Acute Myelogenous Leukemia in Older Adults

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Key Words. Acute myelogenous leukemia • Elderly • Geriatric assessment • Treatment

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Target audience: Physicians who wish to advance their current knowledge of clinical cancer medicine in geriatric oncology.

LEARNING OBJECTIVES
1. Outline the influences of tumor biology on clinical outcomes in older adults with acute myelogenous leukemia (AML).
2. Enumerate patient-specific characteristics that influence clinical outcomes for older adults with AML.
3. Formulate an algorithm to guide treatment decisions for older adults with newly-diagnosed AML.

ABSTRACT
The incidence of acute myelogenous leukemia (AML) increases with age. Older AML patients, generally defined by age ≥60 years, have worse treatment outcomes than younger patients. While selected older patients can benefit from standard therapies, as a group they experience greater treatment-related toxicity, lower remission rates, shorter disease-free survival times, and shorter overall survival times. Outcome disparity is in part explained by age-related biologic features. Older patients are more likely to present with unfavorable cytogenetic abnormalities, multidrug resistance phenotypes, and secondary AML. However, even older adults with favorable tumor biology have a worse prognosis than younger patients.

Patient-specific factors, including impaired physical function and comorbidity, independently predict greater treatment toxicity and shorter survival. Improving patient assessment strategies is critical to identify those patients who are most likely to benefit from induction and postremission therapies. In addition, continued efforts to identify more effective and tolerable induction and postremission strategies are needed for this population. Investigations of hypomethylating agents and signal transduction inhibitors hold promise for the treatment of AML patients. Steady advances in the field of hematopoietic transplantation, including use of reduced intensity transplants, may result in additional curative options available to selected older adults. Finally, improved supportive care strategies are needed to maximize treatment outcomes. The Oncologist 2009;14:222–232
INTRODUCTION
Acute myelogenous leukemia (AML) is a disease of older adults, and is characterized by worse survival associated with increasing age [1, 2]. The AML incidence increases with age, with a median age at diagnosis of 67 years [1] (see Fig. 1). Optimal therapy for this heterogeneous population remains controversial because of poor treatment outcomes demonstrated in clinical trials [3–7].

Selected older adults can tolerate and benefit from standard therapies [2, 8]. However, as a group, older adults are more likely to experience treatment-associated toxicity and less likely to benefit from treatment when undergoing standard induction and postremission therapies [2, 5]. Tumor biology has been identified as a strong predictor of prognosis but does not completely explain outcome disparity [2, 5, 9–13]. Patient-specific characteristics such as comorbidity and impaired physical function also influence outcomes [2, 14, 15]. As the population ages, acute leukemia will become an increasingly common clinical problem warranting careful consideration of management options to guide decision making. Treatment decisions for older adults should be individualized after systematic assessment of patient characteristics and tumor biology.

TREATMENT OUTCOMES FOR OLDER ADULTS ARE SUBOPTIMAL
Survival with AML is age dependent, with significantly lower survival rates reported for older adults [1, 2, 5, 16]. Surveillance, Epidemiology, and End Results statistics from 1996 to 2002 show 5-year relative survival rates of 34.4% for adults aged <65 and 4.3% for those aged ≥65 years [1] (see Fig. 2). Clinical trials have also demonstrated worse survival outcomes in older adults with AML using age cutoffs of 55, 60, and 65 years [2, 16, 17]. Older adults are less likely to achieve a complete remission (CR) and to remain relapse free if they have achieved a CR. In the Southwest Oncology Group (SWOG) clinical trials, including 968 previously untreated AML patients, the CR rates were 64%, 46%, 39%, and 33% in the age groups <56, 56–65, 66–75, and >75 years, respectively. In responding patients, the median disease-free survival times were 21.6, 7.4, 8.3, and 8.9 months, respectively; the overall survival durations for the whole population were 18.8, 9.0, 6.9, and 3.5 months, respectively [2]. In addition, older adults are more likely to experience treatment-related death, in the range of 15%–30% in clinical trials [2, 4, 5, 18]. Because of concerns regarding inferior outcomes with treatment and greater toxicity, a large proportion of older adults in the U.S. is not considered for chemotherapy treatment for this disease [19, 20].
Tumor Biology Contributes to Poor Prognosis

