Adult Acute Leukemia: Rocky Mountain Blood Cancer Conference Overview

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Today’s Agenda

1. Basic Principles of Acute Leukemias

2. Acute Myeloid Leukemia (AML)
   a. Prognosis
   b. Treatment

3. Acute Lymphoblastic Leukemia (ALL)
   a. Prognosis
   b. Treatment
What is acute leukemia

- Uncontrolled growth of a primitive hematopoietic cell leading to ineffective hematopoiesis
What is acute leukemia

• Syndrome – not a disease (... increasingly recognized to be true of most cancers)
  – Phenotypic manifestation of any of a number of genetic abnormalities causing maturation arrest and growth advantage

• Phenotype:
  – Low red blood cells (decreased energy)
  – Low platelets (bleeding)
  – Ineffective white blood cells (infection)
  – Enlarged lymph nodes (ALL)
  – Rapidly fatal (weeks) if untreated
Treatment Principles

• Treatment options depend on a variety of factors: age, comorbidities, patient wishes, specific abnormalities associated with disease
• Initial goal is to induce remission
• Next goal is consolidate remission and hopefully cure
• Tools include conventional chemotherapy, stem cell transplant, immunotherapy, novel and targeted agents
Acute Myeloid Leukemia
Demographics and Outcomes

- About 13,000 new diagnoses/yr; 9,000 deaths
- Affects all ages, but incidence increases among older pts
Modern Disease Classification

Cytogenetics/FISH

Molecular testing
Recurrent cytogenetic abnormalities

<table>
<thead>
<tr>
<th>Good Risk (Favorable)</th>
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<tbody>
<tr>
<td><strong>MRC</strong>&lt;sup&gt;12&lt;/sup&gt; inv(16)/t(16;16)/del(16q) with or</td>
</tr>
<tr>
<td>without other abnl</td>
</tr>
<tr>
<td>t(15;17) with or without other abnl, t(8;21) with or</td>
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<tr>
<td>without other abnl</td>
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<tr>
<td><strong>CALGB</strong>&lt;sup&gt;14&lt;/sup&gt; t(8;21), inv(16)/t(16;16)</td>
</tr>
<tr>
<td><strong>SWOG/ECOG</strong>&lt;sup&gt;13&lt;/sup&gt; inv(16)/t(16;16)/del(16q) with</td>
</tr>
<tr>
<td>or without other abnl</td>
</tr>
<tr>
<td>t(15;17) with or without other abnl</td>
</tr>
<tr>
<td>t(8;21) without del(9q) or complex karyotype</td>
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<table>
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<tr>
<th>Intermediate Risk</th>
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<tbody>
<tr>
<td><strong>MRC</strong> Normal, 11q23 abnl, +8, del(9q), del(7q), +21,</td>
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<tr>
<td>+22, all others</td>
</tr>
<tr>
<td><strong>CALGB</strong> Normal, -Y, del(5q), t(9;11), t(6;9), del(9q),</td>
</tr>
<tr>
<td>t(6;11), -8 sole, +8 with one other abnl, -7, +11, del(11q), +13, del(20q), +21, t(11;19)(q23,p13.1)</td>
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<tr>
<td><strong>SWOG/ECOG</strong> Normal, +8, +6, -Y, del(12p)</td>
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<tr>
<th>Poor Risk (Unfavorable)</th>
</tr>
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<tbody>
<tr>
<td><strong>MRC</strong> Complex karyotypes (≥ 5 unrelated abnl) del(5q),</td>
</tr>
<tr>
<td>-5, -7, abnl (3q)</td>
</tr>
<tr>
<td><strong>CALGB</strong> Complex karyotypes (≥ 3 unrelated abnl) inv(3)/</td>
</tr>
<tr>
<td>t(3;3), -7, abnl (12p), +21, t(6;9), t(6;11), -7, +8</td>
</tr>
<tr>
<td>sole, +8 with one other abnl, +8</td>
</tr>
<tr>
<td><strong>SWOG/ECOG</strong> Complex karyotypes (≥ 3 unrelated abnl)</td>
</tr>
<tr>
<td>del(5q), -5, -7/del(7q), abnl 3q, 9q, 11q, 20q, 21q,</td>
</tr>
<tr>
<td>17p, t(6;9), t(9;22)</td>
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</tbody>
</table>

![Graph showing overall survival percent over years after diagnosis]

- Favorable risk
- Intermediate risk
- Adverse risk
Molecular testing

FLT3 ITD carries negative prognosis

CEBPA and isolated NPM1 carry favorable prognosis

Schlenk RF, NEJM 2008
AML in the young (<60-65): Induction

• 7 + 3 standard induction regimen for decades
  – 7 days cytarabine
  – 3 days anthracycline (daunorubicin, idarubicin, or mitoxantrone)

• Numerous studies comparing alternative agents and novel combinations of agents have not improved survival, though investigations continue
AML in the young: Consolidation

