Objectives

• Epidemiology of Childhood Leukemia
• History of Leukemia
• Current knowledge and treatment strategies for ALL
• Future directions for ALL diagnosis and treatment
Acute Leukemia

Normal Bone Marrow

Bad!

http://imagebank.hematology.org/
Epidemiology of ALL

ALL

Other Cancers
Incidence of Childhood Cancer in the United States and Canada

Epidemiology of ALL in the United States

• ALL is the most common cancer diagnosed in children
• Represents ~ 25% of cancer diagnoses among children <15 years
• ~ 3000 children and adolescents diagnosed with ALL each year in the US
A sharp peak in ALL incidence at age 2 to 3 years

Gradual Increase in the Incidence of ALL
“Your child has ALL. It is treatable and curable”
History of Leukemia

Rudolf Virchow
1821-1903

Sidney Farber
1903-1973
Leukemia in the 19th Century

Early Understanding of Leukemia
Infected Blood?

- **1811**: Peter Cullen defined a case of “splenitis acutus” with “milky blood”
- **1825**: Alfred Velpeau defined the leukemia associated symptoms and observed “pus” in the blood vessels
- **1845**: Craigie and Bennett described 2 cases of “suppuration of the blood” Bennett referred to the disease as *leukocytthemia*
Reversed Balance Between RBCs and WBCs

• **1845**: Virchow published a case on “white blood”
• He related blood findings to simultaneous splenic enlargement
• **1847**: Virchow introduced the name *Leukemia*
Importance of the Bone Marrow

• **1855**: Neumann reported dirty green-yellow bone marrow

• **1869**: Neumann connected pathophysiology of leukemia to the bone marrow
Classification

• 1900: cytochemistry confirmed 4 main leukemia types:

  ➢ ALL
  ➢ AML
  ➢ CLL
  ➢ CML
Acute Lymphoblastic Leukemia in the 20th Century

Modern Chemotherapy and Cooperative Research Groups
Discovery of Antimetabolites

- **1946:**
  - The structure of folic acid was discovered by the Lederle Group
  - Farber observed that folic acid accelerated the leukemic process
  - He asked Lederle Labs to synthesize an “antifolate”
  - Aminopterin (methotrexate) was made
1948: Farber published his landmark study

The New England Journal of Medicine

Volume 238 June 3, 1948 Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

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Boston

It is the purpose of this paper to record the results of clinical and hematologic studies on 5 children with acute leukemia treated by the intramuscular injection of a synthetic compound, 4-aminopteroylglutamic acid (aminopterin). This compound is a folic acid antagonist. The rapid response of the blood and bone marrow to the drug, the 50% remission rate of leukemia were obtained from studies on a four-year-old girl with a rapidly progressing acute myelogenous leukemia. Treatment from February 17 to March 24, 1947, with pteroyldiglutamic acid (dipterin), in a dosage of 100 to 300 mg. intramuscular injections. This patient was discharged on March 24, 1947, and has been well ever since.

- Of many analogs, methotrexate was best tolerate
- Produced a 40% remission rate
- Increased median survival by several months but cells soon became unresponsive
Steroids

• 1950: Pearson noted cortisone and ACTH were active in ALL
• 1951: Fessas et al established clinical efficacy
• Produced a 60% remission rate but not sustained
• Trials of methotrexate and steroids showed an additive effect:
Early Trials of Methotrexate and Steroids
Mercaptopurine

• 1953: Watson and Crick published there discovery of DNA structure
• Hitchings theory: since all cells required nucleic acids, it might be possible to stop the growth of rapidly dividing cells with antagonists of the nucleic acid bases
• Burroughs-Wellcome Research Lab synthesized a purine antagonist (mercaptopurine)
Mercaptopurine (Continued)

• Burchenal (Memorial Sloan-Kettering) demonstrated a clinical effectiveness similar to methotrexate (1950’s)
• Later trials of mercaptopurine, methotrexate and steroids showed an additive effect:
Early Trials of Mercaptopurine Methotrexate and Steroids
Vincristine
Vincristine
Refining Induction Therapy - 1963

- Periwinkle extracts were found to inhibit microtubules
- National Cancer Institute studies showed marked anti-leukemia effect
- Produced 90% remission rate when combined with prednisone
Refining Induction Therapy

