AML in AYA

Shedding some light on the unique biology and care issues associated with this age group

Fabiana Ostronoff, MD
Overview

• Epidemiology of AML and define AYA
• Biology of AML in AYA
• Treatment differences between pediatric and adult protocols
• Treatment and outcome of AYA with AML: peds vs adult protocols
• Specific challenges and care issues to AYA with AML
• Strategies for improvement
Acute Myeloid Leukemia
EPIDEMIOLOGY

SEER

Children (< 15 yrs)
0.4-1.5/100 000
15–20% of all leukemias

AYA (16 to 39 yrs)
0.9-1.3/100 000
33% of all leukemias

Adults (> 40 yrs)
1.6-23.2/100 000
40-50% of all leukemias
Survival of AML by age group

SEER:
- Lesser improvement in survival in AYA as compared to children or older adults
- Survival rate for AYA plateau since 1990s

OS based on successive CCG/COG trials

Courtesy from Drs. William Woods, Alan Gamis and Todd Alonzo
Why AYA survival has lagged behind?

- Biology disease?
- Treatment?
- Access in clinical trials?
- Compliance?
- Psychosocial issues?
Cytogenetic and Molecular pathogenesis of AML

• Complex and heterogeneous disease
• Over 300 recurrent translocations
• Mutations
  – Deletions, insertions, duplications
  – Splice variants
• Translocations cooperate with other molecular events to lead to leukemic phenotype
Age and Cytogenetics

<table>
<thead>
<tr>
<th>Age Group</th>
<th>NL</th>
<th>CBF</th>
<th>11q23</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>8%</td>
<td>4%</td>
<td>55%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>9%</td>
<td>11%</td>
<td>38%</td>
</tr>
<tr>
<td>2-5 years</td>
<td>20%</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>5-10 years</td>
<td>25%</td>
<td>31%</td>
<td>13%</td>
</tr>
<tr>
<td>10-15 years</td>
<td>33%</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>37%</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>Adults &lt;56 years</td>
<td>40%</td>
<td>20%</td>
<td>8%</td>
</tr>
</tbody>
</table>
MRC AML 10 Trial data

0-14 yrs
N=340

- NK 27%
- t(15;17) 9%
- Tri 8 14%
- CBF 17%
- Complex 6%
- Other structural 32%
- Other num 18%
- 5q 7q 11q 8%

35 yrs +
N=461

- NK 51%
- t(15;17) 10%
- Tri 8 7%
- CBF 9%
- Complex 6%
- Other structural 19%
- Other numerical 19%

14-34 yrs
N=811

- NK 38%
- t(15;17) 19%
- Tri 8 10%
- CBF 12%
- Complex 6%
- Other structural 19%
- Other Numerical 14%
- 11q 5%
- abnl 3q
- del7q
- del5q

Grimwade D. Blood 1998; 92: 2322
Prevalence of mutations by age category
**NPM1**

**Pediatric**
Prevalence: 22% NK
No mutations in patients < 3 years

**Adult**
Prevalence: 52.9% NK

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**CEBPA**

**Pediatric (0-21 yrs)**
Prevalence: 17% NK

CEBPA<sub>d</sub>: 82%

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**Adult (16 – 60 yrs)**
Prevalence: 12.8% NK

CEBPA<sub>d</sub>: 60%

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Ho P A et al. Blood 2009;113:6558-6566

Fröhling S et al. JCO 2004;22:624-633
Age and Prevalence of FLT3/ITD
Overall Survival

**FLT3-ITD Peds vs Adults**

**Adult 16 to 60 yrs**
Prevalence: 20-27%

**Pediatric 0 to 20yrs**
Prevalence: 12%

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Fröhling S et al. Blood 2002;100:4372-4380

CBF AML with and without cKIT mut

Median age: 11 yrs (>19yrs)
Prevalence: 19%

Median age: 39 yrs (> 60 yrs)
Prevalence: 29% inv 16 and 22% t(8;21)

