Welcome and Introductions

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Memorial Sloan-Kettering Cancer Center
New York, NY

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ALL Topics

• How ALL is diagnosed and how risk assessment is determined?

• Risk assessment and treatment plan development

• Treatment options

• The role of clinical trials in the advancement of ALL treatment for patients

• Communication touch points among patients and healthcare providers

Epidemiology
Age Specific Incidence Per 100,000 Population

• In 2013: 6,300 new cases in US

• In the United States: more in Hispanics

• Most common cancer in children (30% of all pediatric cancers)

• Pediatric ALL, the most curable cancer

Leukaemias: age-specific incidence rates per 100 000 population. Female, — — —; male, — — [5].
ALL - Not Just a Pediatric Disease
Treatment Age Groups

Annual Incidence of ALL
(SEER 1998-2002)

40% Age >20 years

15 --- 21
39
60

Survival by Age at Diagnosis
2 Year Age Intervals, 2000-2007, SEER17

5-Year Survival (%)

Acute Lymphoblastic Leukemia

Age > 20 = 40%

Acute Leukemia
Clinical Features (I)

• Acute presentation

• Blood
  – Anemia → weakness, tiredness
  – Low platelets → bleeding
  – Low neutrophils → infections
  – Blast cells appear with time

• Bone marrow
  – Blast cells ≥ 20%
  – Normal hematopoiesis suppressed or not detectable

Acute Leukemia
Clinical Features (II)

• Extramedullary infiltrations
  – Spleen, liver
  – Lymph nodes (ALL)
  – Non-hematological tissues
    • Skin
    • Gums
    • CNS (ALL)
    • Other organs
Diagnostic Evaluation for Acute Leukemia

- CBC with differential
- Examination of peripheral blood smear
- Coagulation studies
- Blood chemistries
- Bone marrow aspiration and biopsy
  - Leukemia blast:
    - Immunophenotype
    - Cytogenetics
    - Molecular genetics

Diagnostic Tests

- Immature cells: CD34
- Myeloid/monocytic: MPO, CD13, CD33, CD15, CD14
- Immature lymphoid markers: TdT
- Pre B-cells - TdT, CD10, CD19, CD22, CD20
- T-cells - CD3, CD5, CD7, CD8, CD4, CD1a
- True biphenotypic acute leukemia (very rare)
**T-cell ALL**
25% of Adult ALL

- Young adults
- Without marrow involvement - T-cell lymphoblastic lymphoma (mediastinal mass)
- High WBC
- Better prognosis
- Higher rate of CNS relapse

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**ALL: Karyotype and Outcome**

<table>
<thead>
<tr>
<th>Decreased event-free or overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(9;22) (Ph+)</td>
</tr>
<tr>
<td>t(4;11)</td>
</tr>
<tr>
<td>Complex karyotype</td>
</tr>
<tr>
<td>(&gt; 5 abnormalities)</td>
</tr>
<tr>
<td>Low hyperdiploidy / near triploidy (Ho-Ti)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improved event-free or overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploidy</td>
</tr>
<tr>
<td>Del (9p)</td>
</tr>
</tbody>
</table>

Ph = Philadelphia chromosome

Other Poor Prognostic Indicators

- Increasing age
- Increasing WBC count
  - 30,000 for B-cell lineage
  - 100,000 for T-cell lineage
- Immune phenotype
  - Non T-cell lineage
  - Pro B ALL - CD10 negative
- Slow response to therapy
  - Adults, CR 4 weeks
  - Minimal residual disease (MRD)


<table>
<thead>
<tr>
<th>Gene</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-B</td>
<td></td>
</tr>
<tr>
<td>IKZF 1 (IKAROS)</td>
<td>Poor</td>
</tr>
<tr>
<td>RCLF2</td>
<td>Poor</td>
</tr>
<tr>
<td>MLL-v t(v;1)</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>T-cell</td>
<td></td>
</tr>
<tr>
<td>FBXW7</td>
<td>Good</td>
</tr>
<tr>
<td>NOTCH 1 (70%)</td>
<td>Good</td>
</tr>
<tr>
<td>NUP-ABL1 (6%)</td>
<td>Response to TKI</td>
</tr>
</tbody>
</table>
**ALL: Treatment Elements**

Induction, consolidation, maintenance phases and CNS prophylaxis

- **CNS Prophylaxis (IT MTX)**
- **Induction** → **Consolidation** → **Maintenance**
  
