Management of Acute and Chronic Leukemia
PG-CME 2017

Vikram Mathews
Department of Haematology
Vellore 632004
- Principle of Treatment
- Overview of treatment schedule
- Rationale for existing schedules
- Risk stratification
- Cost of treatment
- Anticipated clinical outcomes
- Recent advances
Principle of treatment

- **Morphology**
- **Cytogenetics**
- **Southern Blot**
- **FACS**
- **PCR**

- **“MOLECULAR REMISSION”**
- **COMPLETE REMISSION**
- **MINIMAL RESIDUAL DISEASE**
- **PARTIAL REMISSION**
- **RELAPSE**
- **INDUCTION**
- **CONSOLIDATION**
- **REMISSION**

**TUMOUR CELL BURDEN**

- **Detection**
  - Morphology
  - Cytogenetics
  - Southern Blot
  - FACS
  - PCR
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
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

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

## Rome Risk criteria (1985)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
<th>% B cell</th>
<th>% T cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>WC &lt; 50 x 10⁹/l and Age 1-9 yrs</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>High</td>
<td>WC &gt; 50 x 10⁹/l or Age &gt; 9 yrs</td>
<td>25</td>
<td>75</td>
</tr>
</tbody>
</table>
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 >20,000cmm
- 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
- Myelofibrosis
- Autoimmune diseases (e.g., systemic lupus erythematosus)
- Infectious mononucleosis
- Juvenile rheumatoid arthritis
- Idiopathic thrombocytopenia purpura
- 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)
- Multiple myeloma

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

<table>
<thead>
<tr>
<th>JRA/JIA</th>
<th>Acute Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>Nocturnal pain</td>
</tr>
<tr>
<td>stiffness</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Nonarticular bony pain</td>
</tr>
<tr>
<td>LAD</td>
<td>LAD</td>
</tr>
<tr>
<td>HSM</td>
<td>HSM</td>
</tr>
</tbody>
</table>
Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Table 65–1</th>
<th>Chemotherapy of Childhood ALL: Historical Perspective</th>
</tr>
</thead>
</table>

**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

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 (days 12, 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**

**INDUCTION**
- Pred 60mg/m²
- VCR 1.4mg/m²
- DNR 30mg/m²
- ASP 70,000U/m²
- CP
- ARA-C 75mg/m²
- VP-16 50mg/m²

**CONSOLIDATION**
- Pred 60mg/m²
- VCR 1.4mg/m²
- DNR 30mg/m²
- ASP 70,000U/m²
- CP
- ARA-C 75mg/m²
- VP-16 50mg/m²

**REINDUCTION**
- Pred 60mg/m²
- VCR 1.4mg/m²
- DNR 30mg/m²
- ASP 70,000U/m²
- CP
- ARA-C 75mg/m²
- VP-16 50mg/m²

**MAINTENANCE**
- Pred 60mg/m²
- VCR 1.4mg/m²
- DNR 30mg/m²
- ASP 70,000U/m²
- CP
- ARA-C 75mg/m²
- VP-16 50mg/m²

**PHASE 1**
0  4  8  12  16  20  24  28  136

**PHASE 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednolone</td>
<td>60mg/m²</td>
<td>5 days</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m²</td>
<td>5 days</td>
</tr>
<tr>
<td>DNR</td>
<td>30 mg/C</td>
<td></td>
</tr>
<tr>
<td>ASP-L</td>
<td>70,000U/m²</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>650mg/m²</td>
<td></td>
</tr>
<tr>
<td>ARA-C</td>
<td>75mg/m² x 4 days</td>
<td></td>
</tr>
<tr>
<td>MTX-IT</td>
<td>12.5 mg</td>
<td></td>
</tr>
<tr>
<td>CR-RT</td>
<td>2400 cGy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednolone</td>
<td>60mg/m²</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4mg/m²</td>
<td></td>
</tr>
<tr>
<td>DNR</td>
<td>30 mg/C</td>
<td></td>
</tr>
<tr>
<td>ASP-L</td>
<td>70,000U/m²</td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARA-C</td>
<td>75mg/m² x 4 days</td>
<td></td>
</tr>
<tr>
<td>MTX-IT</td>
<td>12.5 mg</td>
<td></td>
</tr>
<tr>
<td>CR-RT</td>
<td>2400 cGy</td>
<td></td>
</tr>
</tbody>
</table>

