



Evidence based Series #6-14: Section 1

Treatment of Acute Myeloid Leukemia in Older Patients: Guideline Recommendations

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The full Evidence-based Series #6-14 is comprised of 3 sections
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PEBC Hematology DSG page at:

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Section 1: Guideline Recommendations

Section 2: Evidentiary Base

Section 3: EBS Development Methods and External Review Process

QUESTIONS

1. What is the relative efficacy of aggressive induction chemotherapy as compared with less aggressive treatments used in the treatment of older patients (> 55 years) with newly diagnosed acute myeloid leukemia (AML)?
2. What is the optimum induction regimen for older patients with AML?
3. What is the optimum post-remission therapy?
4. What are the roles of granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) in conjunction with chemotherapy in this group of patients?
5. What disease and patient-related parameters can be used to identify patients age > 55 years who are more likely to benefit from aggressive induction therapy?

Outcomes of interest include survival, response rate, response duration, and toxicity.

TARGET POPULATION

The recommendations apply to adult patients over the age of 55 years with newly diagnosed, previously untreated, AML.

RECOMMENDATIONS

- Based on the consensus of the Hematology Disease Site Group (DSG), intensive induction chemotherapy is recommended for patients with good performance status and minimal organ dysfunction or comorbidity. Intensive induction treatment has resulted in superior outcomes (remission rates, remission duration, and survival) without an increase in toxicity, in comparison with therapy that includes reduced doses or is of palliative intent.

Key Evidence

- Buchner et al (1) compared two doses of daunorubicin (60 mg/m² versus [vs.] 30 mg/m²) in patients aged 60 years or older. More intensive therapy resulted in fewer early deaths and a superior remission rate, and because the duration of remission was similar in both groups, the superior remission rate in the more intensively treated patients translated into superior overall survival.
- Comparative data fail to demonstrate superior outcomes associated with use of a specific anthracycline or anthracenedione agent in induction. No consistent differences in treatment-related toxicities were observed. Thus, the decision as to which agent to use may be determined by other factors, such as drug acquisition costs, that may vary among institutions. For those reasons, each individual institution should determine their specific policies regarding the agent of choice.

Key Evidence

- The Hematology DSG conducted separate meta-analyses for the categories of comparisons (daunorubicin [DNR] vs. idarubicin [IDR], DNR vs. mitoxantrone [MXT], and IDR vs. MXT), and all failed to detect statistically significant differences between the agents with respect to response rate or overall survival.
- There is insufficient evidence to make a firm recommendation regarding the administration of consolidation therapy to older patients who have achieved a complete remission. Based on DSG consensus, it is recommended that patients in complete remission with a good performance status who have recovered from any toxicity receive at least one cycle of consolidation with conventional or intermediate dose cytarabine with or without anthracycline.

Key Evidence

- No randomized trials of consolidation therapy compared to placebo or observation were identified.
 - The decision that patients with a good performance status who have recovered from toxicity should receive at least one cycle (and up to two) of consolidation therapy with conventional or intermediate dose cytarabine with or without anthracycline was based on an extrapolation of the evidence from younger patients (age < 55 years) (2) and on the consensus of the Hematology DSG.
- There is no role for maintenance therapy for patients in first complete remission.

Key Evidence

- Four randomized trials of maintenance therapy showed no significant differences in relapse-free or overall survival compared to the control (3-6).

- For patients with important comorbidities who are deemed ineligible for induction chemotherapy by their physicians or whose personal preferences are for a palliative approach, treatment with low-dose cytarabine is recommended to optimize disease control while avoiding serious treatment-related toxicities.

Key Evidence

- Burnett et al (7) demonstrated that, in older AML patients deemed unfit for intensive chemotherapy, low-dose cytarabine was associated with higher remission rates and longer survival compared to hydroxyurea, with no difference in toxicities.
- The routine use of myeloid growth factors (G-CSF or GM-CSF) as an adjunct to intensive chemotherapy in older patients with AML is not recommended.

Key Evidence

- An aggregate data meta-analysis pooling results of the published studies of GM-CSF or G-CSF was performed by the Hematology DSG. The meta-analysis did not detect a difference between groups who did or did not receive growth factors with respect to complete response rate, mortality or disease recurrence, overall survival, infection rates, or infectious death. Toxicity data were inconsistently reported and therefore not pooled.
- There is insufficient evidence to guide a recommendation on the use of specific prognostic factors to guide treatment decisions in older patients.

Key Evidence

- To date there are no prospective trials investigating the use of specific prognostic factors to guide treatment decisions in older patients.

QUALIFYING STATEMENTS

- Treatment decisions in older patients with AML are complex and often influenced by comorbid illnesses, consideration of quality of life, and patient preferences. Thus, treatment recommendations described in this evidence-based series may require alteration after discussions with patients and their families.
- The Hematology DSG recognizes that the trials reviewed for the creation of this guideline included a broad range of patients, from those where currently the use of aggressive attempts at remission might routinely be considered (e.g., those age 56-65) as well as those where only a minority of patients would be treated aggressively (e.g., those age 66 or greater). In the absence of significant weight of evidence to provide recommendations specific to the latter group, the DSG concluded that patient preferences and attention to co-morbidities (physiologic age) remain important considerations in treating elderly patients with AML.

FUTURE RESEARCH

The outcome of conventional cytotoxic chemotherapy in older patients remains extremely poor despite advances in supportive care; thus, several novel therapies are being developed and investigated in clinical trials in this patient population. These include multidrug reversal agents, immunomodulatory therapies, and signal transduction targeting (e.g., PSC-833, UCN-01, gemtuzamab ozogamicin, PS-341, decitabine, ATRA, flt-3 tyrosine kinase inhibitors).

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