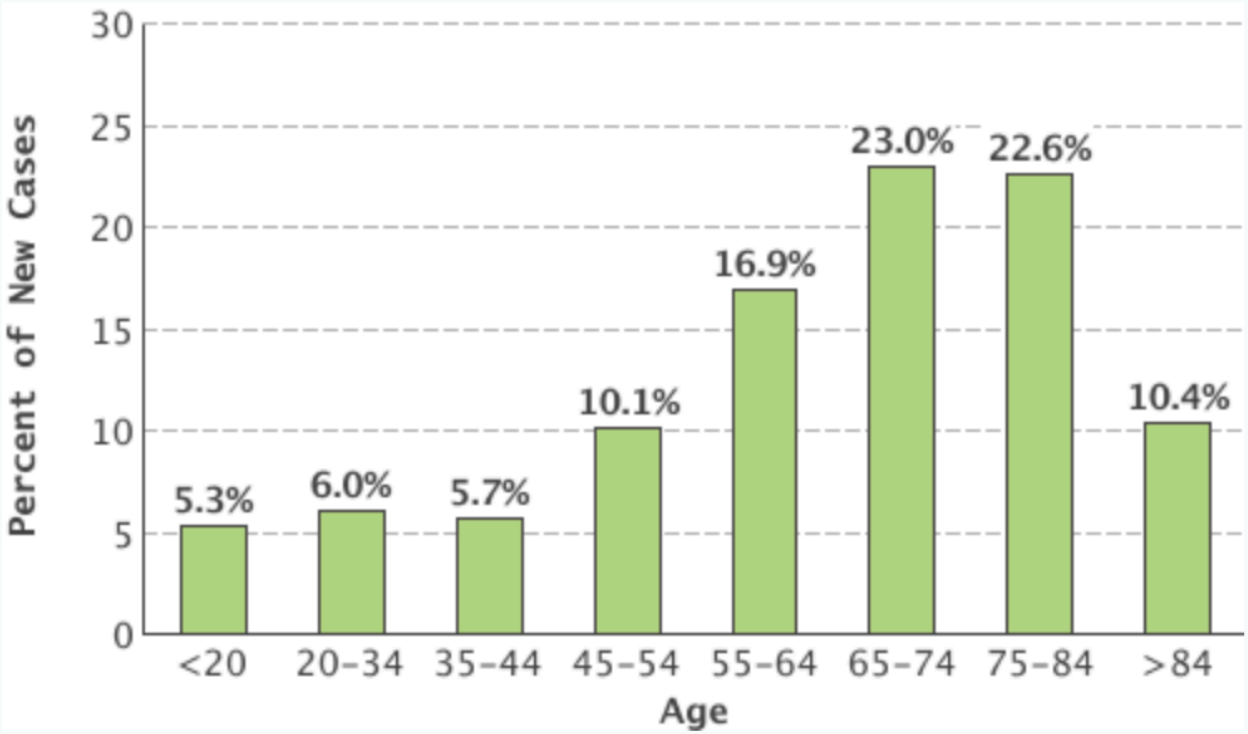
Treatment of AML in the Elderly
Lymphoma Tumor Board
February 17, 2017