Age-related changes in tumor biology are a major determinant of poor outcome in older adults with AML (Table 1). Older patients have a higher percentage of unfavorable cytogenetic abnormalities (i.e., chromosome 5 and 7 abnormalities and complex karyotypes) and a lower percentage of favorable cytogenetic abnormalities (i.e., t(8,21) and inv(16)) than younger patients [2, 12, 21]. Unfavorable cytogenetic abnormalities are associated with lower remission rates and shorter overall survival times [2, 9, 10, 12, 22]. Intrinsic drug resistance, mediated by the expression of a multidrug resistance phenotype (MDR1), is also more common in older AML patients [13]. This provides an advantage to the leukemia cells when treated with conventional agents such as anthracyclines. Finally, older adults are more likely to present with secondary AML arising in the setting of myelodysplastic syndrome (MDS), which is less responsive to standard therapies [11].

Although each of these poor prognostic features can individually influence remission rates, the combination of poor prognostic features is dramatically associated with lower remission rates with standard therapies. In a SWOG analysis of older adults with previously untreated AML, a CR rate of 81% was seen in those patients with the combination of de novo AML, an MDR1− phenotype, and favorable/intermediate cytogenetics, compared with a CR rate of only 12% in those with an MDR1+ phenotype, secondary AML, and unfavorable cytogenetics [13]. Consequently, the National Comprehensive Cancer Network (NCCN) guidelines recommend that older adults with complex karyotypes be offered supportive care, low-intensity therapy, or a clinical trial rather than standard induction chemotherapy. Alternatively, the high CR rates for older adults with favorable tumor biology suggest that this subset of patients should not be denied active therapy based on chronologic age alone.

Recent investigations of age-related differences in tumor biology have also focused on the prognostic significance of mutations of the nucleophosmin 1 (NPM1) and the Fms-like tyrosine kinase 3 (FLT3) genes. Mutations in these genes are seen in a substantial proportion of AML patients with a normal karyotype [23, 24]. In younger patients, FLT3 mutations have been associated with unfavorable outcomes including shorter survival times [25]. Alternatively, NPM1 mutations in the absence of FLT3 mutations are associated with favorable treatment response rates and survival [23]. There have been conflicting retrospective data regarding the prognostic significance of these mutations for older adults with AML [26–28]. A recent study of 1,284 patients treated with induction chemotherapy demonstrated no significant difference in the frequencies of these mutations between patients older and younger than 60 years of age [29]. The prognostic significance was similar for both age groups, with a mutation in NPM1 and wild-type FLT3 predicting better survival and remission duration. The mutation status of NPM1 and FLT3 may help identify subgroups of older adults who are more likely to benefit from standard induction chemotherapy, but it does not appear to explain age-related differences in treatment outcomes for AML.

The Optimal Treatment for Older Adults with AML Remains Controversial

There is significant debate regarding the optimal treatment strategy for older adults with AML, ranging from supportive care alone to standard aggressive therapies [3–7]. This debate is fueled by suboptimal responses to treatment in the older adult population and concerns regarding the impact of treatment and toxicity on quality of life.

Induction Therapy

Standard induction chemotherapy for AML patients typically involves combination chemotherapy that includes cytarabine (Ara-C) and an anthracycline given for 7 and 3 days, respectively [30]. A landmark randomized study by Löwenberg et al. [8] demonstrated longer survival in selected patients ≥65 years of age treated with induction therapy versus supportive care alone. In addition, there was no difference in time spent hospitalized between the two groups. This study paved the way for considering curative therapy options for older adults.

