Discussion:

Should intensive therapy be considered?

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Treatment disparity exists for older adults

SEER data 2000-2009 (N=8336) newly diagnosed AML age >64 years

% treated

Age (years)

60 % untreated

Treated Not treated

Age>80 Poor performance indicator* NCI Comorbidity Score >1

* Claims for oxygen, wheelchair, home health, skilled nursing


@HKlepinMD
What is “guideline-based care” for older adults?

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Moving beyond chronologic age: Considering “fitness” in AML

FIT
Similar tolerance/benefit as middle-aged patients

VULNERABLE
At risk for decreased treatment tolerance
Risk may outweigh benefits

FRAIL
Poor treatment tolerance

UNFIT?

“Will I tolerate and benefit from treatment?”
Moving beyond chronologic age: Considering “fitness” in AML

FIT
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UNFIT?

“Will I tolerate and benefit from treatment?”
(un)Fitness is not well characterized in AML trials

<table>
<thead>
<tr>
<th>Trial/Treatment</th>
<th>Age (yrs)</th>
<th>Target Population</th>
<th>Criteria</th>
<th>% PS 2</th>
<th>% PS 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>7+3 +/- sorafenib¹</td>
<td>≥ 60</td>
<td>Fit</td>
<td>Not specified</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Decitabine +/- bortezamib²</td>
<td>≥ 60</td>
<td>Unfit</td>
<td>Not specified but inclusive eligibility; Core binding factor: ≥ 75 yrs, EF &lt;40%</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Decitabine (DAC)³</td>
<td>≥ 65</td>
<td>Older</td>
<td>Not specified, excluded cardiac comorbidity renal impairment</td>
<td>24</td>
<td>X</td>
</tr>
<tr>
<td>Low dose ARA-C (LDAC) vs hydrea⁴</td>
<td>≥ 60</td>
<td>Unfit</td>
<td>Not specified except &lt;70+comorbidity</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>5-Azacytidine⁵ vs. CC</td>
<td>≥ 65</td>
<td>Unfit</td>
<td>Not specified except non-transplant candidate</td>
<td>&lt;25</td>
<td>X</td>
</tr>
<tr>
<td>LDAC+glasdegib⁶</td>
<td>≥ 55</td>
<td>Unfit</td>
<td>≥ 75 yrs, Cr &gt;1.3, PS 2, cardiac disease (EF &lt;45%)</td>
<td>53</td>
<td>X</td>
</tr>
<tr>
<td>LDAC+venetoclax⁷</td>
<td>≥ 60</td>
<td>Unfit</td>
<td>Comorbidity or performance status (≥ 75 yrs, PS 0-2; &lt; 75 yrs PS 0-3)</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>HMA+venetoclax⁸</td>
<td>≥ 65</td>
<td>Unfit</td>
<td>≥ 75 yrs, cardiac disease, ↑ risk TRM</td>
<td>&lt;20</td>
<td>X</td>
</tr>
</tbody>
</table>

Geriatric assessment can help refine “fitness” in AML
GA measures are associated with survival

### Baseline GA Measures vs. Hazard Ratio for Mortality (95% CI)*

<table>
<thead>
<tr>
<th>Baseline GA Measures</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired physical performance (SPPB score &lt;9)</td>
<td>2.2 (1.1-4.6)</td>
</tr>
<tr>
<td>Cognitive impairment (3MS score &lt;77)</td>
<td>2.5 (1.5-5.5)</td>
</tr>
<tr>
<td>Depression (CES-D score ≥16)</td>
<td>1.0 (0.5-2.0)</td>
</tr>
<tr>
<td>Distress (&lt;4)</td>
<td>1.0 (0.5-1.8)</td>
</tr>
<tr>
<td>IADL impairment (any)</td>
<td>0.8 (0.4-1.6)</td>
</tr>
<tr>
<td>Comorbidity (HCT-CI score &gt;1)</td>
<td>1.2 (0.7-2.2)</td>
</tr>
</tbody>
</table>