Percent of New Cases by Age Group: Acute Myeloid Leukemia



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

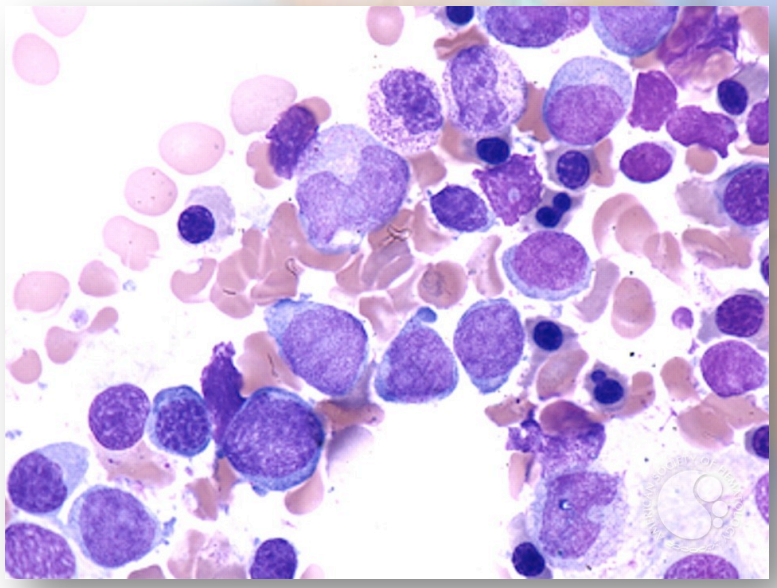
Median Age At Diagnosis

67

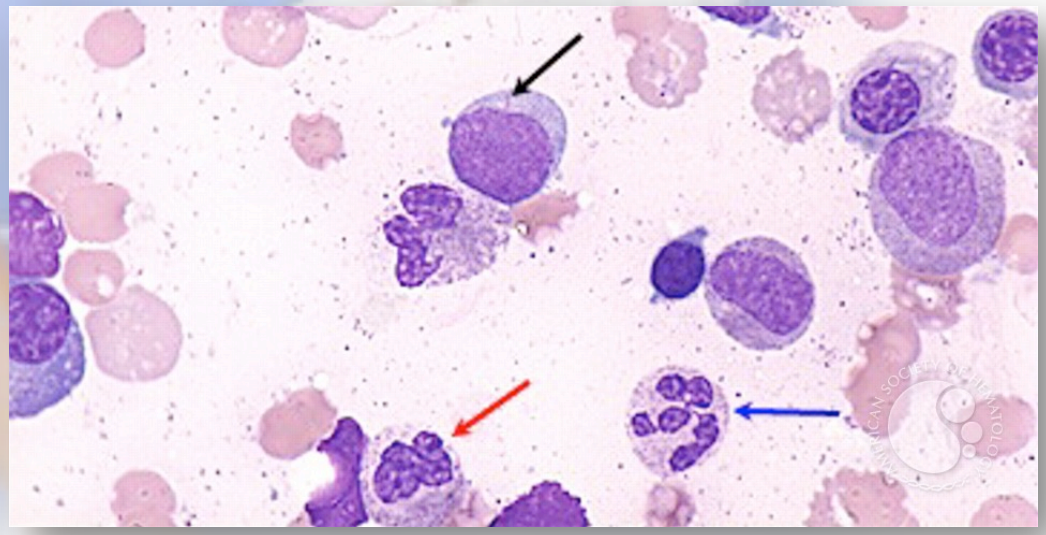
SEER 18 2009-2013, All Races, Both Sexes

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.