**Chemotherapeutic Agents**
- DEXA Dexamethasone 10mg/m²
- 6MP Mercaptopurine 60mg/m²
- ADR Doxorubicin 25mg/m²
- MTX Methotrexate 20mg/m² once a week
- VCR Vincristine 1.4mg/m²
- DEXA Dexamethasone 6mg/m² x 5 days a month
- VP-16 50mg/m² x 5 days a month
- ARA-C Cytosine arabinoside 75mg/m² x 4 days

**Radiation Therapy**
- 2400 cGy Cranial radiotherapy

**Radiotherapy**
- VCR+ PRED PULSE
- MTX
- MTX-IT x 2 years
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

Management
- 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

(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.)

Copyright © 2005 Elsevier Inc. (USA) All rights reserved.
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).
## Impact on Treatment Algorithms in ALL

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Clinical Features</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Hyperdiploid</td>
<td>Conventional antimetabolites</td>
</tr>
<tr>
<td></td>
<td><em>TEL-AML1</em></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>No other adverse features</td>
<td>Intensified antimetabolites</td>
</tr>
<tr>
<td></td>
<td>standard risk</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>High risk features</td>
<td>Intensive chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk</td>
<td><em>MLL</em></td>
<td>Allogeneic SCT</td>
</tr>
<tr>
<td></td>
<td><em>BCR-ABL</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Induction failure</td>
<td></td>
</tr>
</tbody>
</table>
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

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

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

CMC-Vellore: Adult 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.
Patients > 55 years with newly diagnosed AML treated on ECOG protocols since 1973.
Risk group definition: US intergroup

Good:  
- t(15;17)  
- t(8;21)  
- inv16, t(16;16)  
(10-15%)

Standard:  
- +8  
- -y  
- del 12 p  
(Intermediate)  
(65-75%)  
- Normal karyotype

Poor:  
- -5/del 5q  
- -7/del7q  
- inv3q  
- 11q23  
- 20q  
- 21q  
- t(9;22)  
- complex cytogenetics  
(15-20%)

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:

- Intensive chemotherapy (High Dose Cytosine) x 2-4 cycles
  Cytosine arabinoside 3gm/m2 q12h day 1,3,5

<table>
<thead>
<tr>
<th>TRM</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

- Autologous stem cell transplantation

<table>
<thead>
<tr>
<th>TRM</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

- Allogeneic stem cell transplantation

<table>
<thead>
<tr>
<th>TRM</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>
AML outcome based on cytogenetic risk groups

Overall survival by AML cytogenetic risk group


Mrozek and Bloomfield, Blood 2007
Risk group definition: US intergroup

Good: 
(10-15%)
t(15;17)
t(8;21)
inv16, t(16;16)

Standard: 
(65-75%)
+8
-y
del 12 p
Normal karyotype

Poor: 
(15-20%)
-5/del 5q
-7/del7q
inv3q
11q
20q
21q
t(9;22)
complex cytogenetics

Chemotherapy alone. JC0 1999

Chemotherapy alone
Autologous SCT
Allogeneic SCT

CR1

High Risk

Giles et al. Hematology 2002
Blood 2000
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:
Overview of approach – excluding Good Risk group:

Standard 7/3 induction in CR1

Day 14 bone marrow to assess
Day 14 bone marrow shows >5% blasts with >20% cellularity

CR

Donor available

Allogeneic SCT

No donor

HDAC x 3

(Complete remission)

(Stem Cell Transplant)

Not in CR

3/3 re-induction

CR*

Donor available

Allo SCT

No donor

HDACx3

*if not in CR individualize
- **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

CD34 = 1.92%
HLA-DR = 1.13%
CD13 = 70.9%
CD33 = 96.07%

dual fusion signals showing the t(15;17)
Molecular Pathogenesis

NUCLEAR MEMBRANE

Heterodimerization

Retinoid X receptor
Retinoid acid receptor alpha
Co-repressor
Histone de acetylase
ATRA

DNA

mRNA (Retinoid mediated response)

Retinoid elements (on chromosome)
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

European APL 91 trial

EFS at 2 years 84±4%

Estimated 2 year survival 90% in those receiving maintenance 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
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/\text{As}_2\text{O}_3\ combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia

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

\textsuperscript{*}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; \textsuperscript{**}Centre National de la Recherche Scientifique, Unité Propre de Recherche 9051, Laboratoire Associé au Comité de Paris de la Ligue Contre le Cancer, Affilié à l’Université de Paris-VII, Hôpital St. Louis, 1 Avenue C. Veillevault, 75475 Paris Cedex 10, France; and \textsuperscript{**}Division of Neoplastic Disease, Department of Medicine, Mount Sinai Medical Center, New York, NY 10029-6574

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

Elihu Estey\textsuperscript{1}, Guillermo Garcia-Manero\textsuperscript{1}, Alessandra Ferrajoli\textsuperscript{1}, Stefan Faderl\textsuperscript{1}, Srdan Verstovsek\textsuperscript{1}, Dan Jones\textsuperscript{2}, Hagop Kantarjian\textsuperscript{1}

Departments of Leukemia\textsuperscript{1} and Hematopathology\textsuperscript{2}, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe, Houston, Texas 77030

Blood 2005
ARSENIC

- 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 trypanosomiasis

- 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

As$_2$O$_3$
Figure 1. Regimen of single-agent arsenic trioxide

**STUDY PROTOCOL:**

**Induction:** $\text{As}_2\text{O}_3$ 10mg/day till CR [max - 60 days]

- 4 weeks rest

**Consolidation**: $\text{As}_2\text{O}_3$ 10mg/day x 4 weeks

- 4 weeks rest

**Maintenance**: $\text{As}_2\text{O}_3$ 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
- **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

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>Median duration 5–6 years</td>
<td>Median duration 6–9 months</td>
</tr>
</tbody>
</table>
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 infiltrates
- Small M component can be found in a few patients
Diagnosis requires:
- >5000/mm3 B lymphocytes in PB for >3 months
- Clonality has to be confirmed by IPT (flowcytometry)
- >55% prolymphocytes 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
SmIg (with k/l restriction), CD20, CD22, CD79b
and, CD43 weak
CD10, cyclin D1 negative

Rarely CD5+ or CD23 –ve

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

<table>
<thead>
<tr>
<th>Marker</th>
<th>Score points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>SmIg</td>
<td>Weak</td>
</tr>
<tr>
<td>CD5</td>
<td>Positive</td>
</tr>
<tr>
<td>CD23</td>
<td>Positive</td>
</tr>
<tr>
<td>FMC7</td>
<td>Negative</td>
</tr>
<tr>
<td>CD22 or CD79b</td>
<td>Weak</td>
</tr>
</tbody>
</table>

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

CD38+
ZAP-70+
Table IV. Staging systems in chronic lymphocytic leukaemia.

<table>
<thead>
<tr>
<th>Features</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Binet stage</strong></td>
<td></td>
</tr>
<tr>
<td>A    &lt;3 lymphoid areas*</td>
<td>60</td>
</tr>
<tr>
<td>B    &gt;3 lymphoid areas</td>
<td>30</td>
</tr>
<tr>
<td>C    Haemoglobin &lt; 10.0 g/dl or platelets &lt; 100 x 10^9/l</td>
<td>10</td>
</tr>
<tr>
<td><strong>Rai stage</strong></td>
<td></td>
</tr>
<tr>
<td>0†   Lymphocytosis only</td>
<td>30</td>
</tr>
<tr>
<td>I†   Lymphadenopathy</td>
<td>25</td>
</tr>
<tr>
<td>II‡  Hepato or splenomegaly ± lymphadenopathy</td>
<td>25</td>
</tr>
<tr>
<td>III§  Haemoglobin &lt; 11.0 g/dl</td>
<td>10</td>
</tr>
<tr>
<td>IV§  Platelet &lt; 100 x 10^9/l</td>
<td>10</td>
</tr>
</tbody>
</table>

*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.
Table 2. Recommendations regarding indications for treatment in CLL

<table>
<thead>
<tr>
<th></th>
<th>General practice*</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat with Rai stage 0</td>
<td>No†</td>
<td>RQ</td>
</tr>
<tr>
<td>Treat with Binet stage A</td>
<td>No†</td>
<td>RQ</td>
</tr>
<tr>
<td>Treat with Binet stage B or Rai stage I or II</td>
<td>Possible†</td>
<td>Possible†</td>
</tr>
<tr>
<td>Treat with Binet stage C or Rai stage III or IV</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment of active/progressive disease</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treat without active/progressive disease</td>
<td>No</td>
<td>RQ</td>
</tr>
</tbody>
</table>

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.”
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.
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