ACUTE LYMPHOBLASTIC LEUKEMIA
INTRODUCTION- TRIUMPH OF PEDIATRIC ALL

Uniformly fatal disease to disease with overall cure rates of >80%

IAEA Pediatric Radiation Oncology Training
Dr Laskar Version 1 June 2009
1940’s – Effective single agent chemotherapy

1950-early 1960’s - Polychemo, maintenance chemotherapy

1960-1970 - Effective CNS therapy

1970-1980 - Risk stratification, Cytogenetic, immunophenotypic molecular characterisation

1980 onwards - Improving survival
                Minimal residual disease
                Reducing late toxicities
MANAGEMENT OF ALL

- EPIDEMIOLOGY
- PATHOGENESIS AND MOLECULAR EPIDEMIOLOGY
- GENETICS
- RISK GROUP STRATIFICATION
- TREATMENT PRINCIPLES - RISK ADAPTED THERAPY
  H/O THERAPEUTIC APPROACHES
- MINIMAL RESIDUAL DISEASE
- LATE EFFECTS
- FUTURE PERSPECTIVES
Hematopoietic Malignancies

Children

- MDS and MPD
- CML
- Hodgkin’s
- AML
- NHL (Burkitt’s)
- ALL

Adults

- MDS and MPD
- CML
- CLL
- Hodgkin’s
- ALL
- Multiple Myeloma
- NHL (Follicular and Diffuse Large Cell)
**Epidemiology**

Most common malignancy of childhood-1/4th of ped. Cancers

75% cases of childhood leukemia

Incidence – 3-4 cases per 100,000.

- **Age** - peak incidence between 2 and 5 yrs
  
    peaks occurred in different times in different countries
    
    corresponding to major periods of industrialisation

- **Race** - whites > blacks (T-ALL, E2A-PBX fusion)
  
    blacks fare significantly worse (pharmacogenetic differences)

- **Sex** - boys > girls (specially T-cell ALL)

- **Geography** - differences in frequency and age distribution
  
    Northern and western Europe, N.America, Oceana
EPIDEMIOLOGY

- LINK BETWEEN MATERNAL HISTORY AND ALL
  1. Higher Risk With H/O Fetal Loss
  2. Increasing Maternal Age
  3. Higher Birth Weights

- ASSOCIATION WITH SEVERAL KNOWN INHERITED SYNDROMES

- LEUKEMIC CLUSTERS
ETIOLOGY

ENVIRONMENTAL EXPOSURE

1. Ionising radiation- greatest closest to explosion (atomic bomb)
   dose response linear ( >100 cGy)
   related to age at exposure
   more frequently in children
   0.3-0.8 cGy- significant leukemogenic activity -exposed in utero
2. Electromagnetic fields exposure
3. Chemical exposure- benzene products
   Alkylating agents/ topoisomerase inhibitors
   Quinone antibiotics
4. Diet - Flavinoids
VIRAL ETIOLOGY

- Young age
- Association with varicella, influenza other recent maternal infections
- Ebstein Bar Virus- L3 ALL
- HLTV-I and III – Adult T cell ALL and Hairy cell leukemia
IMMUNOLOGICAL ETIOLOGY

- Plays a key role in pathogenesis
- Association with immunodeficiency syndromes
- Immunodeficiency may affect susceptibility of relapse and development of second malignancies
GENETIC ETIOLOGY

- Concordance of acute leukemia in twins
  One twin + then chance is >25%
- One twin aged less than 1 yr - 100% or monozygotic twins
- Association with constitutional chromosomal disorders
- Association with innumerable genetic alterations
Acquired Genetic Defects

Alteration in the number

PLOIDY

Hyperdiploidy  Hypodiploidy

Alteration in structure

- Translocations
- Inversions
- Deletions
- Point mutations
- Amplifications
FREQUENCIES OF SPECIFIC GENOTYPES AMONG CHILDREN AND ADULTS WITH ALL
Diploidy

