Childhood Leukemia

Stephen P. Hunger, M.D
STOP! Children’s Cancer Associate Professor and
Chief, Pediatric Hematology Oncology
University of Florida College of Medicine
Causes of Mortality Before Age 20 in the United States

#1 Unintentional Injury
#2 Homicide
#3 Suicide
#4 Cancer
Epidemiology of Cancer in Children and Young Adults

- 30% of U.S. population is < 20 years old
- 1998 U.S. estimates
  - 12,500 children diagnosed with cancer
  - 2,500 children died from cancer
  - 1/300 males and 1/333 females will be diagnosed with cancer before age 20
Cancer in Children <15 years old: Major Histologic Subtypes

- Leukemia: 32%
- CNS tumors: 11%
- Lymphomas: 11%
- Neuroblastoma: 8%
- Sarcomas: 7%
- Wilms tumor: 6%
- Bone tumors: 5%
- Misc: 11%
Leukemia: Definition

- Clonal neoplastic proliferation of hematopoietic cells that display aberrant or arrested differentiation
- Heterogeneous group of malignancies
- If untreated, can be rapidly fatal or slowly progressive
Leukemia: Clinical Features

• Replacement of normal marrow leads to signs and symptoms of BM failure
  – Increased wbc and extramedullary proliferation
    • infection due to decreased PMNs
    • bone pain due to marrow expansion
    • adenopathy and hepatosplenomegaly
  – Decreased platelets
    • bleeding
  – Decreased red blood cells
    • anemia, pallor, fatigue
Leukemias: Acute vs. Chronic

• Acute leukemias derive from, and biologically resemble, primitive hematopoietic precursors. Rapidly fatal if untreated.
  – ALL and AML

• Chronic leukemias display phenotype and properties of more mature cells. Slowly growing if untreated.
  – CML, CLL, etc.
Subtypes of Leukemia in Children <15 years old

- ALL: 76%
- AML: 19%
- CML: 3%
- Other: 2%
Leukemia Subtypes by Age

0-5 years:
- 81% ALL
- 14% AML
- 2% CML
- 3% Other

15-19 years:
- 51% ALL
- 36% AML
- 9% CML
- 4% Other
Acute Leukemias

• Rapidly fatal in pretreatment era
• 3% of all cancers (30-35% for children)
• #1 cause of death due to cancer at $\leq 35$ years
• $\sim 4000$ ALLs/yr in US (children=adults)
  – Median age 10 years
• $\sim 9000$ AMLs/yr in US (adults $\gg$ children)
  – Median age 65 years
# ALL: Clinical Features at Diagnosis

<table>
<thead>
<tr>
<th>Symptoms/Physical Findings</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>61%</td>
</tr>
<tr>
<td>Bleeding/Petechiae/Purpura</td>
<td>48%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>23%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>50%</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>68%</td>
</tr>
</tbody>
</table>

Adapted from Margolin and Poplack (Pizzo and Poplack, 1997)
Childhood Leukemia: Differential Diagnosis

- Nonmalignant conditions
  - Juvenile rheumatoid arthritis
  - Infectious mononucleosis
  - Idiopathic thrombocytopenic purpura
  - Pertussis/parapertussis
  - Aplastic anemia

- Malignancies
  - Small round blue cell tumors
    - Neuroblastoma, retinoblastoma, rhabdomyosarcoma, Ewing’s sarcoma, Lymphoma

Adapted from Margolin and Poplack (Pizzo and Poplack, 1997)
Childhood Leukemia: Laboratory Evaluation at Diagnosis

• Establish diagnosis and define involvement
  – CBC and review of peripheral smear
  – Bone marrow aspirate
    • Morphology, immunophenotype, cytogenetics, molecular genetics
  – Lumbar puncture
  – Chest X-ray to evaluate for mediastinal mass in T-ALL
    • Must do pre-anesthesia!

• Define other problems
  – Metabolic--evaluate for potential tumor lysis syndrome
    • Lytes, BUN, Cr, Ca, Phos, Mg, Uric Acid
  – Infections
    • Culture and treat with empiric antibiotics if indicated
Leukemia: Initial Medical Management

- Tumor lysis syndrome
  - Triad of increased uric acid, PO₄, K⁺
  - Caused by death of leukemia cells and impaired renal function (may precede or follow Rx)
  - Most problematic in leukemias with high growth fraction
    - Burkitt’s, T-ALL, infant ALL

- Prevention and treatment
  - Hydrate (3000ml/m²/day IV) to get SG <1.010
  - Alkalinate with sodium bicarbonate (40 Meq/L to start)
    - Target urine pH 7.0-7.5
  - Allopurinol to inhibit xanthine oxidase
Therapy of Childhood ALL: Milestones

