Management of Acute Lymphoblastic Leukemia

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Acute Lymphoblastic Leukemia (ALL)

- Approximately 6,000 patients per year diagnosed with ALL
  - 60% of cases diagnosed at < 20 years of age
  - 11.2% of patients > 65 years of age
- 5-year overall survival between 2005-2011 is 67.5%
- Adult outcomes lag significantly behind those in the pediatric population
- Treatment outcomes in patients > 65 years are very poor
  - 5-year relative survival only 9.1%
  - Account for 35% of patients dying from ALL

What can we learn from the paradigm of pediatric hematology?

![Graph showing event-free survival over years from diagnosis for different therapies: Risk-adapted therapy (90’s), Intensive therapy (80’s), CNS preventative therapy (70’s), Combination chemotherapy (60’s), Single-agent chemotherapy (50’s).]

Years from diagnosis

Courtesy Pat Brown, Johns Hopkins
Peripheral Blood Smear in ALL
Bone Marrow Biopsy in ALL
Flow Cytometry in ALL
Advances in the Care of Patients with ALL

- The best opportunity to improve ALL outcomes is to make the best, evidence-based treatment choices early post-diagnosis/relapse
- The inclusion of novel and targeted therapeutic agents in induction and salvage therapy are likely to improve treatment outcomes

**Key Themes – The Need to Think Strategically**

- Other than tyrosine kinase inhibitor (TKI) therapy for Philadelphia chromosome (Ph)+ ALL, many of the improvements in ALL survival outcomes have occurred without the addition of novel therapeutic agents
- Pediatric and pediatric-inspired regimens have improved outcomes by effectively maximizing dose-intensity of existing agents
- Improving treatment outcomes for adult patients requires that we fully leverage diagnostic, molecular, and demographic data to develop individualized treatment plans
- Immunotherapies, particularly monoclonal antibodies, now play an essential role in salvage treatment of ALL
Key Knowledge Opportunities in Caring for Patients with ALL

- Cytogenetic, molecular, genomic data
  - Ph+ ALL
  - MLL, complex, high-risk karyotypes
  - Ph-like ALL
- Patient demographic data
  - Adolescent/Young Adult Patients
  - ALL in the elderly
- Immunotherapy-based salvage strategies
Cytogenetic, Molecular, and Genomic Risk Stratification

Risk-Adapted Treatment in ALL
Prognosis In ALL Is Not Quite That Simple

Q: Why do adults with ALL do worse than kids (40% vs. 80% survival)?

A: Biology (partly)

- BCR-ABL t(9;22) 3%
- MLL rearrangements e.g., t(4;11), t(11;19), t(9;11) 8%
- TEL-AML1 t(12;21) 22%
- T-Cell Lineage 12%
- HOX11L2 5q35 2.5%
- HOX11 10q24 0.7% MLL-ENL 0.3%
- E2A-PBX1 t(1;19) 5%
- MYC t(8;14), t(2;8), t(8;22) 2%
- Hyperdiploidy >50 chromosomes 25%
- Hypodiploidy <45 chromosomes 1%
- Others 22%

Pui et al, NEJM 2004
Patients with High-risk Cytogenetics

- Patients with Ph+ ALL should receive TKIs concomitantly with age-adapted induction and consolidation therapy
  - Mutational analysis should be performed for patients with a poor treatment response
  - Changes among TKIs should be based upon either mutational analysis or issues related to patient tolerance of the agent
  - Adult patients should be considered for early allogeneic hematopoietic cell transplant (HCT) in first complete remission (CR)
- Patients with high-risk cytogenetics – rearranged MLL, complex karyotype – should be considered for early allogeneic HCT in first CR
Overall Survival
ALLO SIB: ALL Patients, FTBI/VP-16/CY
Stratified by Disease Status: 1CR (22 events, 27 censored), >1CR (22 events, 8 censored)
Transplant Date Range: 07/09/1985 (Inception) - 12/31/2005
Run Date: January 18, 2008

