Progress in Treatment of Childhood Leukemia

A Clinician’s Historical Perspective

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Fort Worth, Texas
2016
Caring For Kids with Leukemia

“Forty years and counting…”

- Everyone has a story
  - Here is mine.

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My Inspiring case

- N.R. a 4 year old girl
- Transferred from a community in Northwestern Ontario to:
  - Winnipeg Children’s Hospital Feb. 1973
- Presenting problems: fever, skeletal pain, pancytopenia

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N. R. (cont’d)

- W.P.B. “on-call” as Med. Student with Pediatric Residents the night of her admission
- She was sick, pale, with bruising, petechiae, blast cells in her blood
  - Parents anxious and fearful
- It was late at night, but the attending physician came in!
N. R. (cont’d)

• Attending, Dr. Agnes Bishop, first Pediatric Hematologist – Oncologist in Winnipeg
  – Thoroughly assessed patient
  – Provided supportive care for immediate relief of symptoms and life-threatening risks
  – Laid out short-term plan and long-term goals
  – Gave family hope, confronted and eased their distress
  – And…

N. R. (cont’d)

– Got me hooked!
– “Let’s use the treatment protocol from St. Jude – it has a 50% success rate!” – Dr. Bishop
– AND WE DID.
– N.R. was first of many kids to inspire me over the next 40 years!

What was that breakthrough treatment?

• Based upon St. Jude “Total Therapy V”
  – Remission induction (4 weeks)
    – VCR/PRED
  – Consolidation
    – I.V. MTX, CYCLO, 6MP
  – “CNS Prophylaxis”
    – Cranial R.T. 2400 rad
    – I.T. MTX 5 doses
    – Over 2 1/2 weeks
  – Maintenance - 2 1/2 years
    – 6MP, MTX, VCR, PRED, CYCLO

Agnes J. Bishop M.D.

• First Pediatric Hematologist-oncologist in my hometown
• My role model when I was Med. Student and then Resident in Pediatrics, Winnipeg, Canada, 1973 – 1976
N. R. (cont’d)

• The treatment worked
• I had found my career passion!
• Dr. Bishop: “If you really want to do this you should go to St. Jude.”
• Arriving there as a Pediatric Hem-Onc Fellow in 1976, I learned the history, contributed along the way.
• And…

My tenure at St. Jude
1976 - 82

… Saw a lot of patients!
• So, let’s review the progress that had been achieved by that time.

1940s

• Uniformly fatal in average of 3 months
• Death from bleeding, severe infection, or both
• Blood transfusions the only treatment, occasionally given
Early 1940s

- Thought that acute leukemia might be a folic acid-deficient disease, similar to pernicious anemia, in which megaloblasts resembled leukemia blasts.
- Folic acid retarded cancer growth in some patients but enhanced it in others.
- Heinle and Welch observed that a folate-deficient diet caused a decreased in peripheral blast count.

Late 1940s and Early 1950s

- Seeger synthesized aminopterin in 1947; Farber tried it and observed a definite benefit for 10 of 16 patients in 1948; the era of leukemia therapy began!
- Farber tried ACTH, resulting in some brief remissions in 1950.
- Elion and Hitchings made mercaptopurine in 1951.
- Each given singly; all patients died.

Collaboration Between Scientist and Physician on Anti-fols

Yellapragada SubbaRow
1895-1948

Sydney Farber
1903 – 1973

1958-1962

- 1st systematic chemotherapy trials by Frei, Freireich at NCI; Pinkel, Holland at Roswell Park; Burchenal at Sloan-Kettering.
- 1st combination chemotherapy based on experience with tuberculosis.
- 3% patients survived 5 years.
Obstacles to Cure

• Fear of chemotherapy ("poisons")
• Misguided protectionism of children (send to “Disneyland,” don’t make sick)
• Distrust of clinical trials, protocols ("cookbook medicine")
• Pessimism of physicians, especially in medical schools

1962

• After 7 years of raising funds by ALSAC, Danny Thomas founded St. Jude Children’s Research Hospital (85,000 sq. ft.) in Memphis, Tennessee
• Donald Pinkel - 1st Director and 1st employee at age 34
• 1st patient seen in February, 1962
• “Total Therapy” studies began

Simone Br J Haematol 2003;120:549-555

Aid for Leukemia Stricken American Children

ALSAC

American Lebanese Syrian Associated Charities
• Vincristine, asparaginase, cyclophosphamide, daunorubicin, cytarabine introduced
• Began Total Therapy with remission induction; intensification; CNS therapy; continuation (maintenance) therapy
• Recognition of CNS leukemia as major problem for cure; 5 to 12 Gy cranial irradiation failed.
Total I-III 1962-65