- 50% of cases of ALL have a modal chr no. >46
- Detected by karyotyping and Flow cytometry
- Hyperdiploidy with modal chr no. 51-65- excellent prog.
  - increased propensity of blast cells to apoptosis
  - accumulate greater quantities of MTx and its active polygluatemate residues
Induced by stimulators of apoptosis in lymphoid cells and is detected in blood in a high proportion of normal children with fever (40%)
**BCR-ABL:** A reciprocal t(9;22) fuses the BCR (breakpoint cluster region) gene from chromosome 22 to the ABL (Abelson) gene from chromosome 9. The fusion protein is a constitutive protein kinase that alters signaling pathways that control the proliferation, survival, and self-renewal of hematopoietic stem cells.

**MLL-AF4:** The t(4;11) results in a chimeric protein consisting of the N-terminal portion of MLL (mixed-lineage leukemia) encoded by the gene on chromosome 11 and the C-terminal portion of AF4 (ALL1 fused gene from chromosome 4). The fusion protein disrupts the normal expression pattern of homeobox genes, causing a change in the self-renewal and growth of hematopoietic stem cells and committed progenitor cells.

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*Percentage is higher in infancy and in adult ALL*

*Infant ALL*
**HOX:** Homeobox genes, master transcriptional regulators of early development, play a critical role in regulating hematopoietic stem-cell survival and proliferation.

**MLL-ENL:** The fusion of the MLL gene with the ENL (eleven nineteen leukemia) gene.

**NOTCH1:** This gene (Notch homologue 1, translocation-associated [Drosophila]) encodes a member of the transmembrane protein family, which plays a role in the developmental processes of a variety of tissues. Constitutive Notch signaling in hematopoietic progenitors disrupts both normal T-cell and B-cell development and leads to T-cell cancers.

T-cell ALL
Confer good prognosis
Clinical Features

Signs and symptoms reflect the degree of BM infiltration with leukemic blasts and extent of extramedullary spread.

Anemia- Fatigue, lethargy, Dyspnea, dizziness
Neutropenia- fever- IL-6, IL-1, TNF
Thrombocytopenia- petechiae, purpura, echymosis
Bone pain, arthralgia
Pain abdomen
Hepato/spleenomegaly
Breathlessness-mediastinal mass
T-cell ALL –older boys, high leucocytosis, mediastinal mass
   high incidence of CNS leukemia
HEMATOLOGICAL ABNORMALITIES

1. Elevated TLC- 50% >10,000
   20% >50,000 (single most important prog. marker)

2. Neutropenia < 500/mm³

3. Anemia – normocytic, normochromic

4. Thrombocytopenia – 75% < 100,000

5. Rarely may present with pancytopenia- pre-leukemic state
   Lumbar puncture
   Bone-marrow aspiration with PBS.
   Bone-marrow biopsy->25% blasts is must to define Ac. Leukemia
HEMATOLOGICAL ABNORMALITIES

Giemsa stains (Romanowsky)

- Distinguishes 3 subtypes of ALL-FAB
- Cannot distinguish accurately between ALL and AML
- Has prognostic implications
- L3 fares worst, L2- best
- Lost its significance - emergence of better prognostic markers
Cytopathology

L1 TYPE

L2 TYPE

L3 SUBTYPE
HISTOPATHOLOGY

- Hypercellular marrow with extensive infiltration
- Increased reticulin deposits
- Necrosis with no viable cells
- Hypoplastic marrow with lymphoblasts

CYTOCHEMISTRY

- MPO- negative
- Sudan black- negative
- PAS-positive in 75% of cases
- Terminal deoxynucleotide transferase
## IMMUNOPHENOTYPING WITH FLOWCYTOMETRY

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IgH, immunoglobulin heavy chain; IgL, immunoglobulin light chain. ALL, acute lymphoblastic leukemia; HLA-DR, human leukocyte antigen-DR; sIgH/L, surface immunoglobulin heavy or light chain; TdT, terminal deoxynucleotidyl transferase.
CYTOGENETIC AND MOLECULAR MARKERS

