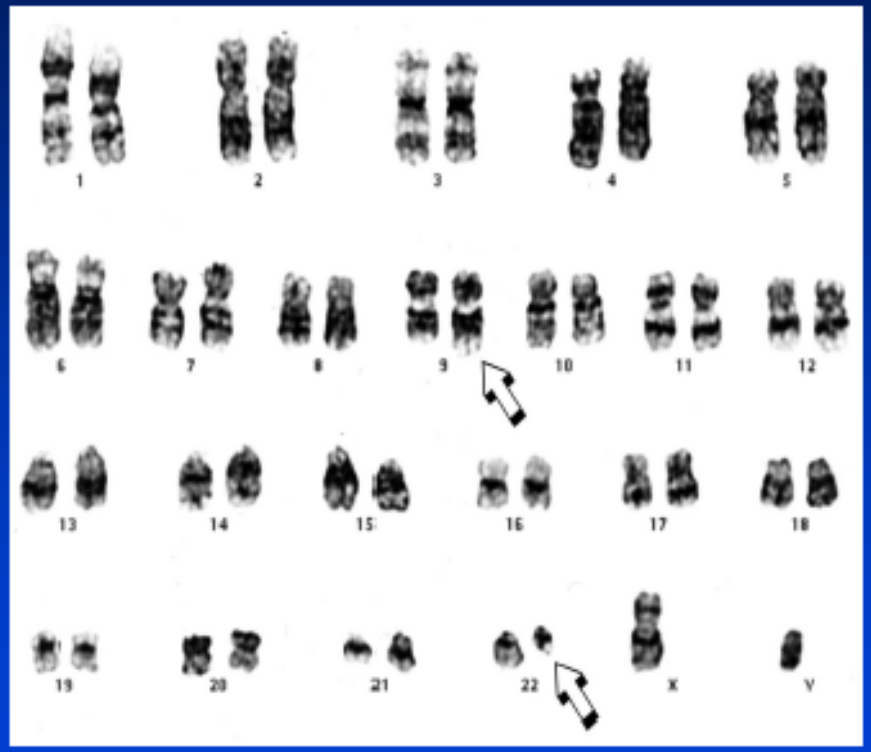
Ph chromosome found in 95% of CML, 5% of ALL in children, 15-30% Adult ALL and 2% of AML

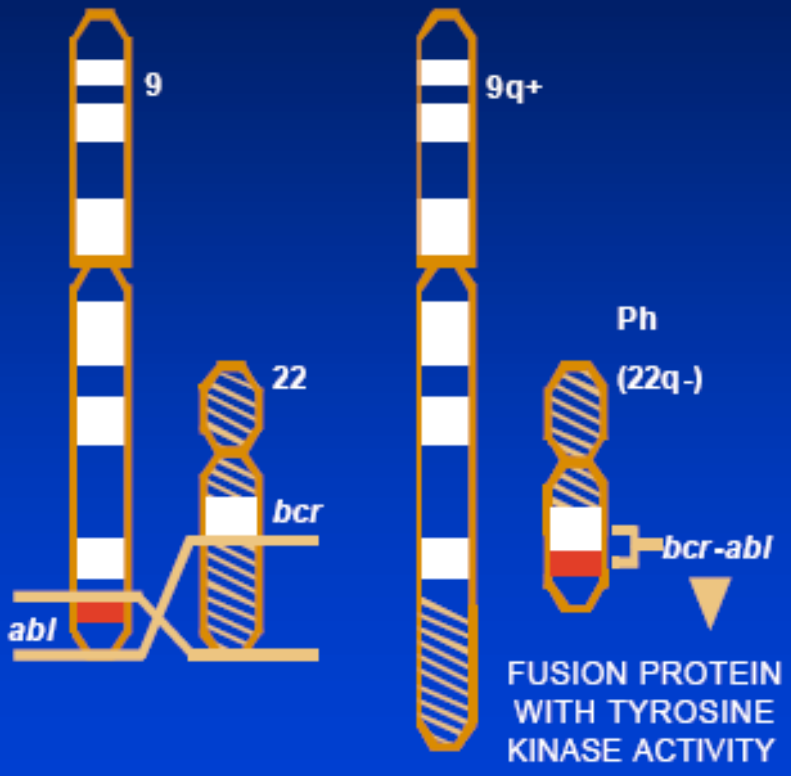
NEJM 1999;341:164

CML: a Progressive and Fatal Disease



CML: Linked to a Single Molecular Abnormality





The Philadelphia (Ph) Chromosome: t(9;22) Translocation

It took around 40 yrs from discovery of the “minute chromosome” to imatinib to come into the market