  *Over a period of months*  
  *2-3 years*

**Challenges in Establishing “State-of-the-Art” Treatment**

- Very wide age range
  - AYA 15 to 39 yrs
  - Adults ("younger") 40 to 60/65 yrs
  - Older adults 60/65+

- Multiple chemotherapy regimens with few comparable trials

- Uncertainty about the role of allo BMT

- Pediatric or “Pediatric-inspired” regimens

**NCCN guidelines – clinical trial or pick your favorite**
Principals of Adult ALL Protocols
(All include maintenance and CNS prophylaxis)

- **“BFM model” variants (CALGB, GMALL, ECOG)**
  - Induction: 2 phases, 8 drugs w/asparaginase
  - Consolidation
    - Complex multi-agent cycles
    - Asparaginase
    - Delayed re-induction

- **Hyper-CVAD (alternate Parts A and B x 4)**
  - More myelosuppressive drugs (inpatient)
  - No asparaginase
  - 6-MP only in maintenance

### Adult ALL - Recent Large Front-line Clinical Trials

<table>
<thead>
<tr>
<th>Years of study</th>
<th>N</th>
<th>Age</th>
<th>Treatment</th>
<th>CR (%)</th>
<th>DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMALL 05/93¹</td>
<td>1000</td>
<td>35</td>
<td>BFM, HD-Ara-C, HD-MTX</td>
<td>87</td>
<td>35</td>
</tr>
<tr>
<td>CALGB 8811²</td>
<td>198</td>
<td>35</td>
<td>BFM, ↑Cy, ↑ASP</td>
<td>85</td>
<td>36</td>
</tr>
<tr>
<td>CALGB 1980³</td>
<td>163</td>
<td>41</td>
<td>BFM, ↑Cy, ↑DNR</td>
<td>78</td>
<td>35</td>
</tr>
<tr>
<td>MRC/ECOG-UKALLXII/E2993⁴</td>
<td>1913</td>
<td>15-64</td>
<td>BFM + HD-MTX ± SCT</td>
<td>90</td>
<td>OS 39</td>
</tr>
<tr>
<td>Hyper CVAD⁷</td>
<td>'92-'00</td>
<td>288</td>
<td>40</td>
<td>A) Cy, DEX, ADR, VCR B) HD-MTX+HD-Ara-C</td>
<td>92</td>
</tr>
<tr>
<td>UCSF 8707⁵</td>
<td>'87-'98</td>
<td>84</td>
<td>27</td>
<td>VPDA + Intensified</td>
<td>93</td>
</tr>
<tr>
<td>LALA 94⁶</td>
<td>922</td>
<td>33</td>
<td>VPD + Cy, HD-Ara-C</td>
<td>84</td>
<td>37</td>
</tr>
<tr>
<td>L-2</td>
<td>78</td>
<td>33</td>
<td>HD-MITO+ HD-Ara-C</td>
<td>85</td>
<td>34</td>
</tr>
</tbody>
</table>

Central Nervous System Prophylaxis

- Intrathecal methotrexate
- Systemic high-dose methotrexate
- Cranial irradiation
  - Probably not necessary with systemic high-dose treatment (methotrexate, Ara-C) and extended intrathecal methotrexate


**Adult ALL – First Relapse Survival**

**Age at Diagnosis**

- Age < 20: 12%
- Age 20 - 34: 7%
- Age 35 - 49: 4%
- Age ≥ 50: 3%

**Therapy in CR1**

- Allo/MUD: 9%
- Chemo: 7%
- Auto: 3%


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**Strategies to Improve Outcome of Adult ALL**

- Transplantation
- Pediatric-inspired regimens
- Identify special subtypes for different treatment
  - Mature B cell (Burkitt’s) ALL
  - Ph+ ALL
- New drugs
Bone Marrow Transplantation
CIBMTR Recommendations

• CR 1
  – Allogeneic transplant in high-risk patients
  – Role in standard-risk patients unclear but not recommended
  – Autologous SCT: no benefit over chemotherapy

• CR 2
  – Allogeneic SCT


Allogeneic Stem Cell Transplantation
MRC/ECOG UKALLXII/E2993 Trial
Ph Negative ALL

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Relapse</th>
<th>Non-relapse death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>No donor</td>
<td>Donor</td>
</tr>
<tr>
<td>High risk</td>
<td>41%</td>
<td>35%</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td><em>P&lt;0.0005</em></td>
</tr>
<tr>
<td>Standard risk</td>
<td>62%</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td><em>P&lt;0.02</em></td>
<td></td>
<td><em>P&lt;0.05</em></td>
</tr>
</tbody>
</table>