Genetic Landscape

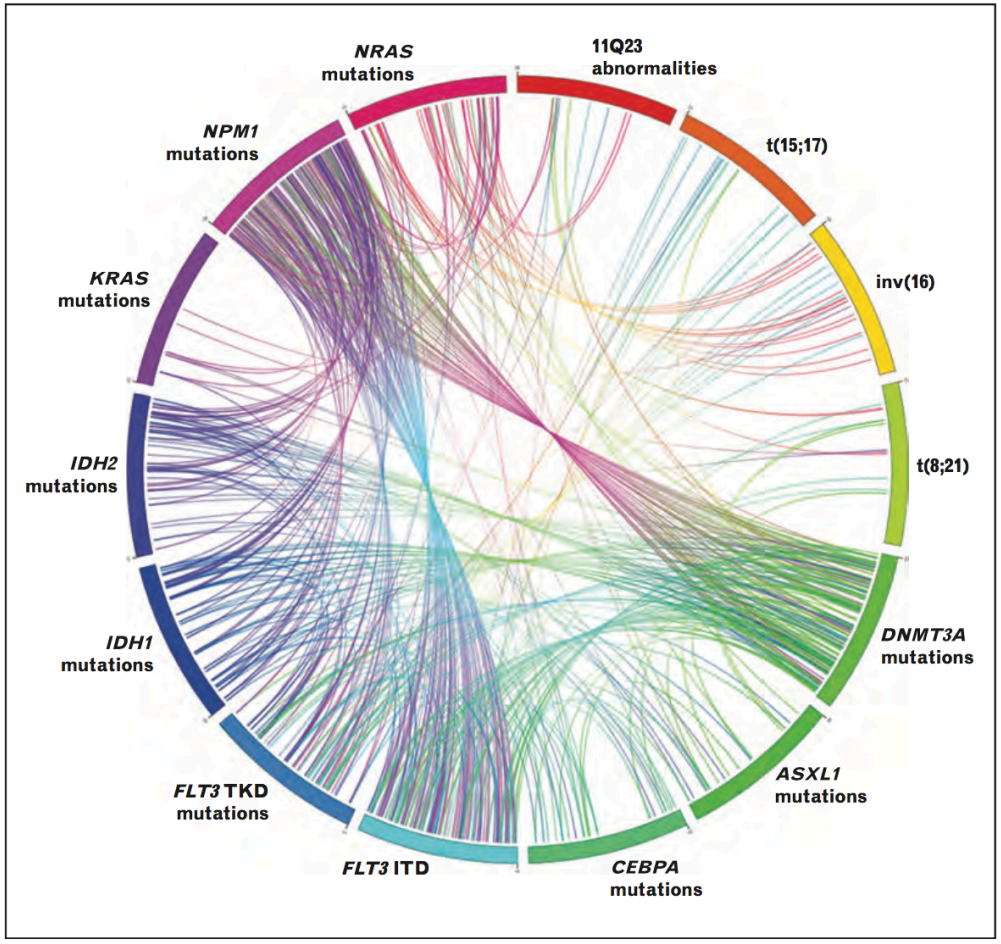


FIGURE 1. Molecular heterogeneity of acute myeloid leukaemia. Circos plot illustrating the molecular heterogeneity of AML by depicting the interrelationship of translocations and/or mutations found in a cohort of 498 primary AML cases. Coloured lines indicate concurrent aberrations found in one AML patient. 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.