Unfortunately, many subsequent studies have failed to improve upon the suboptimal treatment outcomes seen in

<p>| Table 1. Unfavorable tumor biology is more frequent in the elderly |</p>
<table>
<thead>
<tr>
<th>Biologic characteristic</th>
<th>Examples</th>
<th>Proportion of elderly AML affected</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable cytogenetic abnormalities</td>
<td>Chromosome 5 or 7 abnormality Complex karyotype</td>
<td>22%–50%</td>
<td>[2, 5, 9, 13, 22]</td>
</tr>
<tr>
<td>Multidrug resistance phenotype</td>
<td>MDR1 overexpression</td>
<td>58%–71%</td>
<td>[13]</td>
</tr>
<tr>
<td>Preceding hematologic disease</td>
<td>Myelodysplastic syndrome</td>
<td>21%–34%</td>
<td>[21, 22]</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myelogenous leukemia; MDR, multidrug resistance.
the older population (Table 2). While CR rates are in the range of 40%–60%, the median survival duration remains <1 year in clinical trials [5]. Dose-attenuated treatments, designed to minimize toxicity, have not resulted in a substantial improvement in outcomes [31, 32]. Investigation of various anthracyclines, such as mitoxantrone and idarubicin, and the addition of etoposide have not improved survival for older adults [18, 33–35]. Hematopoietic growth factors including G-CSF and GM-CSF have been investigated and have not consistently been shown to improve response rates or survival; likewise they do not clearly decrease costs [18, 33, 36–38]. Modulation of MDR1 was attempted by adding the cyclosporine analog PSC-833 to induction chemotherapy in two randomized trials of older adults [39, 40]. There was no benefit in terms of the response rates or survival, with a greater toxic death rate in the experimental arm of the Cancer and Leukemia Group B trial [39]. To date, no induction chemotherapy regimen tailored to the older adult population has clearly demonstrated superior clinical outcomes.

**Postremission Therapy**

The optimal postremission therapy for older adults also remains unclear [30, 41]. It is generally accepted that postre-