**Objectively measured physical function**
- ECOG >1
- ADL
- Fatigue

**Cognitive function**
- FITTER

**Self-reported activities of daily living**
- Self-reported fatigue

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Multi-morbidity and AML

Comorbidity is associated with survival

Augmented HCT-CI

N=1100, all ages

Months from induction treatment

Retrospective, varied treatments

Comorbidity and mortality among older adults

30-Day Mortality

% 30-Day Mortality

0 1 or 2 >2

High risk conditions

Cardiac disease
Renal dysfunction
Diabetes
Polypharmacy

## Considering a fitness framework: leaving age out of it

<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT</td>
<td>• Adequate objective physical function (SPPB ≥9, gait speed &gt;1m/s)</td>
</tr>
<tr>
<td></td>
<td>• Negative cognitive screen</td>
</tr>
<tr>
<td></td>
<td>• No major comorbidity/low comorbidity burden score</td>
</tr>
<tr>
<td></td>
<td>• Independent in ADLs</td>
</tr>
<tr>
<td>VULNERABLE</td>
<td>• Independent in ADLs but:</td>
</tr>
<tr>
<td></td>
<td>• <strong>Impaired physical performance (SPPB &lt;9)</strong></td>
</tr>
<tr>
<td></td>
<td>• Positive cognitive screen</td>
</tr>
<tr>
<td></td>
<td>• <strong>IADL impairment?</strong></td>
</tr>
<tr>
<td>FRAIL</td>
<td>• Dependent in ADLs</td>
</tr>
<tr>
<td></td>
<td>• Poor ECOG performance status (ECOG &gt;2)</td>
</tr>
<tr>
<td></td>
<td>• High comorbidity burden</td>
</tr>
</tbody>
</table>

**Considerations:** fitness can be context specific, fitness is dynamic, optimal measures are not validated in large AML studies, treatment benefit by fitness have not been evaluated in randomized trials.
Why consider intensive therapy?

• The main cause of death for older adults is ineffective therapy, not treatment-related mortality\(^1,2\)

• Less intensive therapies are not clearly MORE effective - and may be inferior for many older adults\(^3,4,5\)

• QOL or functional outcomes are not “superior” with less intensive therapy\(^6,7\)

• Estey “trade off”: 75 year old woman has additional 13 years of life expectancy\(^9\); median survival with venetaclax+HMA approximately 1.5 years= 88% loss of life expectancy\(^10\)

Personalized decision-making: what matters most?

Bridges et al. Patient Preference and Adherence 2018
Considering quality of life

Quality of life and mood of older patients with acute myeloid leukemia (AML) receiving intensive and non-intensive chemotherapy

El-Jawahri et al. Leukemia 2019  N=100

QOL, anxiety, depression similar pre and post treatment

Treatment Choices: A Quality of Life Comparison in Acute Myeloid Leukemia and High-risk Myelodysplastic Syndrome

Tinsley et al. Clin Lymphoma, Myeloma and Leuk 2017  N=73

Improved QOL in intensive, stable in less intensive

Limitations: Treatment was not randomly assigned
Intensive therapy and function

**Short term decline**

- Balance
- Chair Stand
- Gait Speed
- Total

**Longer term resilience**

- 2 minute walk over 12 months

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**Short Physical Performance Battery (SPPB) score**

- Baseline
- FollowUp

- Baseline: 3.14
- FollowUp: 1.78, 7.58

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**Chair stands over 12 months**

- Young
- Old

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**2 minute walk over 12 months**

- Young
- Old

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Alibhai et al. *J Geriatric Oncol* 2015
Addressing vulnerabilities: Opportunities to modify risk

- Physical function is a modifiable risk factor
- Small studies have support feasibility of intervention\(^1,2\)
- Utilize existing resources early to prevent decline\(^3\)

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Recommendations

• Offer intensive therapy if aligned with values/goals on a clinical trial if possible

• Personalized supportive care with emphasis on early physical therapy to maintain function during treatment