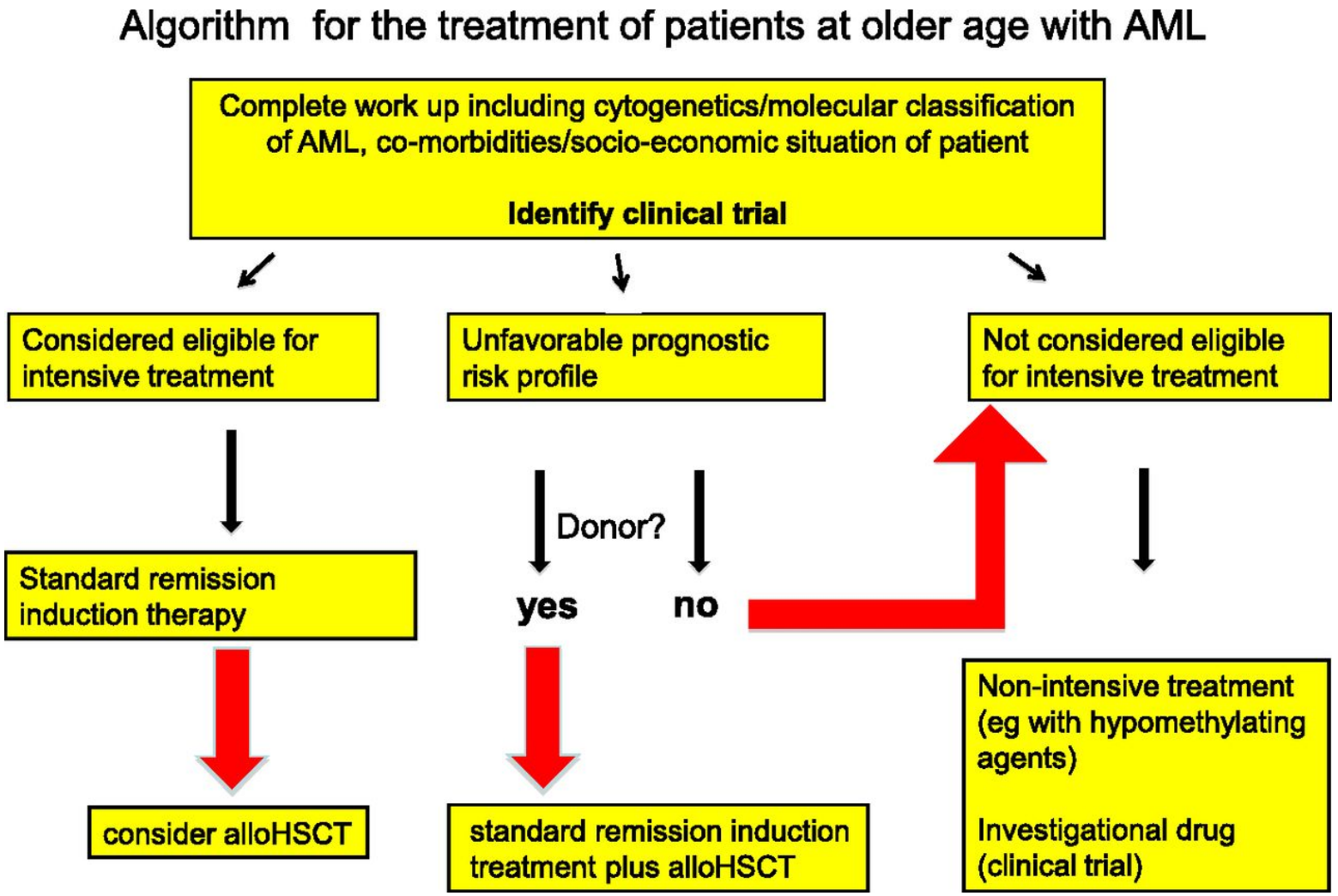
- Psychosocial factors influence outcomes:
  - Cognitive decline
  - Social isolation
  - Lack of caretakers

- 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?

