A Story of ALL

1947 - 2047

As Told By:
Stephen E. Sallan, M.D.
1947 - 2047

Once upon a time ...
1947 - 2047

... and they all lived happily ever after!
Chapters

1. The Sids & The Emils
2. Fairest of them A.L.L.?
3. Collateral damage
4. Serendipity
5. The Watsons
Chapter 1

The Sids & The Emils

Setting the Table
Dr. Sidney Farber

Dr. Siddhartha Mukherjee
Dedication

To

Robert Sandler (1945-1948),
and those who came before
and after him
TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY
FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

Sidney Farber, M.D.,† Louis K. Diamond, M.D.,‡ Robert D. Mercer, M.D.,§
Robert F. Sylvester, Jr., M.D.,¶ and James A. Wolff, M.D.||

BOSTON
Aminopterin

Methotrexate
Emil Frei III/Emil Freireich

(Late 1950’s/Early 1960’s)

• Extrapolated from mouse models to children
• The drugs
  - Vincristine
  - Prednisone
  - Methotrexate
  - 6-Mercaptopurine
• “Optimized” combinations of drugs
  - Doses
  - Schedules
Filling The Drug Quiver

1960’s/1970’s

• Asparaginase
• Anthracyclines
• Cytarabine
• Etoposide

(No new drugs for de novo ALL since 1970’s!)*
Event–free Survival for 2,999 Children
Treated on DFCI Consortium Trials 1973–2010

Probability Event–free Survival

Years

2000's (N=1,043)
1990's (N=868)
1980's (N=878)
1970's (N=210)
Chapter 2

WHO IS FAIREST OF THEM A.L.L.?
35 Years Evolving “Risk Factors”

(Treatment & Technology)

- Age/WBC
- Immunophenotype (T/B-cell)
- Chromosomes
- Response to Rx (MRD)
## Historic Age/WBC Criteria

*(1993 Consensus)*

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>WBC</th>
<th>4-yr EFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCI Standard</strong></td>
<td>1-10</td>
<td>&lt;50K</td>
</tr>
<tr>
<td><strong>NCI High</strong></td>
<td>≥10</td>
<td>&gt;50K</td>
</tr>
</tbody>
</table>

**Relevant today?**
EFS by Age
Dana Farber 2005 - 2010

p=0.08
EFS By Age and Immunophenotype
(DFCI 2005 – 2010)

B-ALL: EFS by Age

T-ALL: EFS by Age
ALL: Chromosomal Abnormalities

- Hyperdiploid: 30%
- Normal: 10%
- Random: 11%
- TCR/X: 7%
- Ig/MYC: 2%
- BCR/ABL: 5%
- E2A/PBX: 4%
- MLL: 6%
- TEL/AML1: 25%
### 2005-2011: Outcome by Cytogenetics

<table>
<thead>
<tr>
<th>condition</th>
<th>N (%)</th>
<th>4 yr EFS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEL/AML1 (ETV6/RUNX1)</td>
<td>97 (18)</td>
<td>98%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperdiploid (51-65) + 4/10</td>
<td>145 (26)</td>
<td>89%</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>88 (16)</td>
<td>95%</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>57 (10)</td>
<td>85%</td>
<td>0.96</td>
</tr>
<tr>
<td>No abnormality</td>
<td>131 (24)</td>
<td>87%</td>
<td>0.92</td>
</tr>
<tr>
<td>MLL-R</td>
<td>10 (2)</td>
<td>60%</td>
<td>0.007</td>
</tr>
<tr>
<td>Ph+</td>
<td>16 (3)</td>
<td>69%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- EFS $\geq$95% in 34% of children!
- Overtreated?
Ph+ ALL

AALL0031 (n=43)
Historical Controls (n=120)
P < 0.0001

Schultz & Devidas, Leukemia 2014
Ph-like ALL

• Distinctive gene expression profile
• 15% B-ALL (esp. older)
• High frequency:
  - CRLF2 over-expression
  - JAK mutations
  - IK2F1 gene deletions
Outcome by IKZF1

2005 - 2011

Low MRD patients

EFS

p=0.0001

No IKZF1 deletion 5-yr EFS 87% [95% CI 03-00]
IKZF1 deletion 5-yr EFS 61% [95% CI 48-72]

N at risk
IKZF1 Normal 259
IKZF1 Deleted 40

Years from randomization

EFS
Minimal Residual Disease

Matters ... A lot

<table>
<thead>
<tr>
<th>End-Induction MRD</th>
<th>N</th>
<th>5-yr DFS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;0.001)</td>
<td>246</td>
<td>89%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High (&gt;0.001)</td>
<td>38</td>
<td>33%</td>
<td></td>
</tr>
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</table>
# Intensified Therapy for Patients with High MRD

## 1996-2000

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<th>p-value</th>
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## 2005-2011

<table>
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<tr>
<th>End-Induction MRD</th>
<th>N</th>
<th>5-yr DFS</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Low (&lt;0.001)</td>
<td>338</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>High (&gt;0.001)</td>
<td>40</td>
<td>77%</td>
<td>0.016</td>
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</table>

Place AE et al. Lancet Oncol 2015
Is duration of treatment a risk factor for relapse?
Duration of Therapy

• ~2 years
  – Empirically “settled law”
  – BFM randomized 1.5 vs. 2 yrs
  – Boys longer?