Risk stratify

Favorable risk:
High dose cytarabine x 3

Intermediate risk:
Assess donor source; Allogeneic transplant versus high dose cytarabine

Unfavorable risk:
Allogeneic transplant
AML in the young: Relapse

• Attempt reinduction with any of a variety of regimens, including novel agents

• Allogeneic transplant if possible
AML in the elderly (>60-65)

- More nuanced

- Assessment of performance status, prognostic characteristics of AML, patient goals
Why else do older patients do more poorly

- More multidrug resistance phenotypes
  - (33% < age 56, 57% > age 75)

- More often out of MDS

- More often poor cytogenetics

- Comorbidities – less able to tolerate chemo
AML in the elderly: treatment

Initial treatment decision

Aggressive induction

Hypomethylator

Novel therapeutic trial

Best supportive care

Numerous targeted (or at least hopefully less toxic) regimens currently under investigation in various combinations and dosing schedules

No home runs yet

Lowenberg B, NEJM 2009
AML in the elderly: Consolidation

Consolidation (for those who achieve CR)

- Reduced intensity transplant
- Traditional chemotherapy (high dose ara-c very toxic)
- Novel maintenance regimen
The newest drugs

- CD33/CD BiTE antibody
- SGN-CD33a
- ABT-199
- Anti-IL3Rα/Anti-CD123
- DOT1L inhibitor
- IDH1 and IDH2 inhibitors
Acute Lymphoblastic Leukemia
Demographics and Outcomes

SEER data 2000-2003
Cytogenetics as Prognosticators

- 1,522 patients with ALL age 15-65
- Better prognosis:
  - Hyperdiploid
  - del(9p)
- Worse prognosis:
  - Complex karyotype
  - Hypodiploid
  - t(9;22)
  - t(4;11)
  - t(8;14)
Molecular testing

NOTCH

IKZF1

Overall Survival (%)

0 25 50 75 100

Time (years)

1 2 3 4 5

2P = 0.4

53% 45%

Probability of Relapse Free Survival

0.0 0.2 0.4 0.6 0.8 1.0

Patients At Risk

0 12 24 36 48 60 72 84 96

IKZF1 DEL 39%

IKZF1 WT entire cohort 89% 82%

P<0.001
## Minimal Residual Disease

<table>
<thead>
<tr>
<th>Risk category</th>
<th>% of patients</th>
<th>3y relapse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>67%</td>
<td>47%</td>
</tr>
<tr>
<td>High</td>
<td>23%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Principles of ALL therapy

**Induction**
- Vincristine/steroids
- Anthracyclines
  - Asparaginase
  - Cyclophosphamide
- CNS-prophylaxis

**Consolidation**
- Chemotherapy
- Allogeneic transplant
- CNS-prophylaxis

**Intensification**
- Vincristine/steroids
- Mercaptopurine
- Methotrexate
- CNS-prophylaxis

**Maintenance**
## Treatment regimens

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age</th>
<th>Ph+ %</th>
<th>T-cell %</th>
<th>CR %</th>
<th>DFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC/ECOG 2993</td>
<td>1826</td>
<td>31 (15-65)</td>
<td>19</td>
<td>20</td>
<td>91</td>
<td>38 at 5 y</td>
</tr>
<tr>
<td>CALGB 8811</td>
<td>197</td>
<td>32 (16-80)</td>
<td>27</td>
<td>28</td>
<td>85</td>
<td>33 at 5 y</td>
</tr>
<tr>
<td>GIMEMA 0288</td>
<td>778</td>
<td>27.5 (12-60)</td>
<td>22</td>
<td>26</td>
<td>82</td>
<td>29 at 9 y</td>
</tr>
<tr>
<td>GMALL 05/93</td>
<td>1163</td>
<td>35 (15-65)</td>
<td>24</td>
<td>-</td>
<td>83</td>
<td>35-40 at 5 y</td>
</tr>
<tr>
<td>HyperCVAD</td>
<td>288</td>
<td>40 (15-92)</td>
<td>17</td>
<td>25</td>
<td>92</td>
<td>38 at 5 y</td>
</tr>
<tr>
<td>LALA-94</td>
<td>922</td>
<td>33 (15-55)</td>
<td>23</td>
<td>38</td>
<td>84</td>
<td>36 at 5 y</td>
</tr>
<tr>
<td>UCSF 8707</td>
<td>84</td>
<td>27 (16-59)</td>
<td>16</td>
<td>33</td>
<td>93</td>
<td>53 at 5 y</td>
</tr>
</tbody>
</table>
Ph+ ALL: Prednisone + Dasatinib

100% complete hematologic remission
Relapsed Disease

- Attempt reinduction with any of a variety of regimens, including novel agents

- Allogeneic transplant if possible
Newer drugs

• Monoclonal antibodies
  – CD19/ozogamicin (inotuzumab)
  – CD22 (epratuzumab)
• Nelarabine
• Clofarabine
• Liposomal vincristine
• Blinotumomab
CARs

27/30 (90%) complete remission rate