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**Table 2. Selected elderly-specific induction chemotherapy trials for AML**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Age (yrs)</th>
<th>n</th>
<th>Treatment arms</th>
<th>CR (%)</th>
<th>Median OS (mos)</th>
<th>p-value for OS</th>
<th>Induction death rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard dose induction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Löwenberg et al. [8]</td>
<td>1989</td>
<td>&gt;65</td>
<td>31</td>
<td>Ara-C, daunorubicin, vincristine Supportive care</td>
<td>58</td>
<td>5.3</td>
<td>.015</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Löwenberg et al. [34]</td>
<td>1998</td>
<td>&gt;60</td>
<td>242</td>
<td>Ara-C, daunomycin</td>
<td>38</td>
<td>9.0</td>
<td>.23</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ara-C, mitoxantrone</td>
<td>47</td>
<td>9.7</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Goldstone et al. [33]</td>
<td>2001</td>
<td>&gt;55</td>
<td>328</td>
<td>Daunorubicin, Ara-C, thioguanine</td>
<td>62</td>
<td>No difference</td>
<td>Not reported</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daunorubicin, Ara-C, etoposide</td>
<td>50</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mitoxyantrone, Ara-C</td>
<td>55</td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td><strong>Dose-attenuated induction</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Tilly et al. [32]</td>
<td>1990</td>
<td>&gt;65</td>
<td>46</td>
<td>Rubidazone, Ara-C</td>
<td>52</td>
<td>12.8</td>
<td>.12</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low dose Ara-C</td>
<td>32</td>
<td>8.8</td>
<td></td>
<td>10</td>
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<tr>
<td><strong>Growth factor support</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Löwenberg et al. [38]</td>
<td>1997</td>
<td>&gt;60</td>
<td>157</td>
<td>Daunomycin, Ara-C, GM-CSF</td>
<td>56</td>
<td>No difference</td>
<td>.55</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daunomycin, Ara-C</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowe et al. [18]</td>
<td>2004</td>
<td>&gt;55</td>
<td>125</td>
<td>Anthracycline, Ara-C</td>
<td>40</td>
<td>8.5</td>
<td>.11</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anthracycline, Ara-C, GM-CSF</td>
<td>38</td>
<td>5.3</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Stone et al. [36]</td>
<td>1995</td>
<td>&gt;60</td>
<td>195</td>
<td>Ara-C, daunorubicin</td>
<td>54</td>
<td>9.4</td>
<td>.10</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ara-C, daunorubicin, GM-CSF</td>
<td>51</td>
<td>9.4</td>
<td></td>
<td>20</td>
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<tr>
<td><strong>MDR1 modulation</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baer et al. [39]</td>
<td>2002</td>
<td>≥60</td>
<td>61</td>
<td>Ara-C, daunorubicin, etoposide</td>
<td>46</td>
<td>No difference</td>
<td>.48</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ara-C, daunorubicin, etoposide, PSC-833</td>
<td>39</td>
<td></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Van der Holt et al. [40]</td>
<td>2005</td>
<td>≥60</td>
<td>211</td>
<td>Daunorubicin, Ara-C, PSC-833</td>
<td>48</td>
<td>No difference</td>
<td>.52</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Abbreviations:** AML, acute myelogenous leukemia; Ara-C, cytarabine; CR, complete remission; NA, not applicable; OS, overall survival.
mission therapy or consolidation is required to eradicate residual leukemia after induction and to allow for the possibility of cure [30]. Typical postremission treatment includes high-dose cytarabine or hematopoietic stem cell transplantation. In a randomized study of low-, intermediate-, and high-dose cytarabine for consolidation in patients who had achieved a CR, younger patients benefited from dose escalation whereas older patients experienced more cerebellar toxicity and no benefit in terms of disease-free survival [16]. For younger patients, high-dose cytarabine (3 g/m²) is a standard postremission treatment option for patients with good-risk cytogenetics [30]. This treatment is too toxic for older adults and likely contributes to the suboptimal outcomes seen in older adults with good-risk cytogenetics. In elderly-specific trials, lower dose Ara-C regimens as a single agent or in combination with an anthracycline have been tested [33, 42]. In this population, there is no clear evidence to date that multiple courses of consolidation or maintenance therapy lead to better outcomes when compared with a single course of consolidation therapy [31, 33, 42].

Hematopoietic stem cell transplantation is another postremission therapy option [30]. In younger adults, high-dose chemotherapy followed by autologous stem cell transplantation can be considered for patients with intermediate-risk cytogenetics. Autologous hematopoietic stem cell transplantation is feasible in highly selected older adults with AML [43]. However, there is no randomized trial data to suggest superiority of this strategy over conventional chemotherapy, and treatment-related mortality remains high (15%–30%) [43, 44].

Allogeneic stem cell transplantation remains a standard postremission treatment option with a potential for producing long-term survival in younger adults with poor-risk cytogenetics [30]. Traditional allogeneic hematopoietic stem cell transplantation is associated with very high treatment-related mortality in older adults and is therefore not recommended as postremission therapy for most patients aged >60 years [45]. Advances in supportive care and the use of reduced-intensity allogeneic transplantation regimens (nonmyeloablative regimens) have resulted in a trend toward greater use of allogeneic transplantation in adults aged >50 [46]. This type of transplantation uses the graft-versus-leukemia effect and reduces acute toxicities associated with the use of myeloablative therapies [47–49]. While this therapy may be feasible in highly selected older adults, it is yet unclear if this treatment strategy is superior to conventional approaches.

Postremission therapy for older adults is further complicated by a higher likelihood that patients will no longer be candidates for additional treatment because of functional impairment or end organ damage resulting from induction therapy. In many cases, a curative treatment approach must be aborted because of a poor performance status that precludes postremission treatment. In randomized trials, up to 20% of older adults may not go on to receive any consolidation therapy after achieving a CR [42]. Attrition is much higher for older adults considered for postremission transplantation [47]. Outside of clinical trials, even fewer older adults are likely to receive postremission therapy because these patients are often less fit than those enrolled in clinical trials [50].