Paschka P et al. JCO 2006;24:3904-3911
**DNMT3A**

Adult Study: S-9031 and S-9333  
Age: >55 yrs  
N=191  
Prevalence 19%  


Pediatric Study: OP31  
Age: 1 month to 21 yrs  
N=180  
Prevalence: 0  

Cryptic \textit{NUP98-NSD1} translocation

Whole Genome Sequencing

\textit{NUP98} and Nuclear Pore Complex

\begin{itemize}
  \item \textbf{t(5;11)(11p15;5q35)}
  \item \textit{NUP98} Chromosome 11 (Exon 12)
  \item \textit{NSD1} Chromosome 5 (Exon 6)
  \item Cytogenetically normal
  \item \textit{FLT3}-ITD +
\end{itemize}
FLT3-ITD and NUP98-NSD1

**FLT3-ITD**
- Others: 41%
- NUP98-NSD1: 13%
- WT1: 19%
- CEBPA dm: 7%
- NPM1: 20%

**NUP98-NSD1**
- WT1, ITD: 5%
- CEPBA, ITD: 5%
- NPM1: 0%
- FLT3-ITD: 79%
**FLT3-ITD and NUP98-NSD1**

**COG-AAML0531**

- Median Age 12 yrs (range, 0.2 - 28 yrs)
Outcome

*FLT3-ITD* and *NUP98-NSD1*

![Bar chart showing outcomes for FLT3-ITD and NUP98-NSD1](image)

- All FLT3-ITD: 67%
- NUP98-NSD1: 72%
- NUP98-NSD1+: 28%

`p < 0.002`

![Progression-free survival curve](image)

- FLT3-ITD+: 67%
- NUP98/NSD1-: 28%

`p = 0.002`

Ostronoff F et al. ASH annual meeting 2012
Conclusion

• Differences in cytogenetic distribution
• Molecular abnormalities
  – Prevalence
  – Prognostic impact
• Suggesting age-related differences in the biology of the disease
## Pediatric versus Adult Protocols

<table>
<thead>
<tr>
<th>Component</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction Cycles</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CNS prophylaxis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Consolidation</td>
<td>Multiple agent</td>
<td>Single Agent</td>
</tr>
<tr>
<td>Allo-SCT</td>
<td>High-risk patients cytogenetics molecular response to tx MRD</td>
<td>Intermediate and high-risk cytogenetics molecular, secondary vs primary AML</td>
</tr>
</tbody>
</table>
Treatment Approach on “standard arm” of recent phase 3 US AML protocols

<table>
<thead>
<tr>
<th>Component</th>
<th>AAML0531 (COG)</th>
<th>E1900 (ECOG)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction I</strong></td>
<td>AraC 100mg/m2 D1-10 Dauno 50mg/m2 D1,3,5 VP-16 100mg/m2 D1-5</td>
<td>AraC 100mg/m2 D1-7 Dauno 45mg/m2 D1-3</td>
</tr>
<tr>
<td><strong>Induction II</strong></td>
<td>AraC 100mg/m2 D1-5 Dauno 50mg/m2 D1,3,5 VP-16 100mg/m2 D1-5</td>
<td></td>
</tr>
<tr>
<td>(regardless of remission status)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Treatment Approach on “standard arm” of recent phase 3 US AML protocols

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<thead>
<tr>
<th>Component</th>
<th>AAML0531 (COG)</th>
<th>E1900 (ECOG)</th>
</tr>
</thead>
</table>
| Consolidation | **Intensification 1**  
AraC 1g/m2 q12hrs D1-5  
VP16 150mg/m2 D1-5  

**Intensification 2**  
AraC 1g/m2 q12hrs D1-4  
Mitoxantrone 12mg/m2 D3-6  

**Intensification 3**  
AraC 1g/m2 q12hrs D1-4  
L-asparaginase 6000IU/m2 D2,9 | Cycle 1  
HiDAC  
Cycle 2  
HiDAC  
Cycle 3  
HiDAC |
COG AAML1031

LOW RISK

Induction I
ADE 10+3+5

Induction II
ADE 8+3+5

Intens. I
AE

Intens. II
Mitox / Ara-C

HIGH RISK

Induction I
ADE 10+3+5

Induction II
Mitox / Ara-C

Intens. I
AE

Intens. II
Mitox / Ara-C

FLT3/ITD+

Induction I
ADE +Soraf

Induction II
ADE +Soraf

Intens. I
AE +Soraf

HSCT
AYA with AML
Adult vs Pediatric Protocol?