1960 – Nowell and Hungerford

1973 – Janet Rowley

1984 – Detection of bcr / abl gene

1985 – Product of the gene bcr / abl protein discovered

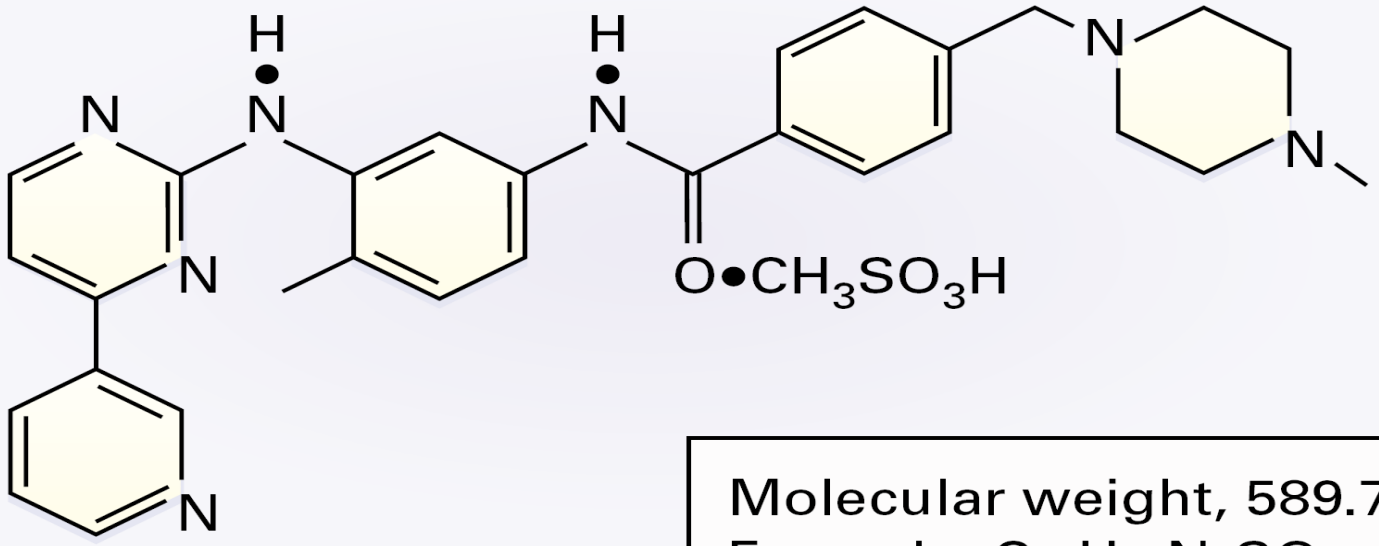
Being an enzyme and it’s presence in the cytoplasm it was amenable to inhibition by a drug.

1998 – 1st human volunteer to take Imatinib.

2001 – FDA approval for imatinib in newly diagnosed CML in CP.

Formerly known as CGP57148B or STI571

Imatinib mesylate



Molecular weight, 589.7
Formula, $C_{30}H_{35}N_7SO_4$

Formerly STI571.