- Total Patients: 41
- Complete Remission (CR): 37

Pinkel et al. JAMA 216:648-52, 1971

Total IV Survival 1966-1967

- Proportion Dead: 57/59 (97%)


Facial Palsy in ALL
Extramedullary ALL

- Induction: prednisone + vincristine
- Intensification: mercaptopurine, methotrexate and cyclophosphamide intravenously in 7 days
- CNS: 24 Gy cranial + 5 intathecal methotrexate over 2.5 weeks
- Continuation: mercaptopurine daily, methotrexate + cyclophosphamide weekly, pulses of prednisone + vincristine every 10 week

Optic Changes in ALL

Study V 1967–1968

- Induction: prednisone + vincristine
- Intensification: mercaptopurine, methotrexate and cyclophosphamide intravenously in 7 days
- CNS: 24 Gy cranial + 5 intathecal methotrexate over 2.5 weeks
- Continuation: mercaptopurine daily, methotrexate + cyclophosphamide weekly, pulses of prednisone + vincristine every 10 week

Total V 1967-1968

- Total Patients: 35
- Complete Remission: 31

Immunophenotyping of Childhood ALL

- High WBC; near normal Hgb and platelet count, L2 morphology
- Age typically > 10; more common in boys
- Rosetting with Sheep RBC, slg negative
- Poor Prognosis with standard ALL therapy

Borella, Sen- NEJM 1975

ALL with Mediastinal Mass

Vertebral Compression Fracture in ALL

Total VI-IX 1969–1979

- Successful prophylaxis for Pneumocystis carinii (jiroveci) pneumonitis (Hughes et al. NEJM 297:1419-26, 1977)

- "Cure" of one third of all cases of childhood ALL forecasted for the first time (George et al. NEJM 300:269-73, 1979)
Total X and XI 1979 – 1988

- First two specific translocations [t(11;14), t(1;19)] described (Williams et al. Cell 36:101-109, 1984)
- Blast cell DNA content has prognostic importance (Look et al. 65:1079-86, 1985)
- Began risk-directed therapy; introduced high-dose methotrexate; reduced cranial irradiation; recognized the importance of pharmacokinetics (Evans et al. NEJM 314:471-7, 1986)
- Improved 5-year event-free survival to 70% (Rivera et al. Lancet 337:61-6, 1991)

Total Therapy
B
Murphy and Bowman
1981 – 1985

- A diversion into advanced Burkitt’s and mature B-cell ALL Therapy
- With marked survival increase!

“Total B”

- Exported: - First, to Fort Worth – Dallas
- Second, to Pediatric Oncology Group Protocols 8617, 9317
- Third, to France where modified to ↑ dose intensity (LMB)
- And, to adult ALL as “Hyper CVAD”
November 1982

Bowmans move to Fort Worth, Texas!

1980’s

- Beginning to recognize adverse consequences of increasing treatment intensity…
- Refinement of treatment based upon clinical and biologically defined “risks”

Total XII - XIV 1988 – 1999

- Individualized therapy based on pharmacodynamics improved outcome (Evans et al. NEJM 338:499-505, 1988)
- First to apply pharmacogenetics (i.e., TPMT) to reduce toxicity (Evans & Relling Nature 429:464-8, 2004; Relling et al. Blood 107:843-44, 2006)
- Minimal residual disease level is the most important prognostic factor (Coustan-Smith et al. Lancet 301:650-94, 1998)
- Early intensification of triple intrathecal therapy reduced CNS relapse and boosted 5-year event-free survival to 80% (Pui & Evans NEJM 339:605-15, 1998)

Event-free Survival According to Treatment Era at St. Jude

- 81%±8% XIII–XIV (1991–99) n=465
- 70%±2% XI–XII (1984–91) n=546
- 53%±2% X (1979–83) n=428
- 35%±2% V–IX (1967–79) n=828
- 9%±3% I–IV (1962–66) n=90

Chemotherapy for ALL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year approved in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercaptopurine</td>
<td>1953</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1953</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1955</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1958</td>
</tr>
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<td>1959</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1964</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1969</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>1978</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>1979</td>
</tr>
<tr>
<td>Etoposide</td>
<td>1983</td>
</tr>
<tr>
<td>Teniposide</td>
<td>1990</td>
</tr>
</tbody>
</table>