• Children are treated with more aggressive regimens than adults

• ALL AYA
  ✓ better outcomes when treated on pediatric protocols

• AML AYA
  ✓ no randomized studies
Treatment Outcome AYA

• Treated on adult protocols
  – MRC10 trial

• Treated on pediatric
  – CCG 2891

• Retrospective studies comparing treatment on adult vs pediatric protocols
MRC10 trial

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5-years OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>56%</td>
</tr>
<tr>
<td>15-24</td>
<td>47%</td>
</tr>
<tr>
<td>25-34</td>
<td>49%</td>
</tr>
<tr>
<td>&gt;35</td>
<td>33%</td>
</tr>
</tbody>
</table>
AYA Treated on Pediatric Protocol

• CCG 2961
• AYA (16-21 years)
• Inferior survival relative to younger patients
• Define the impact of older age
• Identify factors responsible for inferior outcome in AYA
• Analysis from 4 COG trials: CCG 2891 (intensively timed arm), CCG 2941, CCG 2961, AML03P1

## Results

<table>
<thead>
<tr>
<th></th>
<th>AYA N=238 (16 to 21 yrs)</th>
<th>Peds N=1602 (&lt;16yrs)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs)</td>
<td>17.2</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Risk disease (poor)</td>
<td>16.6%</td>
<td>10.4%</td>
<td>0.026</td>
</tr>
<tr>
<td>TRM (infection)</td>
<td>25+/-6%</td>
<td>12+/-2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative incidence of relapse</td>
<td>30+/-7%</td>
<td>41+/-3%</td>
<td>0.002</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>49+/-7%</td>
<td>54 +/-3%</td>
<td>0.058</td>
</tr>
</tbody>
</table>
Conclusion

• AYA treated on adult protocols
  – better outcome than adult patients
  – age is a strong prognostic factor in AML
  – with a poorer outcomes in each successive decade of life
• AYA treated on pediatric protocols
  – worse outcome than pediatric patients
  – relapse rate lower
  – higher TRM
• Comparison: adult vs pediatric protocols
Comparison between Adult vs Pediatric for AYA with AML

• Adult (CALGB and SWOG) vs Pediatric (COG)
• Retrospective
• Trials from 1986 to 2008

<table>
<thead>
<tr>
<th></th>
<th>CALGB/ SWOG</th>
<th>COG</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>36 + 7%</td>
<td>45 + 6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Median Age (yrs)</td>
<td>20.1 (CALGB)</td>
<td>17.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19.8 (SWOG)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The age difference between the arms might have influenced the results

Franklin ER et al. ASH annual meeting 2010; 116(21): Abstract 183
Pediatric vs Adult Protocol

Age: 16 to 21 yrs

• CCG 2891 (intensive timing arm)
• N=59

✓ Groups similar with regard to known prognostic factors
✓ Median age: 18.8 yrs (MDA) vs 17.2 yrs (CCG)

• Adult protocol (MDACC) from 1980-2000
• N=54
  – 1980-85: AraC+Dauno
  – 1986-93: HiDAC +/‐ Anthracycline
  – 1994-96: : HiDAC + Flu +/‐ Anthracycline
  – 1996-2000: AraC + VP16 +/‐ Cyclophosphamide