2 Phenylamino pyrimidine

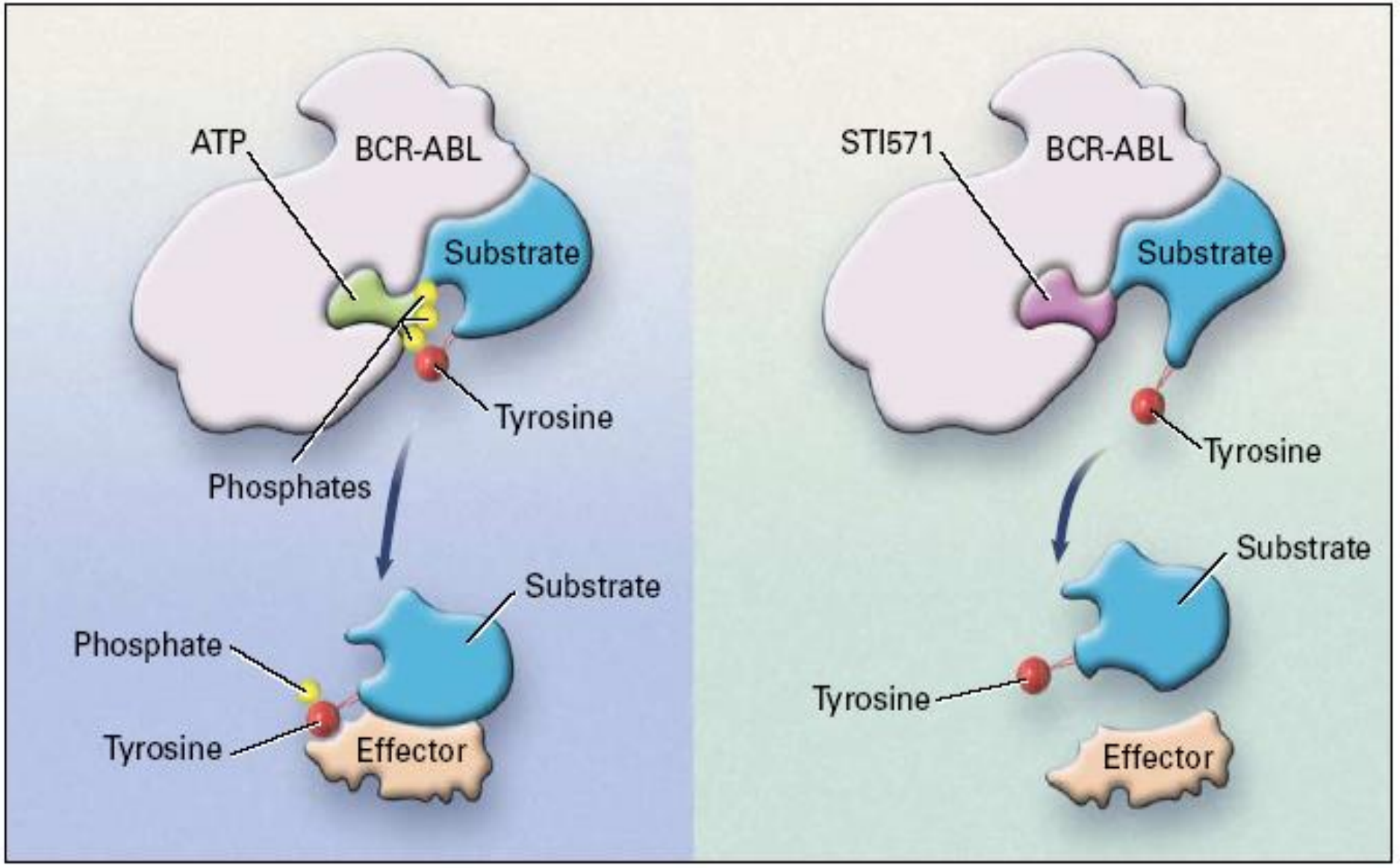
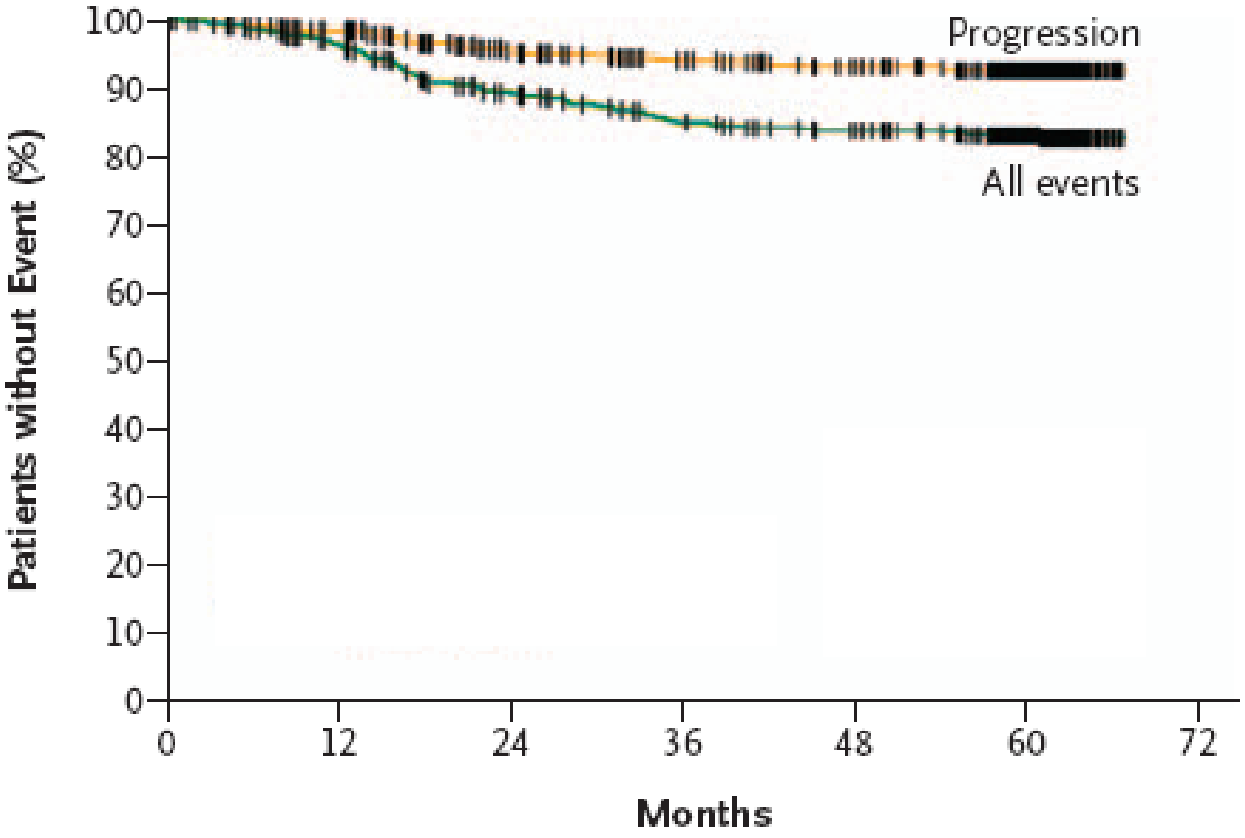