• 1948: Aminopterin induces temporary remissions in children with leukemia (Farber)
  – First effective chemotherapy for cancer
• Early 1960s: First cures of childhood ALL
• Early 1970s: Adoption of prophylactic CNS Rx
  – Radiation initially; most now receive intrathecal chemotherapy
• 1960s-present: Empiric optimization of chemo regimens
• 1980s-present: Improved understanding of biology paves way for new era of targeted biological therapies
CCG: Survival of Children with Acute Lymphoblastic Leukemia

Years from Diagnosis | Number of Children
--- | ---
1989-93 | 3,080
1983-89 | 3,712
1978-83 | 2,979
1972-75 | 1,313
1972-75 | 936
1970-72 | 499
1968-70 | 402

Total Number of Patients Treated: 12,921

CNS prophylaxis introduced
Improvements in Outcome of Children with ALL: Reasons

• Critical improvements in supportive care
  – Transfusion support + treatment of infections
• Introduction of new chemotherapy agents has played a relatively minor role
• Major improvements have come through a series of empirically-designed clinical trials
  – Essential role of US and European cooperative groups
  – Importance of treatment stratification and risk-adjusted therapy
Chemotherapy Agents Used in Childhood ALL: FDA Approval

- 6-Mercaptopurine 1953
- Methotrexate 1953
- Prednisone 1955
- Dexamethasone 1958
- Cyclophosphamide 1959
- Vincristine 1964
- Cytosine Arabinoside 1969
- L’Asparaginase 1978
- Daunorubicin 1979
Childhood ALL: Role Of Cooperative Groups

- Single institutions important in early advances in ALL therapy but large sample sizes needed to answer current questions
  - 1000-2500 patients needed in most current trials
- Multi-institutional cooperative groups have developed and evolved over past 30-40 years
  - US + Canada: POG and CCG
  - Europe: BFM, UKALL, Fralle, AIEOP
Children’s Oncology Group (COG)

• Formed in 99 by merger of POG, COG, NWTSG, and IRSG
• 235 member institutions
  – All major US and Canadian centers are members
  – Also some Australian and Western European centers
• Over 40,000 children under Rx on COG protocols and over 100,000 have been treated over past 30 years
• Major reason for treatment advances in US/Canada
• COG protocols are de facto standard of care
• We encourage all eligible patients to enroll in COG clinical trials and biology studies
Pediatric Cooperative Groups: A Model for Success

• Children and adolescents <20 years old account for <1% of all cancer patients

• Children and adolescents <20 years old account for 22% of accruals onto NCI-sponsored cooperative group trials

• Enrollment in a clinical trial is considered the standard approach for children with cancer but only 1-5% of adults with cancer are enrolled in clinical trials

• What other questions in pediatric medicine could be answered effectively with similar systems?
Treatment of Childhood ALL: General Overview

- **Remission induction**
  - Remission = normal blood counts, normocellular marrow with <5% leukemia blasts; no extramedullary disease
  - 99% of patients enter CR with 4 weeks of therapy
    - 3 (steroids, VCR, Asp) or 4 (+anthracycline) drugs

- **Consolidation**
  - Various 2-10 month intensification phases

- **Presymptomatic CNS treatment/prophylaxis**
  - 90+% now get IT therapy only without irradiation

- **Maintenance**
  - Modest therapy lasting until 2.5-3 years from diagnosis
Risk Group Stratification and Risk-Adjusted Therapy

- Patients are grouped to select proper treatment strategy
  - High risk patients fare poorly when treated with less intensive regimens appropriate for standard risk patients but do much better with more intensive therapy
  - Data based on groups, but Rx applied to individuals

- Risk group definitions
  - Original NCI/Rome criteria
    - Based solely on age and initial WBC
  - New COG criteria
    - Framework clear but details evolving
  - Further incorporation of more sophisticated measures of treatment response
Clinical Risk Groups in Childhood ALL: Original NCI/Rome Criteria

- **Standard risk (~60% patients with EFS ~80%)**
  - Age 1.00-9.99 years
  - Initial white blood count <50,000
  - Current 5 year EFS ~85%
- **High risk (~40% patients with EFS ~65%)**
  - All others
  - Current 5 year EFS 70-75% for non-infants
    - Achieved with more intensive therapy
  - Outcome still poor for infants < 1 year old
    - ~3% of patients with EFS <50%
    - Unique biology and supportive care issues
Biological Features Refine Clinical Risk Groups

• Immunophenotype
  – T vs B-precursor not a critical determinant of outcome
    • Different Rx strategies may be appropriate for pre-B vs. T
  – Mature B-ALL (Burkitt’s) treated very differently
    • Increase cure from 20% to >75% with very intensive, very short Rx

• Ploidy
  – Hyperdiploid (DI >1.16) good
    • Best group defined by “triple trisomies” (4, 10, 17)
  – Hypodiploid very bad (<45 chromosomes)