Novel, High-Risk Genetic Subtypes of ALL: Philadelphia-Like ALL

• Ph-like ALL
  • Utilizing microarray analysis in 400 children identified subgroup of 43 precursor B-cell ALL patients lacking bcr-abl fusion gene with a gene expression profile similar to that of Ph+ ALL
    • Predominantly male
    • Age > 10 years
    • Presenting WBC > 20,000/µL
  • Ph-like ALL patients had an inferior prognosis to that of other patients with precursor B-cell ALL
    • 5-year EFS 54.8% vs. 83.1%
    • Relapse incidence 33.9% vs. 14.9%

Overall Survival Among Patients With Ph-like ALL


Overall survival

Survival rate (%)

No. at Risk

Children, high risk

| Years | 105 | 101 | 85 | 61 | 37 | 13 |

Adolescents

| Years | 76 | 63 | 53 | 28 | 11 | 4 |

Young adults

| Years | 41 | 20 | 12 | 4 | 0 | 0 |

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Recurring Kinase Alterations in Ph−like ALL.

Actionable Genetic Lesions in Ph-like Precursor B-Cell ALL

Treating Patients with Ph-like ALL

- Genomic alterations potentially responsive to inhibition with approved tyrosine kinase inhibitors (TKIs) (Ph+ and “Ph-like” ALL)
- Agents such as crizotinib, imatinib, ruxolitinib are being investigated
- Patients with Ph-like ALL should be considered for participation on a clinical trial
Patient Demographic Data

Risk-Adapted Treatment in ALL
AYA Patient Population

- AYA patients defined as those between the ages of 15-39 years
- This patient group is fitter and less likely to have significant comorbid conditions
- Patients in this age group can benefit significantly from treatment with pediatric or pediatric-inspired regimens
  - These regimens make use of greater chemo-therapeutic dose-density
  - They include intensive dosing schemes for L-asparaginase
- Patients need to be screened carefully for their candidacy for use of pediatric/pediatric-inspired regimens
- Practitioners need to be prepared to treat potential complications associated with the use of these regimens
AYA: Superior Outcomes With Pediatric Protocols

- Prospective studies of “pediatric-inspired” regimens in “young adults” (variably defined) have demonstrated feasibility and better outcomes compared to historical controls – intergroup C-10403 trial is ongoing for patients up to 40*

*“Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis.”

Pediatric and Pediatric-Inspired Regimens

GRAALL-2003 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <60 years)

COG AALL-0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegaspargase; nelarabine added to consolidation regimen (ongoing study)

CCG-1961 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (patients aged ≤21 years)

PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <30 years)

CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (ongoing study in patients aged <40 years)

DFCI ALL regimen (based on DFCI Protocol 00-01): doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase (ongoing study in patients aged <50 years)

USC ALL regimen (based on CCG-1882 regimen): daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged 18–57 years)
Treatment of Older Patients with ALL

- Patients with ALL > 65 years of age have poorer survival outcomes
  - These patients are more likely to suffer treatment-related complications/toxicities
  - Many of these patients may have poor outcomes when treated with standard therapeutic regimens
- Patients need to be screened carefully for comorbidities that might impact treatment
  - Physiological fitness and performance status need to guide therapeutic choices
- Perform Comprehensive Geriatric Assessment (CGA)
- Where possible, patients should be considered for participation in clinical trials
- Selected patients may be considered for more intensive therapeutic approaches, including allogeneic HCT
Trends in Survival of Elderly Patients with B-Lineage Acute Lymphoblastic Leukemia: Analysis of SEER 13 SEER Registry Sites (70+ years)

Mehta P, Venkitachalam R. Blood 2013;122:1404
©2013 by American Society of Hematology
Comprehensive Approach to Managing Older Patients with ALL

**Older Fit (55-75 years)**
- Age
- Performance status
- Comorbidities
- CGA
- Age specific life expectancy

**Older Unfit (> 75 years)**
- Frail

**Moderate intensity protocol for older patients with consolidation and maintenance**
- Asparaginase in consolidation
- IDMTX, IDAC reinduction
- Consider RIC SCT in HR pts
- Ph+: TK-inhibitor+reduced induction

**Optimised management**
- MRD evaluation
- Targeted and alternative drugs e.g. antibodies, nelarabine, TK inhibitors
- Intensive supportive care
- Psychosocial support