• Can cure leukemia <2 years
  – Chemotherapy-cured AML
  – Burkitt B-cell ALL
  – Favorable risk - Japan
The Japanese Experience
N = 280 (in CR @ 1 yr)

• Is 1 year of treatment sufficient?
  – DFS @ 10 yrs = 66%
    • Girls 75%     Boys 58%
    • ETV6/RUNX1 = 94%
    • TCF3/PBX1     = 91%

Fairest Treatment of A.L.L.?

- Less is better? LR - Japan
- More is better? HR - DFCI
- Better is better? Ph+ - COG
Chapter 3

Collateral Damage
Harmless Cures Are Elusive

Acute complications

• Infection –
  – Myelosuppression
  – Immunosuppression

• Drug toxicities
  – Mucositis
  – Allergy
  – Seizure
  – Pancreatitis
Long-term Concerns

Joint Damage
Heart Failure
Second Neoplasms
Neurocognitive
Stature/Obesity

(steroids/anthracycline)
Steroid Yin & Yang

Vrooman LM et al. JCO 311:1202, 2013

<table>
<thead>
<tr>
<th>Steroid</th>
<th>5-year (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>90</td>
<td>85 to 94</td>
</tr>
<tr>
<td>Prednisone</td>
<td>81</td>
<td>75 to 87</td>
</tr>
</tbody>
</table>

p = .01
Prevent Heart Damage

• Dexrazoxane
  – Cardioprotectant
  – Safe & effective
Event-free Survival in ALL
1996 - 2000

Number at risk
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>100</td>
<td>86</td>
<td>75</td>
<td>67</td>
<td>54</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin plus dexrazoxane</td>
<td>105</td>
<td>90</td>
<td>72</td>
<td>66</td>
<td>49</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>
Conundrums

• Many cured with little or no:
  – Asparaginase
  – Anthracycline
  – Radiation
  – Dexamethasone

• But on “similar but different” regimens

• For whom should we “turn the screw to the left”?

• How to safely measure “take away” questions?
Chapter 4

Serendipity
MILLENNIAL OBSERVATION
Hidden in Plain Sight

Log Rank $p<.0001$

CCG (pediatric group)

CALGB (adult group)

Ages 16-20

Blood 112:1646, 2008
Adolescent/Young Adult

• Untangling the interplay of:

  Biology
  Therapy
  Sociology
AYA Biology

- Leukemia –
  - More Ph+ & T-ALL
  - More de novo resistance
  - No ETV6/RUNX1

- Host –
  - More drug intolerance
    e.g. PEG asparaginase
  - Co-morbidities
## Pediatric-like Treatments

### Non-Comparative Reports of Pediatric Regimen in AYAs

<table>
<thead>
<tr>
<th>Location</th>
<th>Program</th>
<th>Age</th>
<th>Follow-up</th>
<th>DFS (%)</th>
<th>EFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.: Dana Farber</td>
<td>DFCI 01-175</td>
<td>18-60</td>
<td>4 Years</td>
<td>69%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>DFCI 06-254</td>
<td>18-50</td>
<td>3 Years</td>
<td>73%</td>
<td>75%</td>
</tr>
<tr>
<td>U.S.: CALGB,ECOG,SWOG</td>
<td>C10403</td>
<td>16-30</td>
<td>5 Years</td>
<td>55%</td>
<td>67%</td>
</tr>
<tr>
<td>France</td>
<td>GRAALL 2003</td>
<td>15-60</td>
<td>4 Years</td>
<td>55%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>Adult ALL Group</td>
<td>18-39</td>
<td>3 Years</td>
<td>67%</td>
<td>86%</td>
</tr>
<tr>
<td>Spain</td>
<td>GIMEMA ALL0496</td>
<td>14-18</td>
<td>2 Years</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>AIEOP ALL95, 2000</td>
<td>14-18</td>
<td>2 Years</td>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>
AYA Disease-Free Survival

Median f/u 42.2 mos
3-yr DFS 73%

Overall Survival Based on Age

- 18–19 yrs (N=9)
- 20–29 yrs (N=38)
- 30–39 yrs (N=30)
- 40–50 yrs (N=33)
Overall Survival
Based on Immunophenotype
ARE THERE PHYSICIAN “CULTURAL” OR “SOCIOLIGIC” DIFFERENCES?
SOCIOLOGIC DATA

• Boissel & colleagues: “disparities in treating attitudes”

Median days from CR to next treatment

   Pediatric trial    2 days
   Adult trial      7 days

p=0.002
“The Mother”

• As caretaker
• As patient
AYA
Standard of Care

Transplant vs Chemotherapy

Cumulative Incidence of TRM

HR = 6.88 (3.02-15.70); P < 0.0001

Chemo (N=107)
HCT (N=422)
Chapter 5

The Watsons
What Will Be “Hot”
2017 – 2047

• Precision approaches
  – Aimed at small genetic subsets
  – Technology-driven
    • RNA seq. determined Rx
    • Recognition of those destined to relapse

• Immunotherapies
  – CAR-T or AB+ drug combinations for de novo ALL

• Therapies based on predictive animal models

• Months, not years, of treatment?
• End of stem cell transplant?
• Attacking the microenvironment
  – Anti-angiogenic therapy
• Artificial intelligence
Angiogenesis in Leukemia
Response to Dexamethasone
The Watsons

The Art & Science of Medicine

Watson Sallan

IBM Watson
Dedication

To

Robert Sandler (1945-1948),
and those who came before
and after him
“If you miss the joy in it... you miss it all!”