- TEL-AML
- Ph chromosome
- MLL-A4
- MLL-ENL
- Karyotyping for diploidy
- MYC oncogene alterations

Gene Expression Profiling
Bone marrow disease → Peripheral Blood → Extramedullary Disease
CNS LEUKEMIA

- <5% of children with ALL- CNS Leukemia
- Lumbar puncture now must pretherapy for asymptomatic pts.
- Should not be a traumatic puncture
- Light microscopy after centrifugation – inc. sensitivity

NCI Consensus

CNS-1 no lymphoblasts
CNS-2 <5 WBC/micL with definable blasts on centrifuge
CNS-3 >5 WBC/micL with blast cells or cranial N palsies

In suspicious but equivocal cases, TdT determination is done

- Hematoenous spread
- Direct extension from involved cranial Bone marrow
CNS LEUKEMIA

Signs/symptoms:
- Raised intracranial pressure
- Cranial nerve palsies, hypothalamic obesity syndrome
- Leukemic subdural involvement and spinal epidural leukemia
- Cord compression
- With improved systemic therapy- CNS is the most common site

Predictors:
- High leukocyte conc.
- T-cell disease
- Prominent LNpathy
- Leukemic cells in CSF/traumatic puncture
- Splenomegaly
- Significant thrombocytopenia
TESTICULAR LEUKEMIA

- Demonstrable testicular disease is rarely present at presentation
- Occult disease –25%
- No investigations upfront are recommended upfront
- Usually overt
- Painless testicular enlargement most often unilateral
- Diagnosis by testicular biopsy – wedge biopsy
- Presently incidence of isolated relapse -<3%
- Prophylactic testicular irradiation- was advocated previously
- Isolated testicular relapse - much less problem with new prot.
- Permanent sterility
PROGNOSTIC FACTORS

- Residual disease after chemotherapy
- Initial TLC
- Age
- Rapidity of leukemic cytoreduction
- Cytogenetics/ ploidy
- Immunological subtypes
- FAB morphology
- Mediastinal mass
- Organomegaly/lymphadenopathy

- Sex
- Race
- Platelet count
- Serum Ig
- Myeloid Ag expr.
- Nutritional status
RISK STRATIFICATION

Various risk stratifications proposed by several co-operative groups

- BFM consortium
- St. Jude
- CCG
- POG

Various risk classifications with minor changes

RISK ADAPTED THERAPY
MINIMAL RESIDUAL DISEASE

Presence of low no. of malignant cells.

Monitoring of MRD- predicts clinical outcome

Useful for evaluating early response- improves stratification
TECHNIQUES FOR DETECTION OF MRD

Conventional cytogenetics
- FISH
- Southern Blotting
- Immunophenotyping
- Older PCR tech

Multiparameter Flow Cytometric immunophenotyping
- PCR based Approaches

High sensitivity
High specificity
Quantitative

RQ PCR

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PROGNOSTIC SIGNIFICANCE OF MRD

- Detectable MRD
- Overall % MRD positivity
- % of cases with MRD at end of induction
- High-risk features
- p(trend)<0.001

- MRD-based low-risk group (n = 55)
- MRD-based intermediate-risk group (n = 55)
- MRD-based high-risk group (n = 19)
ST. JUDE’S RISK STRATIFICATION

**B-Lineage**
- t(9:22)/BCR-ABL
- WBC < 50 x 10^9/L
- Age 1–9:9 years
- DNA Index ≥ 1:16
- TEL-AML1

**Minimal residual leukaemia detection at remission date**
- ≥ 1%
- < 0.01%
- 0.01%–1%

- Very high-risk
  ~5%

- Standard-risk
  ~45%

**T-Lineage**
- WBC ≥ 50 x 10^9/L
- Age ≥ 10 years
- CNS leukaemia
- Testicular leukaemia
- MLL rearrangement
- t(1:19)/E2A-PBX1
- < 45 chromosomes

**Minimal residual leukaemia detection at remission date**
- ≥ 1%
- 0.01%–1%

- High-risk
  ~50%
PHARMACODYNAMIC AND PHARMACOGENETIC ASPECTS

- Plausible explanation for unpredictable relation between biological features and response to therapy.
- Wide variations in the rate of metabolism and systemic clearance of anti-leukemic agents.
- Low systemic exposure and low dose intensity - poor outcomes.