**PATIENT-SPECIFIC FACTORS INFLUENCE PROGNOSIS**

**Tumor biology** is clearly a major determinant of inferior treatment outcomes for older adults with AML. Recent analyses, however, demonstrate striking differences between treatment outcomes in older and younger adults after stratifying for cytogenetic risk group [2]. Older adults with favorable cytogenetic profiles continue to experience inferior outcomes relative to younger patients with the same disease. While other biologic characteristics may contribute to this persistent disparity, these analyses also suggest that tumor biology alone may be insufficient to explain the differences in toxicity and response seen in older adults with AML. Despite advances in understanding tumor biology, less is known about how patient-specific factors influence outcomes.

Treatment decision making for older adults is hampered by the difficulty of accurately predicting vulnerability to toxicity. Increasing age alone is a risk factor for poor response to therapy. In one retrospective analysis of older adults treated for AML, age >70 was independently associated with poor outcomes [10]. Older adults of the same chronologic age, however, represent a heterogeneous population. Multiple patient-specific factors may impact an older adult’s ability to tolerate tumor burden and treatments. Comorbid disease, functional status, and cognitive status are examples of factors that reflect an individual patient’s reserve capacity; none of these can be adequately assessed with chronologic age alone.

Translating geriatric assessment strategies into the evaluation of older patients with acute leukemia should help refine the treatment approach to this population. One strategy commonly used in geriatric medicine is the comprehensive geriatric assessment (CGA). CGA refers to a multidisciplinary evaluation of geriatric domains, including comorbid disease, physical function, cognitive function, psychological state, nutritional status, and medication management. In older cancer patients, CGA can identify problems that may interfere with cancer treatment and is recommended by the NCCN guidelines for “senior adult oncology” [51]. The optimal measures to use and how to change management based on results are less clear.

Traditional CGA evaluations can be time-consuming.
and resource-intensive, and therefore may not be practical for evaluating older adults with newly diagnosed acute leukemia. However, incorporating the principles of CGA through simple screening tools to evaluate comorbidity, physical function, and cognitive status is likely to prove more feasible. Better assessment of these domains in older adults with AML can maximize the estimation of physiologic age and reserve capacity to inform decision making.

### Assessing Comorbidity

Recent analyses have confirmed the importance of assessing comorbid disease in older patients with AML. In a retrospective study, 133 patients aged ≥70 years who received induction chemotherapy for AML were evaluated using an adapted form of the Charlson Comorbidity Index (CCI) to assess comorbidity burden (Table 3) [14]. Thirty-two percent had major comorbidity. A score >1 on the CCI

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Score</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>Coronary artery disease, congestive heart failure, myocardial infarction, EF ≤50%</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>Atrial fibrillation or flutter, sick sinus or ventricular arrhythmia</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
<td>Transient ischemic attack or cerebrovascular accident</td>
<td>1</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>1</td>
<td>Requiring treatment</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic disease (mild)</td>
<td>1</td>
<td>Chronic hepatitis, bilirubin &gt; ULN to 1.5× ULN, or AST/ALT &gt; ULN</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (mild/moderate)</td>
<td>1</td>
<td>Requiring treatment with medication</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary disease (mild/moderate)</td>
<td>1</td>
<td>DLCO and/or FEV₁ 66%–80% or dysnea with slight activity</td>
<td>2</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1</td>
<td>SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatic</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes (severe with end organ damage)</td>
<td>2</td>
<td>Crohn’s disease or ulcerative colitis</td>
<td>1</td>
</tr>
<tr>
<td>Renal disease (moderate or severe)</td>
<td>2</td>
<td>Serum creatinine &gt; 2 mg/dl, on dialysis, or prior renal transplant</td>
<td>2</td>
</tr>
<tr>
<td>Solid tumor (without metastases)</td>
<td>2</td>
<td>Treated at any point in patient’s past history, excluding nonmelanoma</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic disease (moderate or severe)</td>
<td>3</td>
<td>Liver cirrhosis, bilirubin &gt; 1.5× ULN, or AST/ALT &gt; 2.5× ULN</td>
<td>3</td>
</tr>
<tr>
<td>Solid tumor with metastases</td>
<td>6</td>
<td>Body mass index &gt; 35 kg/m², requiring use of antimicrobial treatment</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>Depression or anxiety requiring psychiatric consult or treatment</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td></td>
<td>Except mitral valve prolapse</td>
<td>3</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td></td>
<td>DLCO and/or FEV₁ ≤ 65% or dysnea at rest or requiring oxygen</td>
<td>3</td>
</tr>
<tr>
<td>Severe pulmonary</td>
<td></td>
<td>Total score</td>
<td></td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