Figure 1. Likely Mode of Action of STI571.

The left-hand panel shows the BCR-ABL oncoprotein with a molecule of ATP in the kinase pocket. The relevant substrate is phosphorylated on a tyrosine residue and, in its phosphorylated state, can then interact with other downstream effector molecules. When STI571 occupies the kinase pocket (right-hand panel), the action of ATP is inhibited, and the substrate cannot be phosphorylated.

Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia



Chronic Lymphocytic Leukemia

- Most common leukemia in the Western world accounting for 40% of all leukemias in those above 65 years
- Median age 65 – 70 years
- Overall incidence about 3/100,000/yr
- 20-30 times more common in Europe, North America than in India, China and Japan
- M:F = 2:1

BJH 2004

Clinical features:

- Most patients at diagnosis are asymptomatic
- Fatigue
- AIHA
- Generalized lymphadenopathy
- Hepatosplenomegaly
- Extranodal infilterates
- Small M component can be found in a few patients

Blood 2008

Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines

Michael Hallek,[1] Bruce D. Cheson,[2] Daniel Catovsky,[3] Federico Caligaris-Cappio,[4] Guillaume Dighiero,[5] Hartmut Döhner,[6] Peter Hillmen,[7] Michael J. Keating,[8] Emili Montserrat,[9] Kanti R. Rai,[10] and Thomas J. Kipps[11]

[1]Klinik I für Innere Medizin, Universität zu Köln, Köln, Germany; [2]Georgetown University Hospital, Lombardi Cancer Center, Washington, DC; [3]Institute of Cancer Research, London, United Kingdom; [4]Universita Vita-Salute Istituto di Ricovero e Cura a Carattere Scientifico (IRCSS) San Raffaele, Milano, Italy; [5]Institute Pasteur, Montevideo, Uruguay; [6]University of Ulm, Ulm, Germany; [7]Pinderfields Hospital, Wakefield, United Kingdom; [8]Department of Leukemia, University of Texas, M. D. Anderson Cancer Center, Houston; [9]Hospital Clinic, Barcelona, Spain; [10]Division of Hematology/Oncology, Long Island Jewish Medical Center, New Hyde Park, NY; and [11]Rebecca and John Moores Cancer Center, University of California–San Diego, La Jolla