Genetic polymorphisms of several drug-metabolizing enzymes

- Thio Purine Methyl Transferase - 6 MP metabolizing enzyme
- The null type of GST1 and GSTP1 - lower risk of relapse
- Tandem repeat polymorphisms with enhancer region of Thymidylate synthetase - increased TS - increased relapse.
MANAGEMENT- WHY INSTITUTION BASED?

Heterogenous disorder
Initial evaluation requires sophisticated lab techniques
Treatment complex, lengthy and very costly.
Increased dose intensity of chemo regimens with great toxicity- Need for supportive care facilities
Greater need for nursing care.
Atleast 8:1 nursing care required specially for HD MTx
In centers of excellence- 100% patients enrolled in protocols
Needed for better understanding of biology.
MANAGEMENT

Remission Induction
Pre-symptomatic CNS Therapy
Consolidation with or without Reinduction
Maintenance therapy
INDUCTION THERAPY

Aim is to induce remission

- No evidence of leukemia when evaluated by physical and standard lab examination.
- Peripheral blood values must be within the standard range for age.
- Bone-marrow must be of normal cellularity and should have less than 5% lymphoblasts.
- Absence of CNS or extra-medullary disease.

In clinically overt ALL, leukemic cell burden $\leq 10^{12}$

To induce remission – chemo must reduce the total number by 99% that is fewer than $10^{10}$ blasts.
- MRD after induction is important prognostic factor
- Intervention with intensification of chemotherapy may be able to rescue slow responders so that their EFS is comparable to those with rapid responders.

- VCR + Steroid - 85%
- L-Asparginase +/- Daunorubicin - 95%

Steroid – several cooperative groups prefer Dexamethasone.
More potent and better pharmacokinetic properties
Addition of L-Asparginase improves chances of induction as well as prolongs induction. [Mauer et al Clin Hematol 1978]
Protocols using four drugs induction combination [ BFM86, CCG]-
Improved overall remission induction rates even in high-risk patients.
Some groups because of excessive toxicity because of 4\textsuperscript{th} drug
use only 3 drugs.
What all can you expect after induction?
1. Remission D28/36- 95%
2. Failure of Induction- E/O Leukemia in bone-marrow Progression

Long term EFS of such patients is 16% [Silverman et al Blood 1999]

3. Severe Aplasia- better prognosis than failure of induction.
4. Partial response- marrow > 5% blasts but< 5%- slow responders.

Poor Prognosis

Mortality during induction <3% with modern supportive care
PRE-SYMPTOMATIC THERAPY/ CNS PROPHYLAXIS

Before the biology of ALL was known- striking relapses in CNS.
Recognized as sanctuary site- protected from chemo by BBB
CNS relapse heralds bone marrow relapse.

SJCRH-studies

- I,II,III,IV- no role of low dose irradiation- 2-12 Gy

Established CSI 24Gy/15-16# as a part of CNS prophylaxis.
Reduced the isolated relapses from 67% to 6%.
Very high rate of acute myelosuppression, late musculoskeletal, logistic difficulties
VII study (1967-1972)-

