Treatment of AML in the Elderly Lymphoma Tumor Board
February 17, 2017
Percent of New Cases by Age Group: Acute Myeloid Leukemia

Acute myeloid leukemia is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis
67

SEER 18 2009–2013, All Races, Both Sexes
Diagnosis

- Most common acute leukemia affecting adults
- Incidence increases with age
- Symptoms include:
  - Fatigue
  - Shortness of breath
  - Easy bruising and bleeding
  - Increased risk of infection
  - Drop in red blood cell count & platelet count

“Dysplastic changes are noted in both the granulocytic and erythroid lineages.”

Bone marrow aspirate from this patient with AML shows a blast with an Auer rod (black arrow) as well as neutrophils with hypersegmented (blue arrow) and a hyposegmented (red arrow) nuclei.
Disease classification

- **Classification is based on:**
  - Assessment of blood smears
  - Assessment of bone marrow specimens
  - Analysis of the expression of cell-surface or cytoplasmic markers by flow cytometry
  - Identification of chromosomal findings by cytogenetic testing and screening for specific molecular genetic lesions

- **Major categories of current classification are:**
  - AML with recurrent genetic abnormalities
  - AML with myelodysplasia-related changes
  - Therapy-related AML
  - AML not otherwise specified

Although this new knowledge has not yet had a major influence on the treatment of the disease, strategies under investigation may improve outcomes.
FIGURE 1. Molecular heterogeneity of acute myeloid leukaemia. Circos plot illustrating the molecular heterogeneity of AML by depicting the interrelationship of translocations and/or mutations found in a cohort of 498 primary AML cases. Coloured lines indicate concurrent aberrations found in one AML patient. Of note, patients can have more than two abnormalities. AML, acute myeloid leukaemia.
Considerations in Elderly Patients

• Decreased immune competence of elderly patients results in less tolerability of infections.

• Psychosocial factors influence outcomes:
  • Cognitive decline
  • Social isolation
  • Lack of caretakers

• Higher frequencies of adverse cytogenetics and unfavorable molecular aberrations.

• Disease-related factors predict resistance to current standard therapy.
  • White-cell count
  • Prior myelodysplastic syndrome
  • Cytotoxic therapy for an antecedent disorder
  • Leukemic-cell genetic changes

• Tolerance of intensive chemotherapy?
General algorithm for the treatment of older patients with AML. This algorithm serves as a global guideline and should not be applied dogmatically but with thoughtful consideration of the individual circumstances.

Algorithm for the treatment of patients at older age with AML

Complete work up including cytogenetics/molecular classification of AML, co-morbidities/socio-economic situation of patient

Identify clinical trial

Considered eligible for intensive treatment

Standard remission induction therapy

Consider alloHSCT

Unfavorable prognostic risk profile

Donor?

yes

standard remission induction treatment plus alloHSCT

Non-intensive treatment (eg with hypomethylating agents)

Investigational drug (clinical trial)

no

Not considered eligible for intensive treatment

Gert Ossenkoppele, and Bob Löwenberg Blood
2015;125:767-774
Treatment Algorithm for Older Patients with AML

New diagnosis of AML

Patient-related characteristics

AML-related characteristics

Acceptable treatment-related mortality score or favorable AML score

Focused geriatric assessment or comorbidity index

High treatment-related mortality score or unfavorable AML score

Non-intensive treatment

- Investigational therapy
- Hypomethylating agents
- Low-dose cytarabine

Intensive treatment

- Investigational therapy
- Conventional induction therapy

Abbreviations: AML, acute myeloid leukemia; sAML, antecedent hematologic disorder; t-AML, therapy-related AML; AML-MRC, AML with myelodysplastic syndrome–related changes.
Flowchart for the stratification of primary treatment in older patients with acute myelocytic leukemia (AML)

For patients with acute promyelocytic leukemia (APL), aggressive substitution therapy in case of coagulopathy and the rapid initiation of combination therapy including ATRA can be life-saving. For all other AML patients, intensive chemotherapy is recommended if the patient is a suitable candidate, possibly supplemented by allogeneic stem-cell transplantation in selected patients, once complete remission has been attained. Patients for whom intensive chemotherapy is not feasible and have 30% or fewer blasts in their bone marrow can benefit from hypomethylating therapy with 5-azacitidine, while those with more than 30% blasts can benefit from treatment with low-dose cytarabine. The notion that patients with cytogenetic changes signifying high risk do not benefit from low-dose cytarabine is derived from a subgroup analysis and has not been further tested; this issue must be addressed in a prospective study. No other specific treatments are available for patients for whom the above treatments are not feasible. They should receive supportive care or be enrolled in clinical trials of new drugs according to their wishes.

APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; BSC, best supportive care.
Current care of patients with AML, and indications for allogeneic hematopoietic cell transplantation

Table 3: Current Conventional Care of Patients with AML, Including Indications for Allogeneic Hematopoietic-Cell Transplantation.