**'Palliative' ALL-type chemotherapy and/or experimental treatments**
- Ph+: TK-inhibitor

**HR** - high risk
**Pts** - patients
**IDMTX** - intermediate dose methotrexate
**TK** - tyrosine kinase
**IDAC** - intermediate dose cytarabine

Nicola Gökbuget Blood 2013;122:1366-1375

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Treatment of Less Fit Older Patients or Patients with Significant Comorbidities with ALL

• It is essential to have frank conversations with patients and their families regarding the goals of care
  • Patient goals should inform the treatment plan
  • Patients should be carefully informed of the risks and potential benefits of treatment

• Patients should receive early Supportive Care evaluation and management

• Patients with significant comorbidities, poor performance status should be considered for Palliative Care

• Please refer to the NCCN Guidelines for the Treatment of Older Adult Oncology Patients
Immunotherapeutic Therapies in Relapsed/Refractory ALL
Risk-Adapted Treatment in ALL
Outcome for Relapsed ALL

©2010 by Ferrata Storti Foundation
# Targeted Therapies for ALL

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>CD20</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>When added to conventional chemotherapy has been shown to improve survival in younger adults</td>
</tr>
<tr>
<td><strong>Ofatumumab</strong></td>
<td>Binds to a different epitope than rituximab, which may allow it to overcome rituximab-resistant disease</td>
</tr>
<tr>
<td><strong>Obinutuzumab</strong></td>
<td>Novel glycoengineered type II CD20 monoclonal antibody superior to rituximab and ofatumumab in the induction of direct cell death.</td>
</tr>
<tr>
<td><strong>CD19</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SAR3419</strong></td>
<td>Conjugated to a synthetic maytansinoid that is released intracellularly after antigen internalization</td>
</tr>
<tr>
<td><strong>SGN-CD19A</strong></td>
<td>Humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent. On internalization, it binds to tubulin and induces G2/M arrest and apoptosis</td>
</tr>
<tr>
<td><strong>Blinatumomab</strong></td>
<td>Bispecific antibody that redirects cytotoxic T cells to cells that express CD19</td>
</tr>
<tr>
<td><strong>CD22</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Epratuzumab</strong></td>
<td>Studied as part of combination therapy in adults and children with modest activity</td>
</tr>
<tr>
<td><strong>Epratuzumab-SN38</strong></td>
<td>Antibody conjugated to a topoisomerase I inhibitor to enhance cell killing potential</td>
</tr>
<tr>
<td><strong>Inotuzumab ozogamicin</strong></td>
<td>Antibody conjugated to the cytotoxin calicheamicin</td>
</tr>
<tr>
<td><strong>Moxetumomab</strong></td>
<td>Antibody conjugated to bacterial or plant toxin</td>
</tr>
<tr>
<td><strong>CD52</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Alemtuzumab</strong></td>
<td>Antibody that has only displayed little activity in B- and T-cell disease</td>
</tr>
</tbody>
</table>

Pre B ALL - Monoclonal Antibodies

Epratuzumab
Inotuzumab
Blinatumomab
SGN19a
Alemtuzumab
Rituximab

Lymphoblast

Impact of Rituximab on Patients with Ph–Negative Precursor B-lineage ALL

Deborah A. Thomas et al. JCO 2010;28:3880-3889

©2010 by American Society of Clinical Oncology
Construct of Bispecific Agent Blinatumomab and Mechanism of Activity

Molecular Immunology, 2015, Available online 13 April 2015
Blinatumomab

- Approximately 75% of patients with ALL have B-cell lineage disease
- CD19 expressed in > 90% patients with B-lineage ALL
- Apposition of CD19-expressing tumor cells with T-cells causes granzyme/perforin-related tumor lysis
- Key risk of agent is cytokine release syndrome
  - Patients with high leukemic burden at high risk
- Neurological toxicity seen in a significant number of patients
- Drug has a short half-life; must be administered as a continuous infusion
- Tumor cell escape based upon loss of CD19 expression
- This agent represents a “bridge toward cure”; it increases likelihood that patient can undergo allogeneic HCT
80% of patients achieved molecular complete response (CR) on blinatumomab.

Responses were rapid, all responses occurred after the first cycle of treatment.