Cranial RT+IT MTx  CSI

Found equivalent results- 8% isolated CNS relapses

VIII study (1972-1975)- All patients received Standard CNS therapy

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<thead>
<tr>
<th>Cranial RT+ IT MTx</th>
<th>CNS Relapse</th>
<th>Leukenc.</th>
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<tr>
<td>1. Weekly IV MTx concurrently during RT.</td>
<td>5%</td>
<td>55%</td>
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<tr>
<td>2. Oral MTx + 6MP(2)</td>
<td>1.5%</td>
<td>0%</td>
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<tr>
<td>3. Oral MTx + 6 MP + Cyclophosphamide</td>
<td>20%</td>
<td>7.1%</td>
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<tr>
<td>4. The above three + Ara-C</td>
<td>11.4%</td>
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Leukoencephalopathy- lethargy, seizures, paresis

Major lesson-IV MTx with cranial RT should be avoided

Standard- Oral Mtx + 6MP
CCSG-101 Study

1. 24Gy CSRT + EFRT (liver + spleen + gonads)
2. 24Gy CSRT alone
3. 24Gy cranial RT + IT MTx
4. IT MTx alone

Equivalent results of above three arms and superior to IT MTx.

CALGB, SWOG, POG- Cranial RT with intermediate or high dose IV MTx + IT MTx.

Some protocols incorporated – triple IT chemotherapy.

   IT MTx + Ara-C + Dexe

Essential findings- patients with low or standard risk – CNS relapse rates have been roughly 5% regardless of CNS specific therapy.
Long-term risks of cranial RT were realized - flurry of papers 1980’s

- Learning disabilities
- Growth retardation
- Cognitive defects
- Hypo-pituitarism
- Secondary malignancies
- Leukoencephalopathy

** Long term effects of intensified chemotherapy + IT chemo for ALL are as yet poorly documented.

Reduction in dose of RT is it possible ?
Can RT be avoided ?
Nesbit et al. CCSG study (Lancet 1981); MRC trial, Brazilian etc.

Randomized between

CSRT → 24Gy vs. 18Gy

CRT+ IT MTx → 24Gy vs. 18Gy

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<th>24 Gy</th>
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<td>5%</td>
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<tr>
<td>CRT</td>
<td>8%</td>
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p = 0.84

Conclusion – the reduction in dose did not result in the frequency of CNS relapse, BM relapse or death among any prognostic group of patients.
ALL BFM 83 study (Leukemia 2000)
Randomized std. risk patients to 12 Gy vs. 18 Gy
Chemo dose intensified compared to previous regimes

Conclusion: CNS prophylaxis with 12Gy of cranial irradiation was as effective as 18Gy in the prevention of CNS relapse. Can RT be avoided?
CCG-105 (JCO 1993) Tubergen et al

Phase III trials

2 X 4 design

IT MTx + std. chemo
CRT + std. chemo
IT MTx + intensive chemo
CRT + intensive chemo

Conclusion:

1. IT MTx alone given during the entire duration of therapy affords protection from CNS relapse equivalent to CRT + IT MTx

2. In children aged over 10 yrs, CRT reduced the incidence of systemic relapse

3. CNS relapse rate was also dependent on the intensity of systemic therapy
CCG STUDY-1882 (JCO1998) NACHMAN ET AL

To determine whether CRT can be omitted for CNS prophylaxis in a select subgroup of children with high risk ALL without compromising survival.

Patients who achieved rapid early response -<25% blasts on D7.

Intensified MTx is satisfactory form of CNS prophylaxis in children with high risk ALL if they have a rapid early response.
CURRENT STATUS

1. With intensive chemotherapy CRT can be safely avoided in low and intermediate risk ALL if IT MTx is given throughout.

2. With intensive chemotherapy CRT can be avoided in specific subset of patients. But overall it is safe to give 12Gy CRT in high-risk patients.

3. Trials are ongoing to address the question.

4. Long term toxicity data of 12Gy with intensive chemotherapy awaited

5. Long term data of high dose intensive chemotherapy (substituting CRT) waited.
CONSOLIDATION AND MAINTENANCE

Without additional therapy, most patients relapse within a median of 1 or 2 months.