<table>
<thead>
<tr>
<th>Form of Therapy</th>
<th>Regimen</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Induction therapy</td>
<td>Patients ≤ 60 yr</td>
<td>3 Days of an intravenous anthracycline (daunorubicin 60 mg/m²) and cytarabine (100–150 mg/m²) administered every 12 hr over 3 days, or 5 days</td>
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<td>Patients &gt; 60 yr</td>
<td>For patients with favorable-risk and intermediate-risk cytogenetic findings and no coexisting conditions, induction therapy is the same as that in younger patients, and dose reduction may be considered for individual patients</td>
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<td>Consolidation therapy</td>
<td>Patients with favorable genetic risk (according to ELN) should receive 2–4 cycles of intermediate-dose cytarabine (1000–1500 mg/m² intravenously, usually administered every 12 hr over 3 days, or 5 days) for patients with intermediate-1, intermediate-2, or adverse-risk. Allogeneic hematopoietic-cell transplantation should be strongly considered. If not possible, consolidation therapy should be administered as a dose-escalation chemotherapy (e.g., mitoxantrone, cytarabine) may be superior in patients with adverse-risk AML</td>
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<tr>
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<td>Allogeneic hematopoietic-cell transplantation</td>
<td>Patients with favorable ELN genetic risk (less common) and no coexisting conditions should receive 2–3 cycles of intermediate-dose cytarabine (1500–2000 mg/m² intravenously, every 12 hr on days 1–5, or 500–1000 mg/m² intravenously, on days 1–4)</td>
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<td>Therapy for patients who are ineligible to receive intensive therapy</td>
<td>Only for patients with favorable-risk or intermediate-risk, not with adverse-risk cytogenetic subgroup: low-dose cytarabine (20 mg every 12 hr, subcutaneously, on days 1–16) or 4 wk until progression</td>
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<td>Therapy for patients with relapsed AML or primary induction failure</td>
<td>Hypomethylating agents: decitabine 20 mg/m² intravenously, on days 1–5, 4–6 wk until progression; azacitidine 75 mg/m², subcutaneously, on days 1–7. 4 wk until progression</td>
</tr>
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<td>Patients for whom intensive salvage therapy is considered to be suitable</td>
<td>Conventional intensive salvage regimens: cytarabine (1000–1500 mg/m² intravenously, every 12 hr, on days 1–5; 500–1000 mg/m² in patients &gt; 60 yr; or 500–1500 mg/m² intravenously, on days 1–6 to 1500 mg/m² in patients &gt; 60 yr) with or without daunorubicin 45–60 mg/m² intravenously, on days 1–3; or mitoxantrone 8–10 mg/m² intravenously, on days 1–3</td>
</tr>
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<td></td>
<td>Microemulsion daunorubicin 8 mg/m², on days 1–5, etoposide 100 mg/m², on days 1–3; cytarabine (1000 mg/m²) on days 1–5</td>
<td>MEC: Mitoxantrone 8 mg/m², on days 1–5; etoposide 100 mg/m², on days 1–3; cytarabine (1000 mg/m²) on days 1–5</td>
</tr>
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<td></td>
<td>Patients for whom intensive salvage therapy is considered to be unsuitable Low-intensity regimens, such as low-dose cytarabine, hypomethylating agents, or best supportive care only (including hydroxyurea); preserve quality of life</td>
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</tr>
</tbody>
</table>

a This therapy is for patients who are physically able to undergo the therapy and who do not have major coexisting conditions.

b Some regimens use higher doses of cytarabine (2000–3000 mg/m² per square meter per single dose); however, data from pharmacologic studies and clinical trials suggest that such doses are above the plateau of the maximal therapeutic effect.

c This agent is approved by the European Medicines Agency (EMA), but not by the U.S. Food and Drug Administration (FDA) for patients who are 65 years of age or older, who have newly diagnosed primary or secondary AML, and who are not candidates for standard induction chemotherapy.

d This agent is approved by the FDA and EMA for patients who have newly diagnosed AML with 20 to 30% bone marrow blasts and multilineage dysplasia and who are not candidates for allogeneic hematopoietic-cell transplantation.
Final considerations

Today, older patients with AML can be offered one of the following treatment options:

- Standard induction treatment consisting mostly of a 3+7 regimen of an anthracyclin and Ara-C;
- Hypomethylating agents;
- Investigational drugs within a clinical trial;
- Low-dose Ara-C;
- Best supportive care with oral cytostatic drugs like hydroxyurea and/or transfusions.
Survival

Based on data from SEER 18 2006–2012. Gray figures represent those who have died from acute myeloid leukemia. Green figures represent those who have survived 5 years or more.

Percent Surviving 5 Years

26.6%
Overall survival according to cytogenetic risk in patients above 60 years

Gert Ossenkoppele, and Bob Löwenberg
Blood 2015;125:767-774

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References


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