This table is adapted from research that was originally published in Blood. Sorror ML, Maris MB, Storb R et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: A new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912–2919. © The American Society of Hematology.

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase; CTD, connective tissue disease; DLCO, diffusion capacity of carbon monoxide; EF, ejection fraction; FEV₁, forced expiratory volume in 1 second; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; mCCI, modified Charlson Comorbidity Index; RA, rheumatoid arthritis; SLE, systemic lupus erythmatosis; ULN, upper limit of normal.
those aged 56–65 with the same performance status. Im-
3 died within 30 days of treatment, compared with 29% of
of a poor performance status increased with age; 82% of pa-
lighted the importance of performance status as assessed by
patients with AML enrolled in SWOG treatment trials high-
cology practice, physical function is typically assessed
pendent of comorbidity in older cancer patients [54]. In on-
evaluation of physical function provides information inde-
Assessing Physical Function
Evaluation of physical function provides information inde-
ment of comorbidity scales has demon-
strated that comorbid disease is common in older adults
who have been deemed fit to receive induction chemother-
Comorbidity burden is associated with remission,
treatment-related toxicity, and survival. The use of stan-
standardized comorbidity assessment tools for older adults
AML is practical and can help risk stratify patients who are
less likely to benefit from standard therapies.

Assessing Physical Function
Evaluation of physical function provides information inde-
pendent of comorbidity in older cancer patients [54]. In on-
cology practice, physical function is typically assessed
using the Eastern Cooperative Oncology Group (ECOG) or
Karnofsky performance status scales. An analysis of 968
patients with AML enrolled in SWOG treatment trials high-
lighted the importance of performance status as assessed by
the ECOG scale [2]. Older adults with an ECOG score ≥2
had a very high likelihood of dying within 30 days of initi-
ing induction chemotherapy. The prognostic importance
of a poor performance status increased with age; 82% of pa-
tients aged ≥75 with an ECOG performance status score of
3 died within 30 days of treatment, compared with 29% of
those aged 56–65 with the same performance status. Im-
portantly, it was also noted that the patients who were ≥75
years of age with an ECOG performance status score of 0 at
the time of treatment had a 14% 30-day mortality rate, which
was similar to those in the younger age brackets. An-
other analysis of 998 patients with AML reported similar
findings [5]. In multivariate analyses, a poor performance
status (ECOG score of 3 or 4) was again identified as an
independent risk factor for treatment-related mortality and
shorter survival. Accordingly, the NCCN guidelines rec-
ommend low-intensity therapy or best supportive care for
older adults with an ECOG score ≥2 [30].

Physical function assessment using the ECOG scale alone,
however, may be inadequate to optimally risk stratify many
older patients with AML. Whereas scores of 3–4 correlate
well with overt disability, scores of 0–2 can encompass a
broad range of physical function in the elderly. Many elderly
patients have an ECOG performance status score <3 at the
time of presentation [2]. This scale is insensitive to detect sub-
clinical disability that might predict tolerability and response
to therapy; more sensitive measures are needed.