Vincristine
In the 1950’s and 1960’s

- Development of cooperative oncology research groups
- The process of moving new agents from the lab bench to clinical trials became more efficient
The Development of Cooperative Groups

1950’s
- Acute Leukemia Group A
- Acute Leukemia Group B
- Southwest Cancer Chemotherapy Study Group

1960’s
- Children’s Cancer Group
- Cancer and Leukemia Group B
- Southwest Oncology Group

1980’s
- Pediatric Oncology Group

2000’s
- Children’s Oncology Group
More Antineoplastic Agents

- **Asparaginase**
  - Leukemic cells depend on circulating asparagine
  - Successfully derived from E. coli and later Erwinia

- **Anthracyclines**
  - Doxorubicin and daunorubicin
  - Produced by *S. peucetius*
  - Inhibit DNA repair and replication

- **Cyclophosphamide**
  - Alkylating agent; cross-links DNA

- **Cytarabine**
  - Pyrimidine analog
  - Inhibits DNA chain elongation
Cooperative Group Advances
Pulse Maintenance - 1970

• Induction therapy was 90% effective
  – Vincristine, prednisone
• Maintenance using mercaptopurine and methotrexate was partially effective
• Cooperative group study:
  – 402 patients
  – Adding monthly vincristine/prednisone
  – Produced cure for the first time (9% survival)
Pulse Maintenance
Cooperative Group Advances
L-asparaginase 1972

• Pilot studies suggested that L-asparaginase added to long term remission

• Cooperative group study:
  – 499 patients
  – Confirmed effectiveness and degree of toxicities
L-asparaginase
Cooperative Group Advances CNS Directed Therapy

• Pioneered by Pinkel at St. Jude
  – CSF a sanctuary site for relapse
  – Craniospinal radiation plus IT methotrexate

• Cooperative group study:
  – 4 treatment arms:
    • Craniospinal only
    • Craniospinal + IT methotrexate
    • Cranial only + IT methotrexate (superior)
    • IT methotrexate only (quickly discarded)
  – 936 patients
  – 58% cure rate
Cooperative Group Advances
CNS Prophylaxis
Cooperative Group Advances
Reduced Toxicity, Shorter Therapy - 1970’s

- Standard Therapy—5 years of maintenance
- Successful reduction of maintenance with no loss of effectiveness
- Males—3 years (testicular sanctuary)
- Females—2 years

<table>
<thead>
<tr>
<th>Induction</th>
<th>CNS Consolidation</th>
<th>Pulse Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>2 months</td>
<td>2-3 years</td>
</tr>
</tbody>
</table>
Reduced Toxicity, Shorter Therapy
Effective Results
Cooperative Group Advances
BFM Delayed Intensification 1980’s

• Cooperative study in Germany:

- Induction
- CNS Consolidation
- Interim Maintenance
- Delayed Intensification
- Pulse Maintenance

1 month - 2 months - 2-3 years
Cooperative Group Advances
BFM Delayed Intensification

BFM (Berlin-Frankfurt-Munich) Intensification

- 1947-no Rx
- 1951-no Rx
- 1952-MTX, steroids
- 1956-6MP, MTX, steroids
- 1963-vincristine added
- 1970-pulse maintenance
- 1972-asparaginase
- 1975-CNS Prophylaxis
- 1975-shorter maintenance
- 1989-BFM

Percent Alive vs. Months

- 3,712
- 1,313
- 936
- 499
- 402
Cooperative Group Advances
Risk Factor Stratification 1990’s

• Primary Risk Factors (NCI-1996)
  – Standard Risk
    • Ages 1.00-9.99 years, and
    • WBC less than 50,000
  – High Risk
    • Age over 10 years, or
    • WBC over 50,000 (any age)

• Sex: males require longer maintenance
“Your child has leukemia. It is treatable and curable”
The world's childhood cancer experts

Children’s Oncology Group Hospitals in South Dakota

For questions regarding membership, including new contact info, please email us at membershipinfo@childrensoncologygroup.org

Sanford USD Medical Center - Sioux Falls

1305 W 18th Street
Sioux Falls, SD 57117-5039
Phone: 605 333-7171
Website: http://www.sanfordhealth.org
When you see a new child with suspected acute leukemia:

- Does the child have any emergency?
  1. Sepsis
  2. Tumor lysis syndrome
  3. Large mediastinal mass
  4. Leukostasis
  5. DIC

- Is it really leukemia?
When we see a new patient with acute leukemia..