To effectively prevent relapse, post-induction therapy must suppress leukemic growth and provide continuing leukemic cytoreduction without permitting the emergence of a drug resistant clone.

Single agent to polychemotherapy.

Intermittent MTx with oral daily 6MP is part of almost all regimens.

Addition of intermittent pulses of VCR and prednisolone.

Addition of L-Asparaginase and doxorubicin.
BFM group using intensive induction and consolidation plus re-induction and reconsolidation -phases of therapy early in maintenance, reported prolonged EFS for approx 70% of patients, including those with high-risk features.

The principle is to use alternating non-cross resistant combination chemotherapy.

**Dose:** use of drugs in maximally tolerated doses during maintenance is associated with improved treatment outcome.

**Frequency:** patients who receive maintenance therapy on a continuous rather than an interrupted schedule have longer remission durations.

**Route of admin:** Studies of the clinical pharmacology of oral MTx and 6MP have documented that their bioavailability is highly variable.

Compliance for oral drugs – a problem.
Duration: the optimal length of maintenance chemo has not been established. Intensity of therapy has bearing on the optimal duration of therapy.

The current practice of treating 2.5-3 yrs is derived from studies with varied dose intensity, varied chemotherapeutic drugs for varied patients.

The MRC trial-UK ALL-X-(BJH 1997)

18 months of treatment was less effective than 3 yrs in preventing relapse.

Optimal treatment different for girls than that for boys.

1.5 yrs sufficient for girls, but inadequate for boys.

SJCRH- (NEJM 1979)

After 2.5 yrs of therapy- 80% of patients remain disease free.

Most of the 20% patients who relapse did so in the 1st yr off therapy.

In 2-4 yrs off therapy- risk is 2-3%.

Relapse after 4 yrs off therapy- very rare.
TREATMENT OF RELAPSE

• Ascertain whether relapse- original leukemia antigen and immunophenotypic changes
  lineage switch
  secondary leukemia

• Bone marrow –is principle form of treatment failure.

• Chemotherapy and BMT are the options available.

• Chemotherapeutic drugs should include aggressive and intense chemotherapy.

• Generally standard 4 chemotherapeutic drugs are used for induction.

• Reinduction >90%

• For refractory patients-Teniposide, HD ifosfamide + etoposide

• Newer drugs with highest tolerable doses to prevent emergence of resistance.
CNS therapy, phases of reinduction and consolidation/maintenance remain the same as mentioned.

**Results:** Influenced by period of first remission.

Relapse < 3 mo, >3 mo but less than < 6 mo, >6 mo but less than < 12 mo and relapses > 12 months.

**BFM group (Blood 1996):**

Prolonged second complete remissions in approx 50% of patients who had prolonged first remissions and who had Ph-negative blasts.

For relapsed patients with Ph+ disease, the long-term survival was 8%
ROLE OF BMT

II\textsuperscript{nd} or Subsequent remission: Appropriate HLA matched sibling donor.

After first remission: High risk patients

1. Unfavorable cytogenetics- Ph+, t(4;11).
2. Unfavorably ploidy- haploidy or tetraploidy.

- Non-TBI containing regimes are preferred specially for young children.
- TBI containing regimes, but are more effective.
- After BM relapse, patients transplanted in II\textsuperscript{nd} remissions fare better than in those transplanted in relapse or partial remission.
- Patients transplanted in earlier remission > after multiple relapses.
- Length of first remission, high risk features- predictors of success with BMT.
Patients do well with intensive chemotherapeutic regimens without BMT

- Late relapses (>3 yrs) after achieving 1st remission or after completion of maintenance or
- Pts. with swift initial response to the initial chemotherapy

Allogeneic BMT is considered the treatment of choice

- For patients in second BM remission who relapsed initially while undergoing chemotherapy (or within <3 mo) and have a histocompatible sibling.