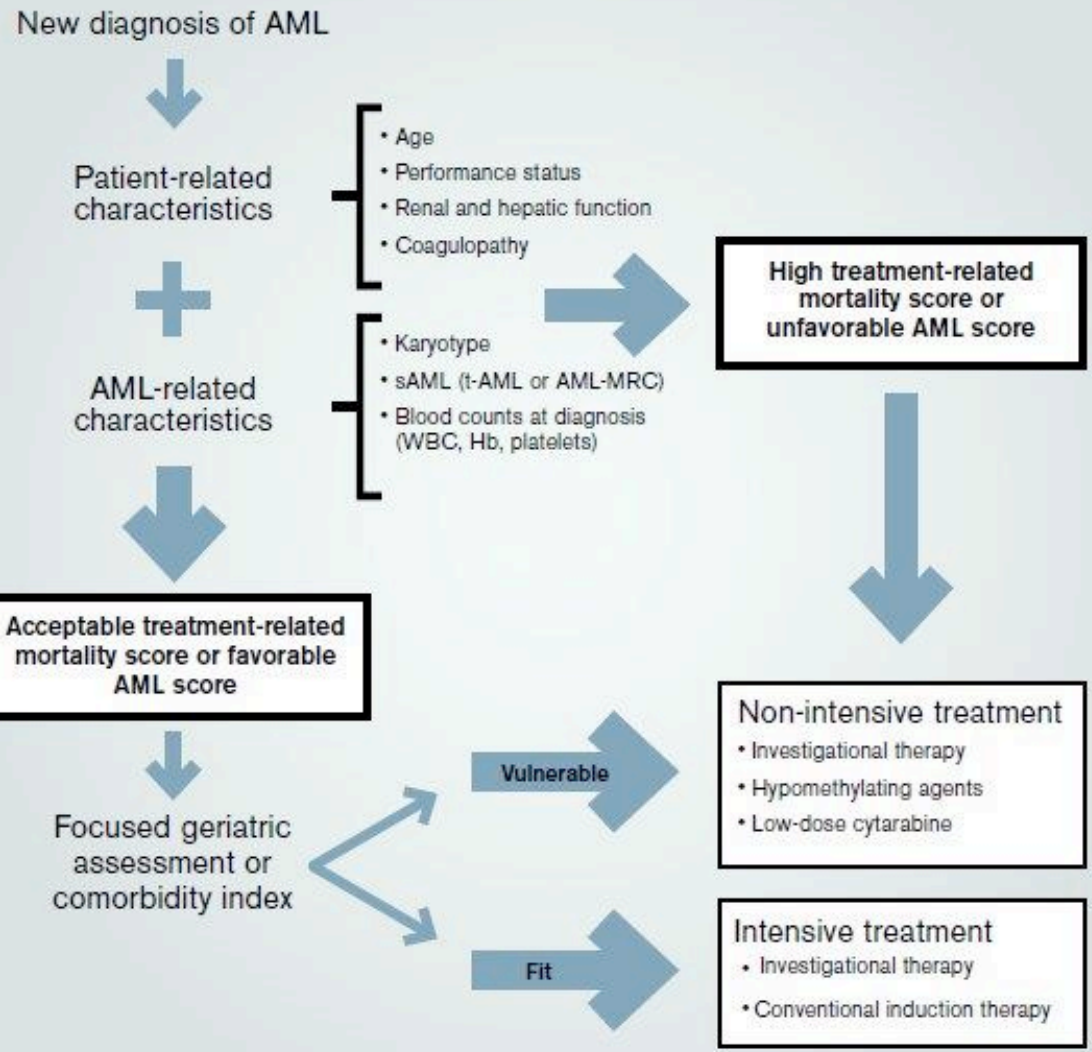
General algorithm for the treatment of older patients with AML. This algorithm serves as a global guideline and should not be applied dogmatically but with thoughtful consideration of the individual circumstances.



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

Figure

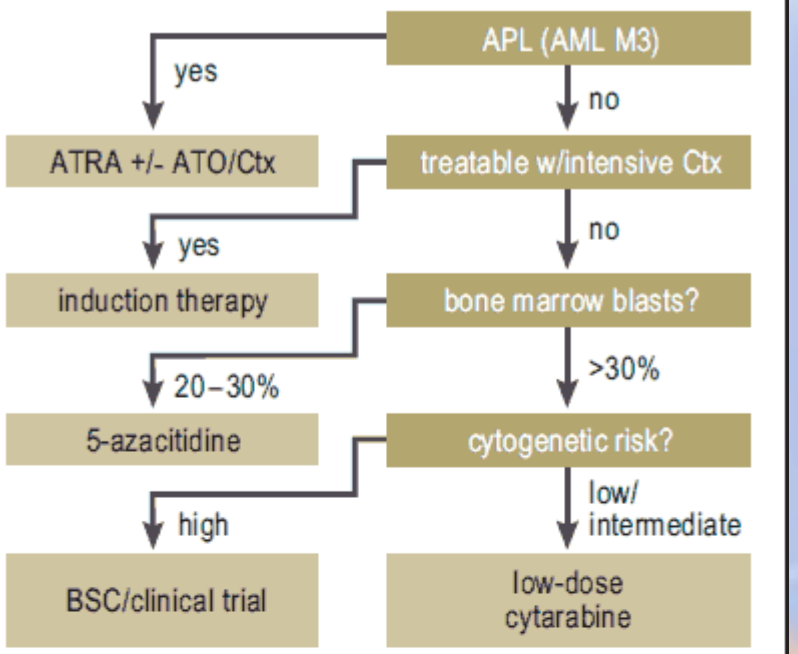
Treatment Algorithm for Older Patients with AML



Abbreviations: AML, acute myeloid leukemia; sAML, antecedent hematologic disorder; t-AML, therapy-related AML; AML-MRC, AML with myelodysplastic syndrome--related changes.