- Acute Leukemia
  - ALL
  - AML
Type and Special Groups

ALL

B
- Precursor B
- Mature B-cell

T

Infant ALL

Children with Trisomy 21

Philadelphia chromosome + ALL
Type and Special Groups

- **B**
  - Precursor B: 80% to 85%
  - Mature B-cell: 2%
- **T**: 15%
- **Infant ALL**: 3%
- **Children With Trisomy 21**: 2%-3%
- **Philadelphia chr + ALL**: 3%
Precursor B

ALL

B

T

Infant ALL

Children with Trisomy 21

Philadelphia chromosome + ALL

Mature B-cell
Case #1

- SR is a 2 year old boy. He was healthy until 6-8 weeks ago. His mother noticed steady decrease in his energy level and increased fussiness. She believes he is “achy all over”. His grandmother repeatedly mentioned to his mom that he looked pale. He developed fever few days prior to presentation and his mother noticed bruises and rash, so she took him to see his PCP.
CBC with diff

- WBC: 30 (H)
- Hemoglobin: 8 (L)
- Hematocrit: 23 (L)
- MCV: 80.1 (L)
- Platelet Count: 20 (L)
- Neutrophils Absolute: 0.3 (L)
- Lymphocytes Absolute: 13.5 (H)
- Blast Absolute: 15.3 (H)
Risk Factors Stratification – Pre Induction

ALL age >1

Age  WBC  CNS  Testicular Involvement

Treatment with systemic corticosteroids in the last 2 weeks?
Risk Stratification – Pre induction

• NCI risk group:
  – Age: ≥10 yrs → high risk
  – Children > 13 years old are considered very high risk (cure rate <80%)
  – WBC: >50,000 → high risk

• CNS disease

• Testicular disease

• Cytogenetics: Ph+ ALL (typically known few days after starting induction treatment)

• Pretreatment with Steroids: If no pre-steroid CBC obtained → Child is considered high risk
Risk Stratification – Post induction

- NCI risk group: Age and WBC at presentation
- CNS disease
- Testicular disease
- Early response determinations: Morphology and Minimal Residual Disease (MRD)
- Cytogenetics: Favorable, unfavorable or unknown significance
The concept of MRD:
The likelihood of leukemia recurrence is related to the amount of residual leukemia cells.
Prognostic Value of MRD

Day 8 Blood MRD

End of induction bone marrow MRD

Borowitz et al. BLOOD, 15 JUNE 2008 VOLUME 111, NUMBER 12
## Current Treatment Groups - COG

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Low Risk</th>
<th>Average Risk</th>
<th>High Risk</th>
<th>Very High Risk</th>
</tr>
</thead>
</table>
| Criteria        | All of the following:  
                  ▪ Age 1-9  
                  ▪ WBC <50000/µL  
                  ▪ Early response  
                  ▪ Favorable cytogenetics  
                  ▪ No pre-treatment with steroids | All of the following:  
                  ▪ Age 1-9  
                  ▪ WBC <50000/µL  
                  ▪ Good response to induction | Any of the following:  
                  ▪ Age 10-13  
                  ▪ Age 1-9.99 yrs with WBC ≥ 50000/µL  
                  ▪ Steroid pretreatment  
                  ▪ Children started as average risk but has poor response | Any of the following:  
                  ▪ Age >13  
                  ▪ Unfavorable cytogenetics  
                  ▪ Induction Failure (M3 BM at Day 29)  
                  ▪ No trisomy 21 |
| Prognosis       | EFS 95%  | EFS 90%      | EFS 82%   | EFS <80%       |
| Current Goal    | Decrease unnecessary toxicity | Refine maintenance | Optimize CNS prophylaxis | Improve outcome by intensifying chemotherapy |
ALL

- B
- T
- Infant ALL
- Children with Trisomy 21
- Philadelphia chromosome + ALL

Precursor B

Mature B-cell
Case #2

• BL is a 12 year old boy presented with 2 weeks history of gradually increasing bone pain and fatigue. He had high fever for a few days prior to presentation. At his PCP office, he was found to have leukocytosis, anemia and thrombocytopenia. Uric acid 14.7. Creatinine 1.27. The following cells were present on blood smear:
Mature B-cell Leukemia (Burkitt’s Leukemia)