Alternatives

1. Autologous BMT
2. Allogeneous BMT from partially matched donors

Survival DFS 15-40% – high-risk pts. with relapse

40-60% - others with relapse
Treatment of CNS Relapse[<10%]

IT MTx induces remission >90%

CSRT (24-30Gy to cranium and 10-12Gy to spinal field) as a part of CNS maintenance therapy

Vigorous systemic chemo must as CNS relapse generally heralds BMR

Success rate for CNS relapse- > 18 mo after remission-83%

< 18 mo after remission-46%

CNS relapse after CRT- poor prognosis.

Treatment of Testicular Relapse[<5%]

Local radiotherapy- Bilateral Testicular RT- 24Gy

Systemic chemotherapy.
## LATE EFFECTS

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<tr>
<th>Commonly occurring late effects after conventional therapy for ALL in childhood and adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse outcome</strong></td>
</tr>
<tr>
<td>Neurocognitive deficits</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Osteopenia/Osteoporosis</td>
</tr>
<tr>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Precocious puberty</td>
</tr>
<tr>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Secondary CNS tumor</td>
</tr>
<tr>
<td>Therapy-related myelodysplasia</td>
</tr>
<tr>
<td>Skin cancer (basal cell, squamous cell, melanoma)</td>
</tr>
<tr>
<td>Dental abnormalities</td>
</tr>
<tr>
<td>Cataracts</td>
</tr>
<tr>
<td>Chronic hepatitis C and HCV-related sequelae (cirrhosis, hepatic failure, hepatocellular carcinoma)</td>
</tr>
<tr>
<td>Cardiomyopathy/congestive heart failure</td>
</tr>
</tbody>
</table>
## Second cancers following childhood acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort size</th>
<th>Time period studied</th>
<th>No. of patients with second cancers</th>
<th>Cumulative incidence (%) (Years)</th>
<th>Standardized incidence ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalton et al. [14]</td>
<td>1597</td>
<td>1972–1995</td>
<td>13</td>
<td>2.7% (18)</td>
<td>—</td>
</tr>
<tr>
<td>Nygaard et al. [12]</td>
<td>981</td>
<td>1958–1985</td>
<td>8</td>
<td>2.9% (20)</td>
<td>5.9</td>
</tr>
<tr>
<td>Loning et al. [10]</td>
<td>5006</td>
<td>1979–1995</td>
<td>52</td>
<td>3.3% (15)</td>
<td>—</td>
</tr>
<tr>
<td>Bhatia et al. [18]</td>
<td>8831</td>
<td>1983–1995</td>
<td>70</td>
<td>1.3% (10)</td>
<td>7.0</td>
</tr>
</tbody>
</table>
## Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences


*Swiss Pediatric Oncology Group (SPOG), University Children's Hospital Inselspital, CH-3010 Berne, Switzerland

Received 18 September 2001; received in revised form 25 April 2002; accepted 17 June 2002

<table>
<thead>
<tr>
<th></th>
<th>ALL (n = 132)</th>
<th>Controls (n = 100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
</tr>
<tr>
<td>gIQ</td>
<td>104.6</td>
<td>16.2</td>
<td>104.6</td>
</tr>
<tr>
<td>pIQ</td>
<td>105.6</td>
<td>16.1</td>
<td>104.2</td>
</tr>
<tr>
<td>vIQ</td>
<td>102.5</td>
<td>16.1</td>
<td>104.1</td>
</tr>
<tr>
<td>I</td>
<td>9.6</td>
<td>2.8</td>
<td>9.7</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>3.2</td>
<td>11</td>
</tr>
<tr>
<td>Ar</td>
<td>10.3</td>
<td>3</td>
<td>10.5</td>
</tr>
<tr>
<td>Si</td>
<td>10.6</td>
<td>2.8</td>
<td>11</td>
</tr>
<tr>
<td>Vo</td>
<td>9.9</td>
<td>2.8</td>
<td>10.2</td>
</tr>
<tr>
<td>DS</td>
<td>9.5</td>
<td>2.9</td>
<td>9.8</td>
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<tr>
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<td>10.4</td>
<td>2.9</td>
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</tr>
<tr>
<td>PC</td>
<td>11.2</td>
<td>3.1</td>
<td>10.7</td>
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<tr>
<td>PA</td>
<td>10.8</td>
<td>2.8</td>
<td>10.9</td>
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<tr>
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<td>11.1</td>
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</tr>
<tr>
<td>OA</td>
<td>11.3</td>
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<td>10.9</td>
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S.D., standard deviation; IQ, intelligence quotient.