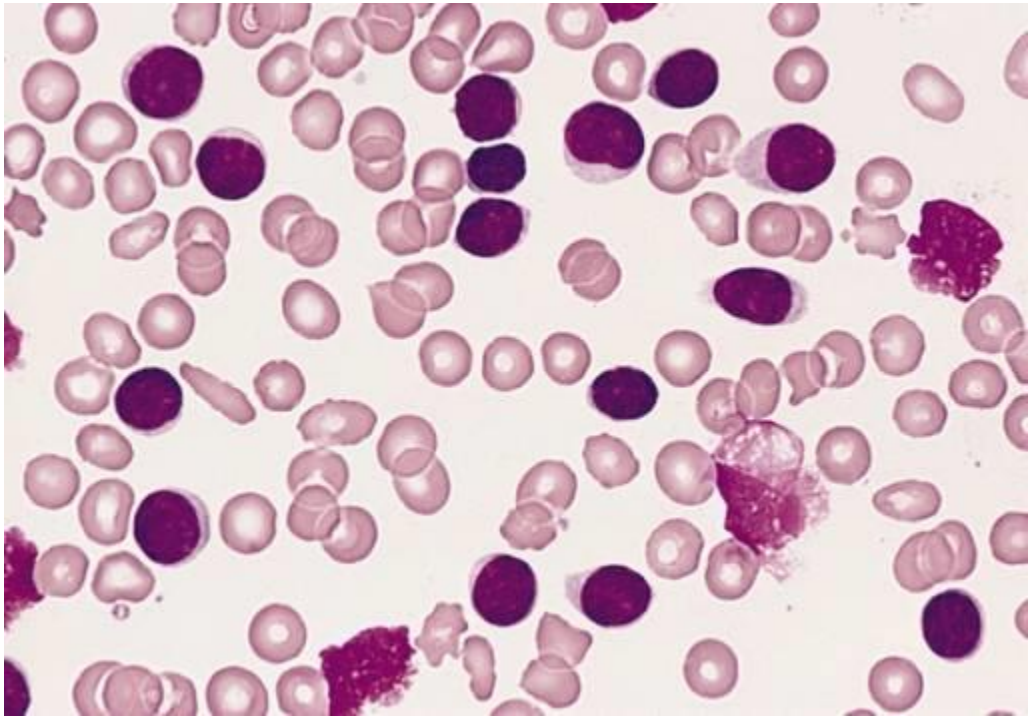
Diagnosis requires:

- >5000/mm3 B lymphocytes in PB for >3 months
- Clonality has to be confirmed by IPT (flowcytometry)
- >55% prolymphoctyes diagnosis of B cell PLL

Peripheral Smear

CLL cells are small lymphocytes with clumped chromatin and scant cytoplasm. Nucleoli indistinct. Smudge cells

Bone marrow involvement can be nodular, interstitial, diffuse or a combination of these



Immunophenotype:

Classically : CD5, CD19 and CD23 positive
Smlg (with k/l restriction), CD20, CD22, CD79b and, CD43 weak
CD10, cyclin D1 negative

Rarely CD5+ or CD23 –ve

CD38+
ZAP-70+

Table II. Scoring system for the diagnosis of chronic lymphocytic leukaemia (CLL).

	Score points	
Marker	1	0
Smlg	Weak	Strong
CD5	Positive	Negative
CD23	Positive	Negative
FMC7	Negative	Positive
CD22 or CD79b	Weak	Strong

Scores in CLL are usually >3, in other B-cell malignancies the scores are usually <3.

Blood 2008

Table IV. Staging systems in chronic lymphocytic leukaemia.

	Features	% of patients
Binet stage		
A	<3 lymphoid areas*	60
B	>3 lymphoid areas	30
C	Haemoglobin < 10·0 g/dl or platelets < 100×10^9/l	10
Rai stage		
0†	Lymphocytosis only	30
I†	Lymphadenopathy	25
II‡	Hepato or splenomegaly ± lymphadenopathy	25
III§	Haemoglobin < 11·0 g/dl	10
IV§	Platelet < 100×10^9/l	10

*The five lymphoid areas comprise unilateral or bilateral cervical, axillary and inguinal lymphadenopathy, hepatomegaly and splenomegaly.

†Risk group at low level.

‡Risk group at intermediate level.

§Risk group at high level.

BJH 2004

Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute Working Group 1996 guidelines

Table 2. Recommendations regarding indications for treatment in CLL

	General practice*	Clinical trial
Treat with Rai stage 0	No†	RQ
Treat with Binet stage A	No†	RQ
Treat with Binet stage B or Rai stage I or II	Possible†	Possible†
Treat with Binet stage C or Rai stage III or IV	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	No	RQ

No indicates not generally indicated; RQ, research question.