4 patients had stable MRD levels as best response.

Responders include:
- 3/5 patients were $BCR-ABL(+)$$
- 13/15 patients were $BCR-ABL(-)$$
- 1/2 patients were $MLL-AF4(+)$$

*One patient not evaluable

Relapse-Free Survival

N=82

Median RFS, months 5.9
95% CI, months 4.8–8.3

**Overall Survival**

### Overall Survival

- **N=189**
- **Median OS, months:** 6.1
- **95% CI, months:** 4.2–7.5

### Landmark Analysis Day 77*

<table>
<thead>
<tr>
<th></th>
<th>CR/CRh</th>
<th>No CR/CRh</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=79</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td>9.9</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>95% CI, months</strong></td>
<td>6.8–NE</td>
<td>1.6–4.5</td>
</tr>
</tbody>
</table>

*After two treatment cycles

NE, not estimable

# Adverse Events (Regardless of Causality)*

<table>
<thead>
<tr>
<th>Adverse events, n (%)†</th>
<th>All Patients (N=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst grade 1 or 2</td>
<td>33 (17)</td>
</tr>
<tr>
<td>Worst grade 3 or 4</td>
<td>127 (67)</td>
</tr>
<tr>
<td>Worst grade 5 (death)</td>
<td>28 (15)</td>
</tr>
<tr>
<td>≥3 occurring in ≥5% of patients†</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>48 (25)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (16)</td>
</tr>
<tr>
<td>Anemia</td>
<td>27 (14)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>10 (5)</td>
</tr>
</tbody>
</table>

*During treatment until 30 days post treatment;  †CTCAE v4.0

Topp, et al. 2015. Lancet Oncol. 16(1) 57-66.
Inotuzumab Ozogamicin (InO)

MOA retains activity against tumor cells with slow cycling times

AcBut linker: 4-(4'-acetylphenoxy) butanoic acid dimethyl hydrazide

MOA = mechanism of action.

Inotuzumab Ozogamicin

- CD22 expression in > 80% patients with B-lineage ALL
- Inotuzumab ozogamicin is an antibody drug conjugate
- Initial monthly treatment showed efficacy and tolerability
  - 90 patients treated
    - CR 19%
    - CRp 30%
    - 9% marrow CR without recovery of blood counts
  - 36 of 90 patients underwent subsequent allogeneic HCT
    - VOD in 17% of BMT patients
    - VOD seen less often in patients treated with weekly schedule
- Similar response rates between single-dose scheme vs. weekly dosing (57% vs. 59%)
  - Weekly dosing associated with less toxicity
- Putative registration trial completed
- Agent has not yet received FDA approval

Chimeric Antigen Receptor (CAR) T-cell Therapeutics for ALL

- Form of adoptive immunotherapy
- Autologous T-cells engineered to express T-cell receptor (TCR) with CD19 specificity
- Target cells killed by T-cell specific tumor killing
- Important toxicities
  - Tumor lysis syndrome
  - Cytokine release syndrome
  - Macrophage activation syndrome
  - Neurological toxicities
  - B-cell aplasia
- In vivo persistence of CAR T-cells

CAR T-cell Therapeutics

• Phase I trials from multiple centers
  • University of Washington/Seattle Childrens/Fred Hutch
  • MD Anderson Cancer Center
  • Baylor
  • Memorial Sloan Kettering
  • University of Pennsylvania
• CR rates from 67-90% in high-risk, refractory patients
• On-going phase II trials
• Likely to become an important component in management of patients with relapsed/refractory ALL
Take Home Messages

• Early care decisions in newly diagnosed ALL have an irrevocable impact on patient outcomes
• Prognosis of newly diagnosed ALL can be improved significantly through rigorous risk stratification and use of risk-adapted therapies
• AYA patients should be screened for treatment with pediatric/pediatric-inspired regimens
• Older patients with ALL should have a thorough evaluation of their comorbidities and functional status prior to initiation of aggressive chemotherapeutic treatments
• Immunotherapeutic agents can play a life-saving role in patients with relapsed and refractory ALL
• Immunotherapeutic agents likely to play an increasing role in the care of patients with ALL
Questions?