- Mature B-cell Leukemia = Burkitt’s lymphoma with significant bone marrow involvement
- Very high risk of tumor lysis syndrome
- Treated like a high risk Burkitt’s lymphoma:
  - More aggressive therapy
  - Shorter period of time
Unique to Burkitt’s Leukemia

• Cells express CD20
• Rituximab is a monoclonal antibody against CD20
  * Experimental use
ALL

- B
  - Precursor B
  - Burkitt’s

- Infant ALL
- Children with Trisomy 21
- Philadelphia chromosome + ALL
Case #3

• TC is a 7 year old boy. He presented with fatigue, shortness of breath and intermittent chest pain. In the local ED, he was found to have hepatosplenomegaly, enlarged cervical lymph nodes, WBC 110,000 with many blasts, anemia and severe neutropenia. His CXR showed the following:
T Cell ALL

- Historically, the diagnosis of T-ALL carried a worse prognosis than non-T childhood ALL
- The introduction of intensive multi-agent chemotherapy has significantly improved the cure rate from 20% to 75%
- If relapse occur, outcome is very poor
Risk Factor Based Treatment

• Treatment structure is similar to high risk pre B ALL: induction, consolidation, interim maintenance, delayed intensification and maintenance

• All patients receive same induction

• Significant genetic abnormalities are rare

• Stratification post induction based on:
  – NCI criteria: age and WBC
  – CNS status
  – Testicular disease
  – Response to induction treatment by morphology and MRD
Current COG Clinical Study

• Experimental Questions:
  – Nelarabine (Traditional chemotherapy. Very effective for T cell malignancies)
  – High Dose Methotrexate
ALL

B
Precursor B

T
Burkitt’s

Children with Trisomy 21

Philadelphia chromosome + ALL

Infant ALL
Case #4

- An adorable 9 weeks old baby girl presented with a single bruise on the left arm. Parents report increased fussiness. Her PCP palpated an enlarged spleen. CBC was obtained at that time. CBC machine was not able to report results. X5 dilution revealed the following:
Case (Continued)

- WBC: 1.2 million, mostly small lymphoblasts
- Hgb: 5.5 g/dL
- Platelets: 25k
Infant ALL

• Rare; 3% of cases of childhood ALL
• MLL gene translocation is common (80%):
  – Cure rate 17% (age <1 month) to 40-50 % (>6 months)
  – Extremely high presenting WBC
  – Epigenetic dysregulation leading to increased or decreased expression of different pathways
Prognostic Value of MLL-R and Age at Diagnosis

Effect of MLL-R on Prognosis of Infant ALL

Effect of Age on Prognosis of Infant ALL

Hilden et al. BLOOD, 2006 VOLUME 108, NUMBER 2
Van der Lindern et al. BLOOD, 2009 VOLUME 114, NUMBER 18
Risk Factors Stratification – Infant ALL

- **Age**
  - age < 90 days at diagnosis
  - age ≥ 90 days at diagnosis

- **Cytogenetics**
  - MLL-rearranged
  - Not MLL-rearranged

- **Very Bad!**
  - age < 90 days at diagnosis
  - MLL-rearranged

- **Bad**
  - age ≥ 90 days at diagnosis
  - Not MLL-rearranged
Treatment for Infant ALL

• Poor prognosis due to early relapse
• Current COG Strategy:
  – Shortened, intensified therapy including early Induction Intensification
  – Elimination of age-related dose reductions typical of infant therapy
  – Novel Treatment for MLL-rearranged Infant ALL:
    • FLT3 inhibition (active COG study using leustatinib)
    • Epigenetic modulation
• Role of allogeneic HSCT during first remission in infants with MLL rearrangement is controversial
ALL

B
- Precursor B
- Burkitt’s

T

Infant ALL

Philadelphia chromosome + ALL

Children with Trisomy 21
Unique to Children with Trisomy 21

- Increased Risk of Treatment Related Mortality:
  - Increased toxicity if anthracycline is added to induction
  - Increased toxicity to IV and IT methotrexate
- Decreased rate of common genetic abnormalities
- Inferior outcome compared to other children with ALL
Modified ALL Treatment for Children with Trisomy 21