High risk any of: Age ≥ 35 years

WBC > 30,000/µL (*B Lineage*)

> 100,000/µL (*T Lineage*)

Time to CR > 4 weeks

### Outcome

**Adults vs. Childhood ALL**

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>LFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>80%-90%</td>
<td>35-40%</td>
</tr>
<tr>
<td>Children (2-10 years)</td>
<td>&gt;95%</td>
<td>80%</td>
</tr>
</tbody>
</table>


### Survival of 18,772 Pediatric Patients With ALL Treated on Sequential CCG Clinical Trials Over Three Decades

<table>
<thead>
<tr>
<th>Years of Accrual</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970-1972</td>
<td>499</td>
</tr>
<tr>
<td>1972-1975</td>
<td>936</td>
</tr>
<tr>
<td>1975-1977</td>
<td>1,313</td>
</tr>
<tr>
<td>1978-1983</td>
<td>2,984</td>
</tr>
<tr>
<td>1983-1988</td>
<td>3,711</td>
</tr>
<tr>
<td>1989-1995</td>
<td>5,121</td>
</tr>
<tr>
<td>1996-2001</td>
<td>3,806</td>
</tr>
</tbody>
</table>

**BFM**

Aug

CNS

Survival of the Leukemias.

Adolescents and Young Adults
Retrospective Comparison
Pediatric vs. Adult Protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>EFS @ 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pediatric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age</td>
<td>Protocol</td>
</tr>
<tr>
<td>US(^1)</td>
<td>321</td>
<td>16-20</td>
<td>63%</td>
</tr>
<tr>
<td>France(^2)</td>
<td>177</td>
<td>15-20</td>
<td>67%</td>
</tr>
<tr>
<td>Netherlands(^3)</td>
<td>120</td>
<td>15-20</td>
<td>69%</td>
</tr>
<tr>
<td>Sweden(^4)</td>
<td>59</td>
<td>15-20</td>
<td>75%</td>
</tr>
<tr>
<td>UK(^5)</td>
<td>128</td>
<td>15-17</td>
<td>65%</td>
</tr>
<tr>
<td>Italy(^6)</td>
<td>248</td>
<td>14-18</td>
<td>83%</td>
</tr>
</tbody>
</table>


Age - A Complex Prognostic Factor

- Age “per se” - children
  - Favorable cytogenetic
  - Better chemotherapy tolerance…..
    but….also in young adults

- Treatment - adults
  - Less intense
  - Very few randomized trials
  - Lower compliance: physician and patient
Pediatric Treatment Approaches
Principals

- More intense non-myelosuppressive agents
- Prolonged asparaginase (asparagine depletion)
- Delayed re-induction
- Early CNS prophylaxis (induction)
- Allo BMT only for very high-risk e.g., t(4:11), Ph+

Asparaginase Activity in ALL
Summary

- Active as a single agent (35%-60% in relapsed children)
- In children several randomized trials showed that asparaginase alone, (with multiple agents) improved overall outcome
- Duration of post-remission asparaginase
  - Children - long (5-6 cycles)
  - Adults - short (0-2 cycles)
Unique Toxicities of Asparaginase

- **Hypersensitivity:** allergic reactions
  - Neutralizing antibodies
  - “Silent hypersensitivity”
- **Pancreatitis**
- **Hemostasis**
  - Clotting: low antithrombin III, protein S
  - Bleeding: low clotting factors
- **Liver dysfunction**
  - Liver enzymes, hyperbilirubinemia
  - Low albumin
- **Diabetes mellitus**
- **Neurological (lethargy, somnolence)**


Asparaginase Intensification
Pediatric and Pediatric - “Inspired” Regimens

<table>
<thead>
<tr>
<th>Asparaginase</th>
<th>Upper age</th>
<th>OS @ 3-7 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True Pediatric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFCI¹ E. coli</td>
<td>50</td>
<td>74%</td>
</tr>
<tr>
<td>CALGB 10403 Pegaspargase 2,500</td>
<td>39</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Pediatric “Inspired”</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHEMA² E. coli</td>
<td>30</td>
<td>69%</td>
</tr>
<tr>
<td>GRAALL-2003³ E. coli</td>
<td>45/60</td>
<td>64%/47%</td>
</tr>
<tr>
<td>USC⁴ Pegaspargase 2,000</td>
<td>57</td>
<td>58%</td>
</tr>
<tr>
<td>Princess Margaret⁵ E. coli (retrospective)</td>
<td>60</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Asparaginase Intensification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMALL 7/03⁶ PEG 500/1000 2,000</td>
<td>55</td>
<td>67%</td>
</tr>
</tbody>
</table>