*General practice is defined as the use of accepted treatment options for a patient with CLL not enrolled in a clinical trial.

†Treatment is indicated, if the disease is active as defined in "Indications for treatment."

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Table V. Indications for treatment.

Progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
Massive (>10 cm) or progressive lymphadenopathy
Massive (>6 cm) or progressive splenomegaly
Progressive lymphocytosis
>50% increase over 2 months
Lymphocyte doubling time <6 months
Systemic symptoms*
Weight loss >10% in previous 6 months
Fever >38°C for ≥2 weeks
Extreme fatigue
Night sweats
Autoimmune cytopenias

*It is important to exclude other causes for these symptoms, such as infection.

BJH 2004

Treatment Options:

- Single agent alkylator – Chlorambucil
- Steroids
- Purine analogues – Fludarabine based
  - Fludarabine
  - Flu / Cyclophosphamide
  - Flu / Cy / Rituximab
  - Flu / Mito
  - Flu / Cy / Mito
  - Flu / Mito / Dexa
  - Cladaribine
- Alemtuzumab
- SCT – Auto / Allo

Survival:

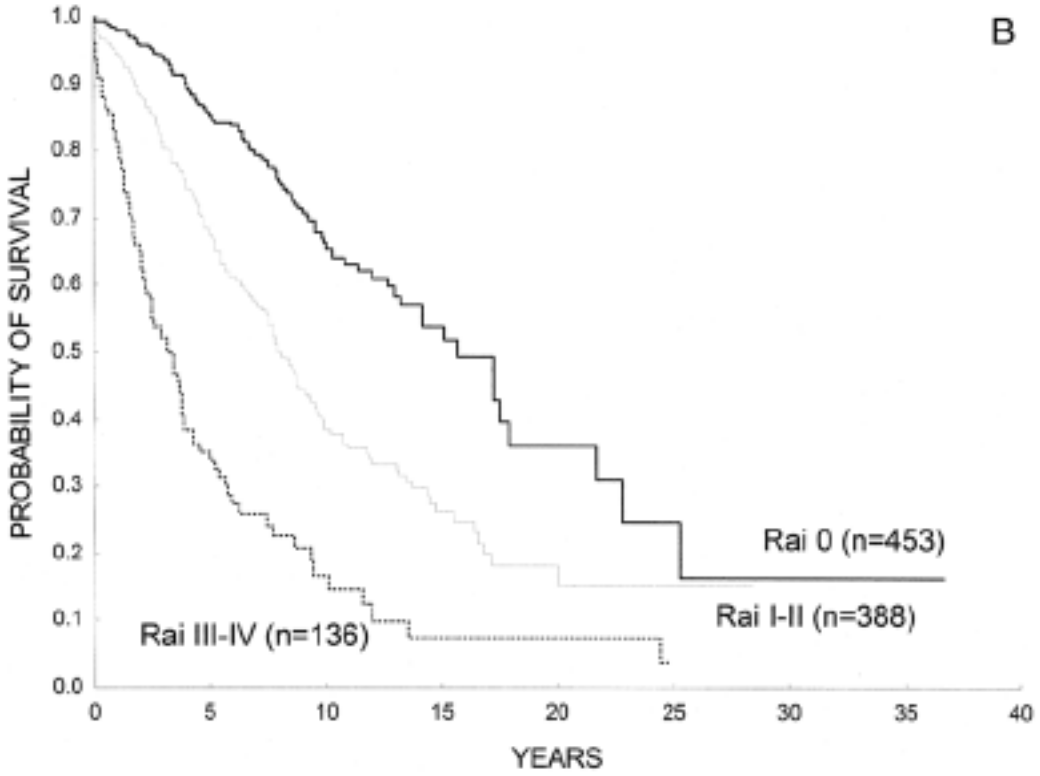

Figure 1. (A) Overall survival of patients with CLL according to Rai stages (Barcelona series).
(B) Overall survival of patients with CLL according to Binet stages (Barcelona series).

- **Median Survival 5 – 10 years**
- **No advantage in treating early asymptomatic disease**
- **Reassure the patient**
- **With minimal therapy often a good quality of life can be maintained**
- **Susceptible to infections – treat early**
- **Antibiotic prophylaxis in the setting of some treatment regimens**
- **Potential role for regular IVIg replacement**
- **Autoimmune disorders treat appropriately**
- **Immunize where applicable**

NOT TO BE MINISTERED UNTO BUT TO MINISTER

CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA