Review Article

Acute Myeloid Leukemia

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REVIEW ARTICLE

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Acute Myeloid Leukemia

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ACUTE MYELOID LEUKEMIA (AML) IS A FORM OF CANCER THAT IS CHARACTERIZED by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system. Although it was incurable 50 years ago, AML is now cured in 35 to 40% of adult patients who are 60 years of age or younger and in 5 to 15% of patients who are older than 60 years of age.[1] The outcome in older patients who are unable to receive intensive chemotherapy without unacceptable side effects remains dismal, with a median survival of only 5 to 10 months.

Although the cytogenetic heterogeneity of AML has been recognized for more than 30 years, the enormous molecular heterogeneity of the disease has become increasingly apparent over the past 15 years. The prognostic importance of this biologic heterogeneity is well accepted, but translation of this new information into improved therapy is just beginning. In this article, we describe recent advances in the disease classification, understanding of the genomic landscape, identification of prognostic factors, current treatment, and new therapies under investigation in types of adult AML other than acute promyelocytic leukemia.

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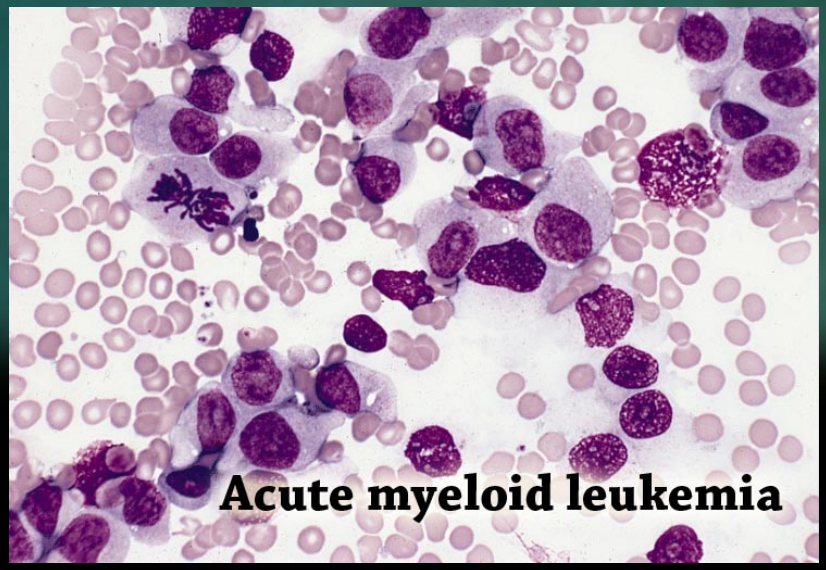
Acute Myeloid Leukemia