Treatment

FIGURE 2



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.

Krug, U; Büchner, T; Berdel, W E; Müller-Tidow, C

The Treatment of Elderly Patients With Acute Myeloid Leukemia

Dtsch Arztebl Int 2011; 108(51-52): 863-70; DOI: 10.3238/arztebl.2011.0863

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.**

Form of Therapy	Regimen	Comments
Induction therapy*		
Patients 16–60 yr	3 Days of an intravenous anthracycline (daunorubicin 60 mg/m^2; idarubicin 10–12 mg/m^2; mitoxantrone 10–12 mg/m^2) and 7 days of continuous-infusion cytarabine (100–200 mg/m^2) ("3+7" induction)	A second induction cycle is commonly used in patients with partial remission only
Patients >60 yr	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	Patients with adverse cytogenetic risk, coexisting conditions, or both are less likely to have a response to induction therapy (see also below under "patients who are ineligible to receive intensive therapy")
Consolidation therapy*		
Patients 16–60 yr	Patients with favorable genetic risk (according to ELN) should receive 2–4 cycles of intermediate-dose cytarabine† (1000–1500 mg/m^2 intravenously, usually administered every 12 hr over 3 days, or 1000–1500 mg/m^2 intravenously on days 1–6); for patients with intermediate-I, intermediate-II, or adverse risk, allogeneic hematopoietic-cell transplantation should be strongly considered; if not possible, consolidation therapy should be administered as above; combination chemotherapy (e.g., mitoxantrone–cytarabine) may be superior in patients with adverse-risk AML	Autologous hematopoietic-cell transplantation may be considered in lieu of consolidation chemotherapy for selected patients who do not have disease with high-risk features
Patients >60 yr	Patients with favorable ELN genetic risk (less common) and no coexisting conditions should receive 2–3 cycles of intermediate-dose cytarabine (500–1000 mg/m^2 intravenously, every 12 hr on days 1–3, or 500–1000 mg/m^2 intravenously, on days 1–6)	For patients with unfavorable genetic risk, coexisting conditions, or both, no value of intensive consolidation therapy has been established; investigational therapy should be considered
Allogeneic hematopoietic-cell transplantation (see Table 4)*		
Therapy for patients who are ineligible to receive intensive therapy	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 1–10, every 4 wk; until progression)	Determination of eligibility is based on assessments of prior medical coexisting conditions, recent complications, performance status, and patient choice
	Hypomethylating agents: decitabine‡ 20 mg/m^2, intravenously, on days 1–5, every 4 wk, until progression; azacitidine§ 75 mg/m^2, subcutaneously, on days 1–7, every 4 wk, until progression	
	Consider investigational therapy in all patients	
	Best supportive care only in patients who cannot safely receive any antileukemic therapy	
Therapy for patients with relapsed AML or primary induction failure		Older age, poor general health status, primary refractoriness, or short duration of remission (<6 mo), adverse genetic factors, and prior hematopoietic-cell transplantation are major risk factors
Patients for whom intensive salvage therapy is considered to be suitable	Conventional intensive salvage regimens: cytarabine† (1000–1500 mg/m^2, intravenously every 12 hr, on days 1–3 [500–1000 mg/m^2 in patients >60 yr]; or 1000–1500 mg/m^2, intravenously, on days 1–6 [500–1000 mg/m^2 in patients >60 yr]); with or without daunorubicin 45–60 mg/m^2, intravenously, on days 1–3; or mitoxantrone 8–10 mg/m^2, intravenously, on days 1–3	
	MEC: Mitoxantrone 8 mg/m^2, on days 1–5; etoposide 100 mg/m^2, on days 1–5; cytarabine 1000 mg/m^2, on days 1–5	
	FLAG-IDA: Fludarabine 30 mg/m^2, intravenously, on days 1–5 (20 mg/m^2 in patients >60 yr); cytarabine 1500 mg/m^2 (500–1000 mg/m^2 in patients >60 yr) intravenously, 4 hr after fludarabine infusion, on days 1–5; idarubicin 8 mg/m^2, intravenously, on days 3–5; granulocyte colony-stimulating factor 5 μg/kg, subcutaneously, from day 6 to white-cell count >1 g/liter	
	Consider dose reductions in individual patients, in particular, in older patients (>60 yr) and in patients with relapse after allogeneic hematopoietic-cell transplantation	
	Allogeneic hematopoietic-cell transplantation for patients in complete remission; investigational hematopoietic-cell transplantation approaches for those with major cytoreduction, but no complete remission; consider reinduction (dose-reduced) and reduced-intensity conditioning allogeneic hematopoietic-cell transplantation in selected patients	
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	