In geriatric oncology, functional status is commonly as-
ssessed using Basic Activities of Daily Living (ADL) and In-
strumental Activities of Daily Living (IADL) scales [55,
56]. ADLs are basic self-care skills (i.e., bathing, dressing)
whereas IADLs are skills needed to maintain independence
in the community (i.e., transportation, taking medications).
Use of these task-specific scales has been proposed as a key
component of geriatric assessment for older cancer patients
(NCCN guidelines) and adds information to the ECOG per-
formance status scale. Repetto et al. [57] evaluated 363 el-
derly cancer patients in a geriatric oncology clinic and
found a 9.3% rate of ADL disability and a 37.7% rate of
IADL disability in patients with a good ECOG performance
status score (ECOG score <2). That study suggests that the
ECOG scale is insensitive to pick up clinically meaningful
functional impairment in a subset of older adults.

IADL assessment adds information to the evaluation of
older patients with newly diagnosed AML. Wedding et al. [15]
evaluated the prognostic value of IADL disability in 63 pa-
tients with newly diagnosed AML and found that IADL im-
pairment was associated with shorter survival independent of
age, Karnofsky performance status score, and cytogenetic risk
group.

Oncology performance scales such as the ECOG and
Karnofsky performance status scales are useful though crude
measures that do not fully capture the spectrum of
functional abilities of older adults. More detailed self-
reported screens, such as the IADL scale, should be used in
clinical practice for those patients who have an ECOG score
<3 to help improve risk stratification. More objective func-
tional measures may better predict impaired response to the
stress of cancer treatment. Simple physical performance
tests, such as walking speed, have been evaluated in commu-
nity-dwelling older adults and are strongly predictive of
future disability and mortality [58, 59]. The feasibility of
this type of testing for older adults with newly diagnosed
AML is currently undergoing evaluation.

Assessing Cognitive Function
Cognitive dysfunction is prevalent in older cancer pa-
tients and can impact a patient’s ability to tolerate and
benefit from treatments [60]. Because of the lengthy hos-
Palmare diaries of AML patients, the relationship between
cognitive impairment and the risk of developing delirium may be of particular importance. Cognitive screening may identify patients who are at higher risk for complications, but research in this area is still very limited. A study of 54 patients with AML/MDS documented impaired performance on a battery of cognitive tests in up to 40% of the study population before treatment [61]. The high prevalence of cognitive impairment in the older population coupled with this finding indicates the need for more research on the prognostic value of cognitive screening in older patients with AML.

Supportive Care for Older Adults
Undertaking Active Treatment Needs to Be Optimized

Older adults deemed candidates for chemotherapy at the time of diagnosis remain at risk for experiencing toxicity that can translate into substantial functional decline during therapy. This debilitation can prohibit consolidation therapy and compromise quality of life. In addition to standard supportive care measures, such as transfusion support and treatment of infections, efforts to minimize unnecessary complications, such as delirium and physical deconditioning, could enhance the potential benefits of treatment.

A randomized trial in nonleukemic acutely ill hospitalized patients aged ≥70 years demonstrated that functional independence can be improved at discharge for adults treated in a geriatric-focused unit [62]. Principles included daily assessment of physical, cognitive, and psychosocial function, nutrition management, medication management, and a focus on rehabilitation with physical therapy.

Medication management may be of particular importance for older adults with AML because of the high prevalence of polypharmacy in this population. Studies of older adults with cancer report average numbers of medications in the range of four to nine [60, 63]. These numbers may be higher for patients being actively treated for acute leukemia. Polypharmacy is associated with more adverse drug reactions and a higher risk for drug–drug interactions [64]. A careful medication review with discontinuation of potentially unnecessary or inappropriate medications may minimize the negative consequences of polypharmacy.

Attention to the maintenance of physical function may also improve treatment outcomes. Currently, an inpatient physical activity intervention is under investigation to maintain functional independence during treatment for older adults receiving induction chemotherapy for AML. Active, rather than passive, supportive care strategies may improve the chances that older adults will be candidates for curative therapies following initial disease control.