¹DeAngelo. ASH. 2007; ²Ribera. JCO. 2008; Abst #587; ³Huguet. JCO. 2009; ⁴Douer. ASH. 2012; Abst #1495; ⁵Storring J. Br J Haematol. 2009; ⁶Goekbuget. ASH. 2010; Abst #404.
USC II Modified CCG Augmented Pediatric Arm (BFM)

PEG Asparaginase 2,000 u/m² IV per dose

Induction1  Induction2  Consolidation1  Consolidation2  Delayed Re-induction1
DNR  VCR  PRED  Peg-ASP  IT-MTX          HD-MTX x2  Days 1-5
VCR  PRED  Peg-ASP  Ara-C  6MP  DNR  Peg-ASP  Ara-C
PRED  Peg-ASP  6MP  IT-MTX  Peg-ASP  Cyclo  DEX
Peg-ASP  Ara-C  6-TG  IT-MTX

Total Peg-ASP Doses = 6

Maintenance: 6 MP/MTX/vincristine/prednisone therapy continues for 2 years

Current CALGB C10403 Trial
Adolescents and Young Adults
Age 15 – 39 years

Stock CALGB 10403
2,500 IU/m² IV or IM

Age ≥16 to <30

Induction (4 weeks)  Extended Induction if needed (2 weeks)  Interim Maintenance (8 weeks)  Delayed Intensification (12 weeks)  Maintenance* (12 weeks)

*Repeat Maintenance Therapy courses (12 week courses; 94-day cycles) until total duration of therapy is 2 years from start of Interim Maintenance Therapy for female patients, or for male patients 3 years from the start of Interim Maintenance Therapy.
Philadelphia Chromosome (Ph+) ALL

- t(9;22) bcr/abl translocation
- Precursor B-cell
- Incidence continuously increases with age (rare in children; ~50% in ages >55)
- Tyrosine kinase inhibitor activity
  - First generation – imatinib (Gleevec®)
  - Second generations – dasatinib (Sprycel®); nilotinib (Tasigna®)
  - Third generation ponatinib (Iclusig™)
Northern Italy Leukemia Group Protocol (Ph+ ALL)

![Graphs showing survival, disease-free survival, and relapse rates with Imatinib]

**Treatment of Ph+ ALL**

**Summary**

- **TKI + concomitant multi-agent chemotherapy**
  - Improved overall survival to 35-50%
  - Ideal chemotherapy?
- **Allo HSCT**
  - May improve outcome but not clear to what extent
  - In children no additional benefit after TKI + chemotherapy
- **Second and third generation TKIs effective in imatinib-resistant or intolerant patient**
- **Changed outcome of Ph+ ALL [t(4;11) is now the worst ALL]**
## New Agents Targeting (Immunotherapy) B-cell ALL

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Single agent activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 20</td>
<td>Rituximab(^1,2)</td>
<td>Minimal (w/chemo may improve outcome in young CD20+)</td>
</tr>
<tr>
<td>CD 19</td>
<td>Blinatumomab(^3,4)</td>
<td>CR 70% in molecular or overt relapsed/refractory</td>
</tr>
<tr>
<td></td>
<td>19-28z CAR-targeted autologous T-cells(^5)</td>
<td>Yes</td>
</tr>
<tr>
<td>CD 22</td>
<td>Epratuzumab(^6)</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td>Inotuzumab ozogamycin(^7)</td>
<td>CR + CRp = ~50%</td>
</tr>
<tr>
<td></td>
<td>Moxetumomab pasudotox (HA22)(^8)</td>
<td>CR 24%</td>
</tr>
</tbody>
</table>

\(^1\)Hoelzer. ASH. 2010;Abst #170; \(^2\)Thomas. JCO. 2010; \(^3\)Topp. JCO. 2011; \(^4\)Topp. ASH. 2011;Abst #252; \(^5\)Davila. ASH. 2012;Abst #356; \(^6\)Raetz. JCO. 2008; \(^7\)Wayne. ASH. 2011; Abst #248; \(^8\)O’Brien. ASH. 2011;Abst #857.

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### Mode of Action of BiTE® Antibody Blinatumomab

- Blinatumomab (MT103) is a Bispecific T-cell Engager (BiTE®) antibody designed to direct cytotoxic T-cells to CD19 expressing cancer cells

### Blinatumomab – Single Agent Refractory/Relapsed Pre-B ALL

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Pts. #</th>
<th>Response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular (MRD+)¹</td>
<td>21 (5 Ph+)</td>
<td>MRD neg: 80%</td>
<td>RFS 78%</td>
</tr>
</tbody>
</table>

*MRD negative after two cycles

²Topp. ASH. 2011;Abst #252.

### MSKCC CAR T-cell Protocol Eligibility and Treatment Schema

- Adult patients (>18 years old)
- Patients B-ALL refractory, relapsed, MRD+, or in CR1
- Ph+, extramedullary disease, CNS leukemia, and/or relapsed after prior allo-stem cell transplant are all eligible

1. **Leukapheresis**
2. **Expectant monitoring**
3. **Re-induction chemotherapy**
4. **CAR T-cell production**
5. **19-28z CAR T-cell infusion**
6. **Monitoring T-cells**

Post CAR T-cell treatment options include:
1. Allo-SCT
2. Different salvage therapy
3. Monitoring

Davila, et al. ASH. 2013;Abst #69.
Adverse Events

- Fevers
- Hypotension
- Hypoxia
- Neurologic changes
  - Mental status change, obtundation, seizures
- Malaise
- ICU care

CAR T-cells Summary

N=16 (overt ALL =8)

- CR=88%, CRm=76
- Median to CR =24 days
- 44% → allo-SCT (70% of eligible patients)
- Steroids
  - Effective at ameliorating the CRS
  - Cost of lymphotoxicity, resulting in eventual relapses
- Tocilizumab effective for CRS without lymphotoxicity
- Similar anti-leukemia efficacy in patients with only MRD as patients with morphologic residual leukemia
- To date, there have been no relapses post allo-SCT
### Novel Targeted Agents

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notch1 (T-ALL)</td>
<td>γ secretase inhibitors (GSI)</td>
</tr>
<tr>
<td>MLL (q11.34)</td>
<td>DOT1L inhibitor, FLT3 inhibitors</td>
</tr>
<tr>
<td>PP2A (Ph+ ALL)</td>
<td>FTY720 Fingolimod (MS)</td>
</tr>
<tr>
<td>PNP (T-ALL)</td>
<td>Forodesine (Bcx-1777)</td>
</tr>
<tr>
<td>NUP214-ABL1 T</td>
<td>Thyrosine kinase inhibitors</td>
</tr>
<tr>
<td>mTOR</td>
<td>Everolimus, temsirolimus</td>
</tr>
<tr>
<td>JAK</td>
<td>JAK inhibitors</td>
</tr>
</tbody>
</table>

### State-of-the-Art Therapy for Adult ALL

**A Changing Landscape**

- **Pediatric or “pediatric inspired” regimens**
  - Young adult: upper age limit is unclear

- **Treatment changes based on new stratification models**
  - Philadelphia positive
  - Early MRD status
  - “BCR-ABL1 – like” ALL (frequency in adults?)
  - Other mutations (RCLF2, IKZF……)

- **No !!! State-of-the art therapy – relapse, older adults**
State-of-the-Art Therapy for Adult ALL
A Changing Landscape

Novel Agents

• Immunotherapy
  – Monoclonal antibodies (CD19, 22, 20)
  – Cell therapy – Chimeric antigen receptor (CAR)

• Small molecule targeting driver mutations (e.g., Notch1, Dot1, JAK2)

Allogeneic Hematopoietic Stem Cell Transplantation in CR1

• Only very high risk ALL?

Communication Touch Points Among Patients And Healthcare Providers

• Complex regimens – optimal adherence
  – Patient compliance
  – Physician compliance
  – Time and effort commitment: travel, parking, work, life events, etc.

• Reduce toxicities
  – Teaching of side effects (e.g. asparaginase)
  – Anticipating side effects
  – Monitoring for early detection of side effects

• Communication with healthcare provider
  – Major cancer center
  – Local community oncologists
THANK YOU

Dan Douer, MD
Memorial Sloan Kettering Cancer Center

ALL
Understanding Diagnosis and Treatment for Adults

Question & Answer Session
The speaker’s slides are available for download at www.LLS.org/programs
ALL
Understanding Diagnosis and Treatment for Adults

For more information about ALL and other programs from The Leukemia & Lymphoma Society (LLS), please contact an LLS Information Specialist:

TOLL-FREE PHONE: (800) 955-4572
EMAIL: infocenter@LLS.org
LIVE ONLINE CHAT: www.LLS.org/informationspecialists