gIQ, global IQ; pIQ, performance IQ; vIQ, verbal IQ; Verbal tests: I, information; C, comprehension; Ar, arithmetics; Si, similarities; Vo, vocabulary; DS, digit span; Performance tests: Co codes; PC picture completion; PA, picture arrangement; BD, block design; OA, object assembling.
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gIQ, global IQ; pIQ, performance IQ; vIQ, verbal IQ; Verbal tests: I, information; C, comprehension; Ar, arithmetics; Si, similarities; Vo, vocabulary; DS, digit span; Performance tests: Co codes; PC picture completion; PA, picture arrangement; BD, block design; OA, object assembling.

<table>
<thead>
<tr>
<th></th>
<th>Girls (n = 66)</th>
<th>Boys(n = 66)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
</tr>
<tr>
<td>gIQ</td>
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<td>16.1</td>
<td>109.5</td>
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<tr>
<td>pIQ</td>
<td>101.7</td>
<td>15.7</td>
<td>109.4</td>
</tr>
<tr>
<td>vIQ</td>
<td>97.8</td>
<td>16.6</td>
<td>107.2</td>
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<tr>
<td>I</td>
<td>8.9</td>
<td>2.6</td>
<td>10.3</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>3.1</td>
<td>12</td>
</tr>
<tr>
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<td>9.6</td>
<td>3</td>
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## RECENT DRUGS BEING TESTED

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Subtype of Leukemia Targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib mesylate</td>
<td>ABL kinase inhibition</td>
<td>BCR-ABL+</td>
</tr>
<tr>
<td>BMS-354825</td>
<td>ABL–SRC kinase inhibition</td>
<td>BCR-ABL+</td>
</tr>
<tr>
<td>AMN107</td>
<td>ABL kinase inhibition</td>
<td>BCR-ABL+</td>
</tr>
<tr>
<td>PKC412</td>
<td>FMS-like tyrosine kinase 3 inhibition</td>
<td>MLL-rearranged, hyperdiploid</td>
</tr>
<tr>
<td>MLN518</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEP701</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tipifarnib</td>
<td>Farnesyltransferase inhibition</td>
<td>All</td>
</tr>
<tr>
<td>MK0752</td>
<td>Gamma secretase inhibition (interference with NOTCH signaling)</td>
<td>T-cell</td>
</tr>
<tr>
<td>Decitabine</td>
<td>DNA demethylation</td>
<td>All</td>
</tr>
<tr>
<td>SAHA</td>
<td>Histone deacetylase inhibition</td>
<td>All</td>
</tr>
<tr>
<td>Valproic acid</td>
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<tr>
<td>MS-275</td>
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<tr>
<td>Bortezomib</td>
<td>Inhibition of ubiquitin proteasome pathway</td>
<td>All</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>Deoxyadenosine analogue</td>
<td>All</td>
</tr>
<tr>
<td>Nelarabine</td>
<td>Deoxyguanosine analogue</td>
<td>T-cell</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Anti-CD20 chimeric murine–human monoclonal antibody</td>
<td>CD20+</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Anti-CD33 monoclonal antibody conjugated with calicheamicin</td>
<td>CD33+</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52 humanized monoclonal antibody</td>
<td>CD52+</td>
</tr>
<tr>
<td>Epratuzumab</td>
<td>Anti-CD22 humanized monoclonal antibody</td>
<td>CD22+</td>
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