* This therapy is for patients who are physically able to undergo the therapy and who do not have major coexisting conditions.
† Some regimens use higher doses of cytarabine (2000–3000 mg 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.
‡ 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.
§ 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.

Döhner H et al. N Engl J Med 2015;373:1136-1152

The NEW ENGLAND JOURNAL of MEDICINE

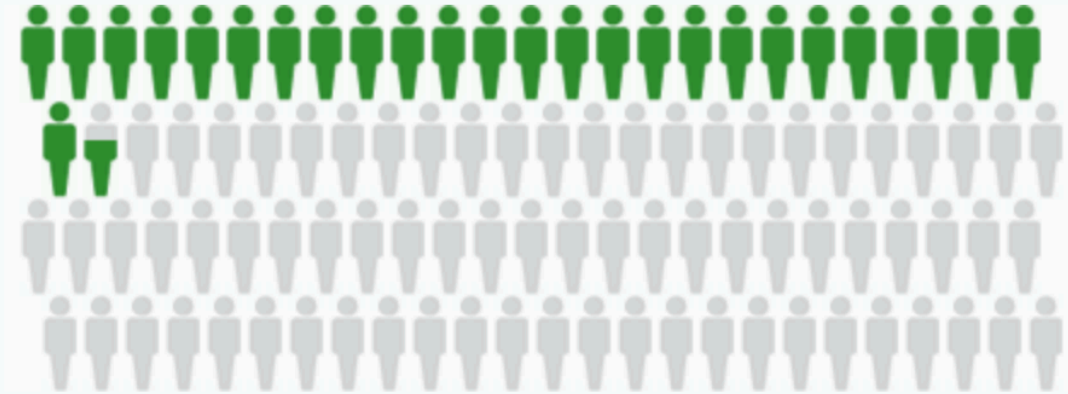
Treatment

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.