• All patients with trisomy 21 receive standard risk induction regardless of age and WBC at diagnosis
• Leucovorin rescue after IT methotrexate
• Low to intermediate dose methotrexate followed by leucovorin rescue even for high risk patients
• Maintenance therapy:
  – Prednisone and vincristine pulses given every 12 weeks
  – Timed from the start of Interim Maintenance I for a total of 2 years for both girls and boys
The Philadelphia Chromosome t(9;22)

- Present in ~3% of children with ALL
- BCR-ABL1 fusion protein with tyrosine kinase activity which drives leukemogenesis
Model for Targeted Therapy for Cancer

Hits the target and cures the patient
Imatinib for Ph+ ALL

Imatinib vs Historical Control

Imatinib vs BMT

Current Treatment Strategy for Ph+ ALL

- Testing for BCR-ABL takes place at time of diagnostic bone marrow
- Ph+ patients are usually transferred to a specially designed protocol by Day 15 of Induction
  - Intensive chemotherapy + BCR-ABL tyrosine kinase inhibitor
  - Current COG study: evaluating dasatinib (second generation BCR-ABL TKI)
FAQs
Where Did It Come From?
Known Risk Factors for ALL

- Prenatal exposure to x-rays
- Postnatal exposure to high doses of radiation
- Genetic conditions that include the following:
  - Down syndrome
  - Li Fraumeni syndrome
  - Neurofibromatosis
  - Shwachman syndrome
  - Bloom syndrome
  - Ataxia telangiectasia
  - Congenital immunodeficiency syndromes
FAQs

• IM vitamin K in the neonatal period?
  – “Controversies Concerning Vitamin K and the Newborn”. *Pediatrics* 2003;112;191

• Vaccinations?

• Pesticides?

• Food?

• Infections?

• Are siblings at risk?
Monozygotic Twins Studies

• Index case < 1 year old:
  – ~100% concordance with short latency (weeks)
    – Prenatal preleukemic event (MLL-r, e.g.)

• Index case 1-6 year old:
  – ~10-20% concordance; longer latency
    – Prenatal preleukemic event (TEL-AML1, AML1-ETO, e.g.)

• Index case > 6 year old:
  – Minimal increased risk
  – No prenatal preleukemic event

Work for a Better Future

1. Risk factors group stratification
2. Biology – targeted therapy
3. Immunotherapy
4. Better bone marrow transplantation
Optimize Risk Groups Stratification

• Ongoing COG studies
• Goal:
  – Decrease morbidity to lower risk patients
  – Improve cure rate for higher risk patients
  – Banking of leukemia and germline specimens for current and future research
Biology

• Genetics
  – Whole exome/genome sequencing of leukemia cells at diagnosis and relapse

• Epigenetics (regulation of gene expression)
  – Busulfite sequencing: hypo vs hypermethylation
  – Histone modification

• Leukemia profiling to allow individualized treatment plans
Immunotherapy

• Pre B: Ongoing early phase clinical trials - CAR therapy
• Mature B: Ongoing phase III clinical trials – Monoclonal antibodies
• T: Promising preclinical data
Chimeric Antigen Receptor (CAR) Therapy

1) T Cell Collection

2) T Cell Transfection
   1. Binding
   2. Fusion

3) T Cell Adoptive Transfer
   3. Integration
   4. Transcription and protein expression
   5. CAR cell membrane insertion
   +/- Lymphodepleting conditioning

4) Patient Monitoring
   a) Disease response
      - CT scans
      - Bone marrow biopsies
      - Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      - Immunohistochemistry of bone marrow biopsy
      - RT-PCR and flow cytometry of blood and bone marrow aspirate
Hematopoietic Cell Transplantation in the Future

- Better stem cells:
  - Amplification (self-renewal)
  - Universal donor line
  - Engineered to distinguish between normal host and leukemia cells

- Less toxic conditioning regimens:
  - Reduced intensity regimens

- Immune tolerance:
  - Decrease risk of graft rejection
  - Decrease risk of graft vs host disease
SEER Delay-Adjusted Incidence and US Mortality. All Childhood Cancers, Under 20 Years of Age. Both Sexes, All Races, 1975-2010
Acknowledgment

John E Neely, MD