Recommendations for Assessment and Treatment of Older Adults with Newly Diagnosed AML

Treatment recommendations for older adults with AML need to be individualized based on tumor biology and an assessment of physiologic age rather than chronologic age alone. Although the optimal therapy for older adults as a group remains debated, there is some evidence to guide decision making for individual patients.

Older adults with newly diagnosed AML who present with any of the following characteristics are more likely to experience toxicity and less likely to benefit from standard induction chemotherapy: an ECOG score >2, significant comorbidity (CCI score >1, HCT-CI score >2), and poor-risk cytogenetics. It would be reasonable to offer these patients supportive care alone, low-intensity therapy, or a clinical trial investigating novel agents in this poor-risk group. Alternatively, older adults with good functional status (ECOG score <2, no impairment in IADLs), minimal comorbidity, and good-risk cytogenetics are likely to benefit from curative therapies regardless of chronologic age. A reasonable treatment regimen for these patients is 7 days of continuous infusion cytarabine at 100 mg/m² per day with 3 days of daunorubicin at 30 mg/m² per day [65]. The optimal treatment for the large population of older adults who fall between these two extremes is unclear. Prospective studies are needed to validate the added prognostic value of risk stratification based on factors other than chronologic age and cytogenetic risk group.

Finally, informed decision making requires careful communication of individualized treatment options and potential outcomes. Limited evidence has suggested that older AML patients may overestimate treatment benefit and often report not being offered treatment options [66, 67]. Careful evaluation of tumor and patient characteristics can help guide communication of treatment options for older adults.

Future Directions for Improving Outcomes in Older Adults with AML

Investigation of novel agents to be used in addition or as a supplement to standard induction may improve outcomes for older adults with AML in the future. Development of less toxic, more targeted agents may provide treatment alternatives for the large proportion of the elderly AML population that has less than optimal functional status, limiting comorbidities, or unfavorable tumor biology. Potential agents include the nucleoside analog clofarabine and the sulfonly-hydrazine alkylating agent cloretazine, which are currently undergoing investigation [68, 69]. For example, a small randomized study using clofarabine in older adults with AML and high-risk MDS compared single-agent clo-
farabine with a combination of clofarabine and low-dose Ara-C for induction [70]. Remission rates were higher in the combination arm (63% versus 31%; \( p = .025 \)). There was a suggestion of overall survival benefit favoring the combination, which was not statistically significant (11.4 months versus 5.8 months; \( p = .1 \)). Unfortunately, the induction mortality rate remained high (19% for the combination arm and 31% for single-agent therapy; \( p = .276 \)).

The hypomethylating agents, including 5-azacytidine and decitibine, have demonstrated activity in MDS and are being evaluated as a novel remission approach for AML [71]. These agents are being investigated as single agents and in novel combinations. A recent, small, phase II study investigating the combination of 5-azacitidine, hydroxyurea, and gemtuzumab ozogamicin for untreated AML in older adults demonstrated promising results, with a CR rate of 70% [72]. Additional promising agents under investigation include FLT3 inhibitors and farnesyltransferase inhibitors (Table 4).

In addition to the development of novel agents, additional research to validate risk stratification for older adults being considered for treatment is needed. Large, randomized studies should include careful assessment of clinical characteristics such as comorbidity indices and more careful assessment of functional status to more clearly identify which patients encountered in clinical practice will benefit from the therapies being investigated. Finally, supportive care strategies need to be developed that focus attention on the maintenance of functional status and quality of life for those patients who are treated with aggressive therapies.

**CONCLUSION**

The majority of patients diagnosed with AML are aged >60. Outcomes remain poor for this population, resulting in controversy regarding the optimal therapeutic approach. Chronologic age alone is inadequate in predicting response to therapy and treatment-related morbidity. Treatment decisions need to be individualized after careful consideration of tumor biology and patient characteristics. Older adults with favorable tumor biology, good functional status, and minimal comorbidity can benefit from standard induction chemotherapy. Research on more tolerable, novel therapeutic agents and better supportive care strategies are needed to improve treatment outcomes for older adults with AML.

**AUTHOR CONTRIBUTIONS**

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