• Translocations
  – Bad: t(9;22), t(4;11) or other MLL
  – Good: t(12;21) and TEL-AML1
Risk Group Classification: The Emerging COG System

- **Low**: NCI SR with triple trisomy or TEL-AML1
  - ~40% of NCI SR with EFS ~90%
- **Standard**: NCI SR non TEL, non TT
  - ~60% of NCI SR with EFS 80%
- **High**: NCI HR
  - EFS 70-75%
- **Very High Risk**
  - Ph+, hypodiploid <45, No CR day 28, (?MLL)
  - ~5% with EFS <45%
Risk Groups Influence Treatment Questions

• Low risk
  – Improve outcome vs. decrease toxicity?
• Standard risk
  – Test treatment strategies effective in HR-ALL
• High risk
  – Further intensification of treatment?
• Very high risk
  – Alternative strategies such as BMT or novel agents
Standard Risk ALL: Lessons and Future Directions

- Modest incremental improvements in outcome result in substantial long term improvements
- Major improvements can be made by optimizing use of standard agents
- Success creates problems in study design
  - Strategies for study design
## Treatment of Childhood ALL: Overview of CCG (BFM-Based) Therapy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>1 month</td>
<td>Vcr, Steroids, L-Asp +/- Anthracyclines</td>
</tr>
<tr>
<td>Consolidation</td>
<td>1-2 months</td>
<td>Presymptomatic CNS treatment +/- Ctx + Ara C</td>
</tr>
<tr>
<td>Interim Maintenance</td>
<td>2 months</td>
<td>Oral 6-MP+Mtx, Vcr, Steroids</td>
</tr>
<tr>
<td>Delayed Intensification</td>
<td>2 months</td>
<td>Repeat Induction + consolidation with Ctx + Ara-C</td>
</tr>
<tr>
<td>Maintenance</td>
<td>20-32 months</td>
<td>Oral 6-MP+Mtx, monthly IV Vcr and steroid pulses</td>
</tr>
</tbody>
</table>
Successful CCG Randomized Trails in Children with SR-ALL

<table>
<thead>
<tr>
<th>Trial/Risk Years</th>
<th>#Patients</th>
<th>Intervention and Outcome (EFS)</th>
<th>Δ Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG-161/Low 1978-1983</td>
<td>631</td>
<td>+/- VCR/Pred pulses 5-yr EFS 77% vs. 64%</td>
<td>36%</td>
</tr>
<tr>
<td>CCG-105/Int. 1983-1989</td>
<td>625</td>
<td>+/- Delayed intensification 5-yr EFS 77% vs. 61%</td>
<td>41%</td>
</tr>
<tr>
<td>CCG-1881/Low 1988-1992</td>
<td>700</td>
<td>+/- Delayed intensification 7-yr EFS 83% vs. 76%</td>
<td>29%</td>
</tr>
<tr>
<td>CCG-1891/Int. 1990-1993</td>
<td>802</td>
<td>Double vs. single D.I. 7-yr EFS 83% vs. 76%</td>
<td>25%</td>
</tr>
<tr>
<td>CCG-1922/Std. 1993-1995</td>
<td>1060</td>
<td>Single D.I., Dex vs. pred 4-yr EFS 88% vs. 81%</td>
<td>37%</td>
</tr>
</tbody>
</table>
Current Problems in SR-ALL

- SR-ALL patients account for ~60% of patients and have an EFS of 85+%
  - About 2/3 of these patients could be cured with much less therapy than they currently receive
- Increasing outcome further is problematic because most patients don’t benefit from the experimental intervention, making it hard to identify effective therapies
  - Increasing EFS from 85 to 90% benefits only 1 in 20 patients
    - 17/20 cured with less Rx and 2/20 still not cured
Identification of Very Low Risk Group Patients

- Ultra low risk patients have 90%+ EFS with current Rx
  - NCI SR with triple trisomy (~20% of SR-ALL)
    - Adding rapid early response increases outcome even further
      - 98% 4 year EFS on latest CCG studies (n ~200)
  - NCI SR with TEL-AML1 (~20% of SR-ALL)

- Two potential approaches
  - No further treatment intensification and eventually back off treatment intensity
    - May be more appealing to MDs than parents
  - Ask randomized questions focused on biology of these groups
    - COG has power to ask randomized question in ~4yrs (90% vs 95%) with one way comparison in triple trisomy or TEL-AML1 group
Removal of Ultra Low Risk Patients Allows Better Study Design

- Remaining SR-ALL patients provide a better group of patients in which to test treatment interventions
  - EFS 75-80%—not much better than HR-ALL
  - CCG 1882
    - SER patients <10 years old with WBC >50,000 randomized to standard vs “augmented” BFM
      - 4 yr EFS 85% VS 42% (~50 patients/group)
    - Superior to SR-ALL patients with lower WBC and better early response
Chronic Myelogenous Leukemia (CML)