CCG2891
Intensive vs Standard timing

Day 0 through 4: DCTER induction
- Dexamethasone 6 mg/m²/d (0.2 mg/kg/d) thrice daily
- Cytarabine 200 mg/m²/d (6.7 mg/kg/d) continuous infusion
- Thioguanine 100 mg/m²/d (3.3 mg/kg/d) twice daily
- Etoposide 100 mg/m²/d (3.3 mg/kg/d) continuous infusion
- Rubidomycin (daunorubicin) 20 mg/m²/d (0.67 mg/kg/d) continuous infusion
- Cytarabine intrathecal (age-based doses)

Randomize

DCTER induction
Intensive timing
Days 0-4 and 10-14 regardless of response

DCTER consolidation
Intensive timing as above (2 additional cycles)

DCTER induction
Standard timing
Days 0-4 and 14-18 or later depending on response

DCTER consolidation
Standard timing as above (2 additional cycles)

### Induction Success

**CCG-2891 INT** and **MDACC**

<table>
<thead>
<tr>
<th></th>
<th>MDACC</th>
<th>CCG-2891 INT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>80%</td>
<td>78%</td>
<td>0.81</td>
</tr>
<tr>
<td>Died during induction</td>
<td>4%</td>
<td>14%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Mantigale residual plot: risk of death vs age as for patients being treated according to MDACC and CCG treatment regimens.
CCG-2891 INT and MDACC

<table>
<thead>
<tr>
<th></th>
<th>CCG</th>
<th>MDACC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr EFS</td>
<td>47%</td>
<td>17%</td>
<td>0.007</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>51%</td>
<td>32%</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**CCG:** no difference in survival between patients > 16 yrs vs 16 to 21 yrs

**MDACC:** 16 to 21 yrs similar survival to 21-41 yrs and to the standard timing arm from CCG

**CONCLUSION:**
- Increase death from toxicity counterbalance an improvement in leukemia free survival
Conclusion

• There is no sufficient evidence at this time to treat AYA in pediatric protocols

• There is no sufficient evidence at this time to treat AYA in adult protocols

CLINICAL TRIALS
Enrollment in Clinical Trials... Not so simple!

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>% treated on trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>15-19</td>
<td>10%</td>
</tr>
<tr>
<td>20-39</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
Compliance with Treatment

• Review between 1980 and 2008
• 27 to 60% poor adherent to treatment
• Factors:
  – Openness of family
  – Support system
• Anticipatory guidance (2 critical points):
  – Before AYA assumes self-management responsibilities
  – Change in a treatment regimen

Psychosocial Challenges

• Delays in diagnosis (going to school, financially support dependents etc)
• Insurance barriers
• Young children at home
Fertility

Specialized team, rather than the primary oncologist, address these issues with AYA patients

Survivorship

- Many AYA will survive their AML diagnosis

Quality of survivorship

Quality of treatment

- Burden of morbid sequelae
- How best to care for this population?
CONCLUSION
AYA with AML

• Discrete group
  – Specific biology
  – Therapeutic and psychosocial needs

• No prospective studies to guide the optimal treatment approach
  – Pediatric-like vs adult-like protocol?
  – Pediatric protocols more myelosuppressive/ TRM
  – Adult protocol more relapse rate/ induction failure
Strategies for Improvement

• Establish academic AYA center of excellence
• AYA patients be referred to cancer centers with expertise and experience in treating this population
• Clinical trials to determine best therapy strategy
• Decrease TRM
• Identification of molecular markers
• Targets for therapies
Resources

• NCI convened an AYA oncology program review group (AYAO PRG)

• ASCO and LIVERSTRONG launched an initiative called Focus Under Forty, an educational curriculum for physician to raise awareness about these issues: http://university.asco.org/focus-under-forty

• NCCN issued new Clinical Practice Guidelines in Oncology for AYA Oncology
Adolescent and Young Adult Oncology: An Emerging Field

David M. Thomas, Peter MacCallum Cancer Center, East Melbourne, Australia
Karen H. Albritton, Cook Children’s Hospital, Fort Worth, TX
Andrea Ferrari, Istituto Nazionale Tumori, Milano, Italy
QUESTIONS?