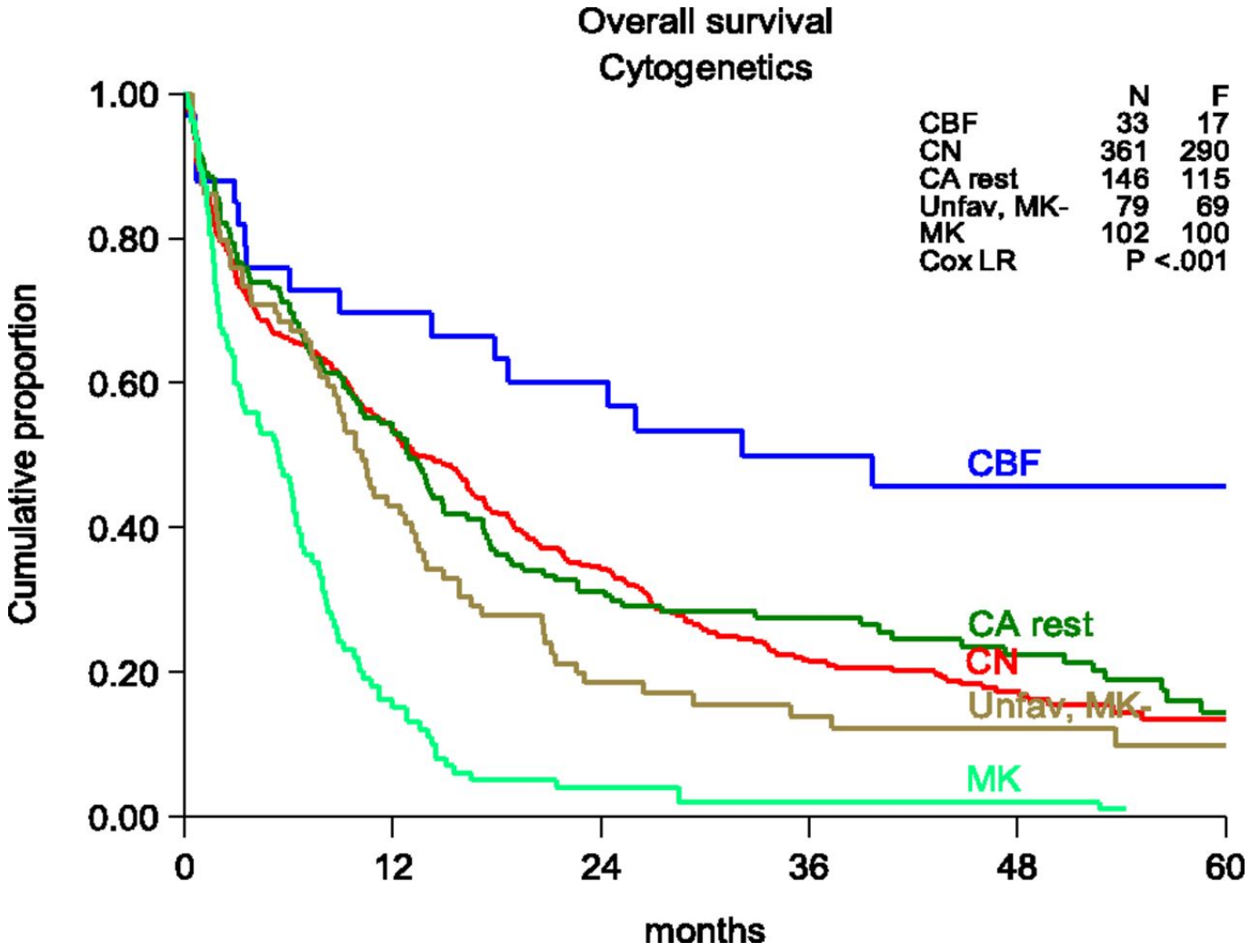
Survival



Percent Surviving 5 Years
26.6%

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.

Overall survival according to cytogenetic risk in patients above 60 years



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

References

- Krug, U., B¸chner, T., Berdel, W. E., & M¸ller-Tidow, C. (2011). The Treatment of Elderly Patients With Acute Myeloid Leukemia. *Dtsch Arztebl International, 108*(51-52), 863-870. doi:10.3238/arztebl.2011.0863

- Döhner, H., Weisdorf, D. J., & Bloomfield, C. D. (2015). Acute Myeloid Leukemia. *New England Journal of Medicine, 373*(12), 1136-1152. doi:doi: 10.1056/NEJMra1406184

- Ash Image Bank http://imagebank.hematology.org/

- Ossenkoppele, G., & Löwenberg, B. (2015). How I treat the older patient with acute myeloid leukemia. Blood, 125(5), 767-774. Accessed February 15, 2017.

- https://doi.org/10.1182/blood-2014-08-551499.

- https://seer.cancer.gov/statfacts/html/amyl.html

- http://media.chemotherapyadvisor.com/images/2015/05/01/chemotherapyinfusionacutemy_765064.jpg?format=jpg&zoom=1&quality=70&anchor=middlecenter&width=320&mode=pad