- Clonal expansion of myeloid progenitors
- Bi- or tri-phasic clinical course
  - Chronic phase (CP) > Accelerated phase (AP) > Blast crisis (BC)
- Paradigm for modern molecular medicine with rationally designed treatment targeted at pathogenetic lesions
CML: Clinical Features and Natural History

• Patients typically present in CP
  – Not acutely ill or toxic
  – High wbc + platelets, splenomegaly
    • BM shows myeloid hyperplasia without excess blasts
• Without definitive Rx, eventually transform into AP/BC
  – BC: analogous to acute leukemia (myeloid or lymphoid BC)
  – AP: transition state that is hard to define
• Statistics
  – ~20% die each year following diagnosis
    • Median survival 6-8 weeks after BC develops
  – ~10-20% survival at 5 years after diagnosis
CML: Cytogenetics and Molecular Genetics

- 1959: Philadelphia chromosome ($\text{Ph}^1$) is first recognized recurrent chromosome abnormality in human cancer
- 1973: $\text{Ph}^1$ shown to be t(9;22)
- 70s/80s: t(9;22) present in $\geq 95\%$ of CML patients
- 1985: t(9;22) produces BCR-ABL fusion
  - $\text{C-abl}$ is human homolog of murine Abelson B cell leukemia virus oncogene
    - One of first known oncogenes
CML: Therapeutic Options

• Hydroxyurea
  – Oral chemotherapy with few side effects
  – Produces hematologic remission in almost all patients
    • Normalization of blood counts and resolution of organomegaly
  – Disease still present as all cells have t(9;22)
  – Is not curative and natural history unchanged
• Intensive chemotherapy is not curative
• Alpha interferon is effective for some patients
CML: Role of Bone Marrow Transplantation (BMT)

- BMT is an effective curative procedure
  - 60-90% cure rate for patients with HLA-matched sibling donor
    - Only ~30-35% of patients have a matched sib donor
  - Unrelated donor BMT also has very good outcome in young patients but has substantial morbidity
  - Outcomes much worse if >40 years old
    - Most patients with CML are >50 years old
- BMT is only an option for a small minority of patients with CML
CML: Rational Design of a New Therapy

• BCR-ABL is a constitutive tyrosine kinase
  – Tyrosine kinases (PTK) are cellular signaling molecules that regulate cell growth and death via phosphorylation of critical tyrosine residues of various proteins
    • Activity is normally tightly controlled
    • BCR-ABL always “on”

• BCR-ABL causes CML-like disease in mice
  – Tyrosine kinase activity essential for transformation
    • Kinase inhibition might be an effective therapy
Development of STI 571 (Gleevec)

• Screened large “library” of compounds to identify inhibitors of Abl class of PTKs
  – Initial compounds weak inhibitors
• Optimized inhibition of Abl PTKs by synthesizing chemically relating compounds and comparing structure to in vitro activity
• STI 571 most potent compound
  – STI = signal transduction inhibitor
STI 571: Preclinical Testing

- Low concentrations inhibit PTK activity
  - Relatively specific for Abl class of PTKs
- Suppresses growth of BCR-ABL expressing cells in tissue culture and mouse experiments
- Colony forming assays with cells from CML patients and normal controls
  - Suppressed formation of BCR-ABL colonies by 92-98% without affecting normal colonies
STI 571: Initial Clinical Trial

- Oral form of STI 571 developed to provide continual inhibition of BCR-ABL activity
- Initial human trials performed in patients with CML resistant to alpha interferon
- Dose escalation trial
  - 23/24 treated with >300 mg/day attained CR
  - Many patients have major cytogenetic responses
    - Reduction in % of Ph+ cells in BM
  - Minimal side effects
  - Results led to FDA approval in 2000
<table>
<thead>
<tr>
<th>Phase</th>
<th>Hematologic response</th>
<th>Complete Hematologic Response</th>
<th>Complete Cytogenetic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Phase</td>
<td>93%</td>
<td>91%</td>
<td>36%</td>
</tr>
<tr>
<td>Accelerated Phase</td>
<td>82%</td>
<td>53%</td>
<td>17%</td>
</tr>
<tr>
<td>Blast Crisis</td>
<td>52%</td>
<td>14%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Gleevec: Clinical Use in CML

• Causes a re-evaluation of treatment algorithms for patients with CML
  – What is role of unrelated donor BMT today in the “Gleevec era”?  
  – Does Gleevec Rx alter response to BMT?
• Most suspect that Gleevec will not be curative as a single agent
  – New trials exploring use as part of combination therapy regimens
• Role in other tumors under study
  – Rational to test in those that over-express c-kit (GIST) or PDGFβ (glioblastoma and some bone tumors)