Comparison of Survival Between 10-year Event-free Survivors and Matched US Population

Cumulative Incidence of Various Second Neoplasms During First Complete Remission

Cumulative Incidence of Second Neoplasms in 10-year Event-free Survivors According to CNS Irradiation
CNS Tumors After Cranial Irradiation

- Meningioma
- Astrocytoma

Neuroimaging Abnormalities After Cranial Irradiation

- Brain atrophy
- Encephalomalacia
- Cerebral lacunes
- Dystrophic calcification
- Leukoencephalopathy
- Necrosis/gliosis

Endocrinopathy After Cranial Irradiation

Dental Abnormalities After Cranial Irradiation

- Salivary gland dysfunction
- Xerostomia
- Dental caries
- Periodontal disease
Outcome According to Total Therapy Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. Patients</th>
<th>% Irradiated</th>
<th>% 5-yr EFS (SE)</th>
<th>% Isolated CNS Relapsed (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1984-88</td>
<td>358</td>
<td>64</td>
<td>72.1 (2.4)</td>
<td>5.5 (1.2)</td>
</tr>
<tr>
<td>12</td>
<td>1988-91</td>
<td>188</td>
<td>37</td>
<td>67.6 (3.4)</td>
<td>10.4 (2.3)</td>
</tr>
<tr>
<td>13A</td>
<td>1991-94</td>
<td>165</td>
<td>22</td>
<td>77.6 (3.2)</td>
<td>1.2 (0.9)</td>
</tr>
<tr>
<td>13B</td>
<td>1994-98</td>
<td>247</td>
<td>12</td>
<td>80.1 (2.6)</td>
<td>1.7 (0.8)</td>
</tr>
<tr>
<td>14</td>
<td>1998-99</td>
<td>53</td>
<td>0</td>
<td>77.4 (5.7)</td>
<td>0</td>
</tr>
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St. Jude – Cook Children’s 21st Century Collaboration

- Total Therapy XV 2004–2007
- AML 02 and 08 (active)
- AML 16 → in development
- R 18 (active)
- Total Therapy XVII 2017→

Total XV: First Trial Using MRD to Direct Treatment

Overall Survival: 93.5%±1.1%
Event-free Survival: 87.5%±1.5%
Cumulative Risk of Off-therapy Relapse by Total Therapy Study

Studies 11 and 12 (n=438)
Studies 13A, 13B and 14 (n=389)
Study 15 (n=444)

P=0.002
**Summary**

- Sequential MRD studies are not indicated in patients with negative MRD after remission induction because the yield is very low and re-emergent MRD is associated with a dismal outcome despite therapeutic intervention.

- Sequential studies were useful in MRD+ cases: most patients with decreasing MRD can be treated successfully with chemotherapy alone; transplantation is probably indicated in patients with increasing MRD.

**Drugs Used to Treat ALL**

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<tr>
<td>Vincristine</td>
<td>1964</td>
<td>2012</td>
</tr>
<tr>
<td>Cytosine Arabinoside</td>
<td>1969</td>
<td>2012</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>2006</td>
<td>2012</td>
</tr>
<tr>
<td>Imatinib</td>
<td>2006</td>
<td>2012</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>2006</td>
<td>2012</td>
</tr>
<tr>
<td>Marqibo</td>
<td>2012</td>
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</tr>
<tr>
<td>Ponatinib</td>
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</tr>
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</table>
All childhood ALL cases have specific genetic abnormality


Two genomes influencing drug response in every patient

Germline

Somatic

Osteonecrosis

Augmented therapy improves outcome for pediatric high risk acute lymphocytic leukemia: Results of Children’s Oncology Group trial P9906

Bowman et al. PBC 2011
Imatinib and Survival in Ph+ ALL

- Overall 5 year: 49.5% ± 3.7%
- Overall 10 year: 42.6% ± 4.0%

ALL—Transplant Survival at Cook Children’s (N=189)

AML16

- Significant improvement of outcomes over time
- Enhanced supportive care
- Risk adapted therapy (MRD, Genetics)
- "New" agents with activity that are available
  - DMTi, HDACi, TKI
- Trial should capitalize on strengths (Science)
- Current enrollment rates make randomized trials with a survival endpoint difficult
- Cooperate with other efforts to help improve outcomes

Ching–Hon Pui M.D.

"Who was once the mentee has become the mentor."
A Final Statement

• “The evaluation and treatment of Childhood Leukemias is one of the most challenging and rewarding fields of modern medicine”.
• Thank-you for your attention!

• W. Paul Bowman, M.D.