- 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



AML

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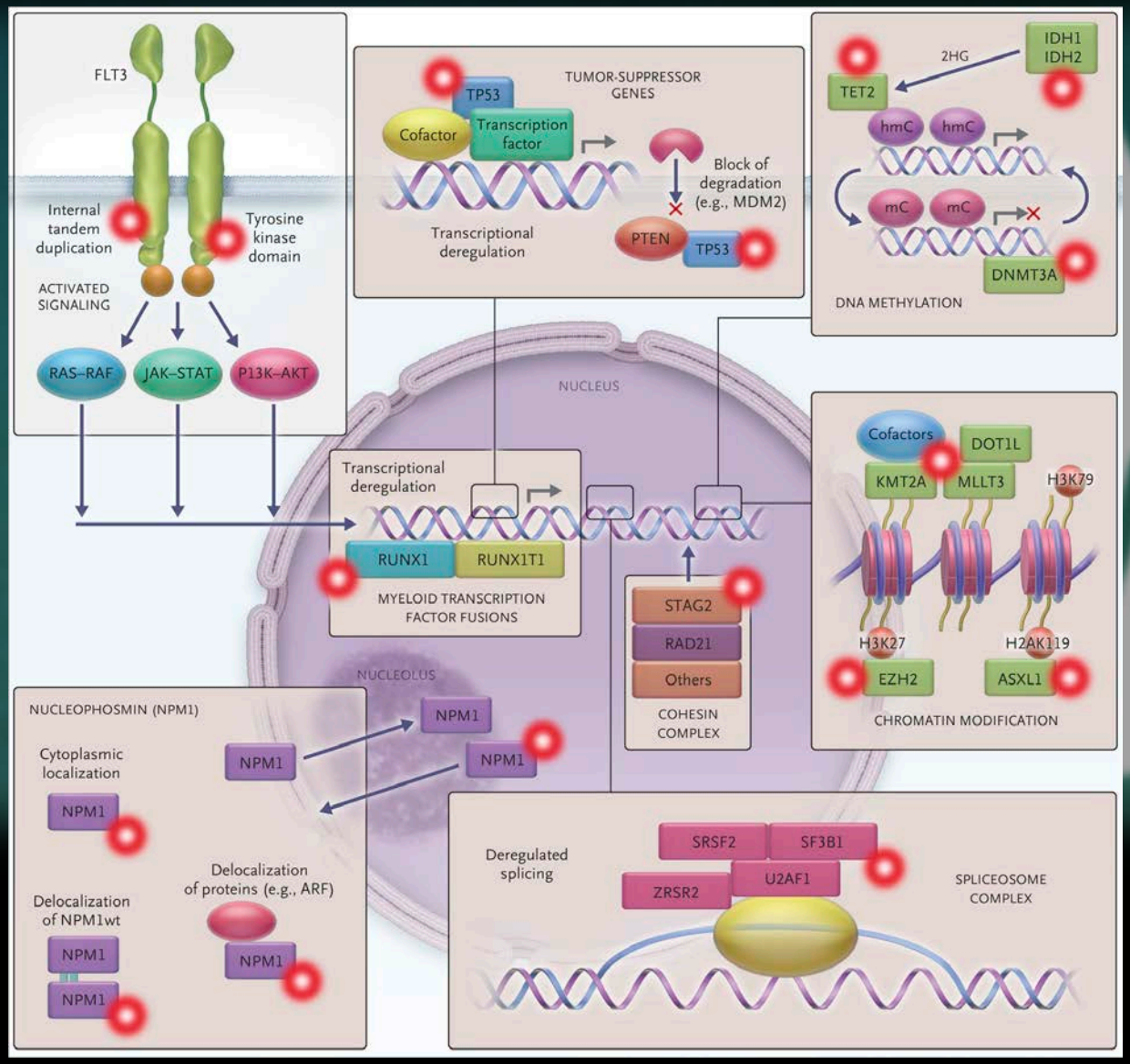
Disease classification

- 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.

Eight functional categories of genes that are commonly mutated in acute myeloid leukemia



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Prognostic factors

- Patient-associated factors commonly predict treatment-related early death:
  - Increasing age
  - Coexisting (“co-morbid”) conditions
  - Poor performance status

- 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

- Active research area: evaluation of molecular genetic lesions as prognostic and predictive markers (Table 1)

Frequency and clinical significance of recurrent gene mutations in adults with AML

Table 1. Frequency and Clinical Significance of Recurrent Gene Mutations in Adults with AML.*

Mutated Gene	Frequency	Clinical Significance
	% *of patients*	
NPM1	25–35	AML with an *NPM1* mutation is a clinicopathologic entity Most frequent in cytogenetically normal AML (45–60% of cases); frequently associated with other mutations (e.g., *FLT3*-ITD and mutations in *DNMT3A*, *IDH1*, *IDH2*, and *TET2*) In younger patients, cytogenetically normal AML with mutated *NPM1* without *FLT3*-ITD is associated with a favorable outcome; in general, there is no benefit from allogeneic hematopoietic-cell transplantation in first complete remission Older patients (>60 yr) with *NPM1*-mutated AML benefit from conventional intensive chemotherapy Genetic marker for assessment of minimal residual disease
CEBPA	6–10	Only AML with biallelic *CEBPA* mutations defines the clinicopathologic entity Incidence decreases with older age; associated with cytogenetically normal AML Associated with favorable outcome Associated with familial AML
RUNX1	5–15	Incidence increases with older age; associated with other mutations (e.g., in *ASXL1*, *SRSF2*, *IDH2*, and *KMT2A*) Associated with secondary AML evolving from a myelodysplastic syndrome *RUNX1* mutations predictive of resistance to induction therapy and of inferior outcome Associated with the autosomal dominant familial platelet disorder conferring a predisposition to AML
FLT3-ITD	Approx. 20	Most frequent in cytogenetically normal AML (28–34% of cases) Associated with unfavorable outcome, particularly in patients with a high mutant-to-wild-type ITD ratio, ITD insertion in the β1-sheet of the tyrosine kinase 1 domain, or both Patients with *FLT3*-ITD–positive AML may benefit from allogeneic hematopoietic-cell transplantation in first complete remission; this beneficial effect may be restricted to patients with a high mutant-to-wild-type ITD ratio Tyrosine kinase inhibitors with activity against FLT3 are in clinical development
KIT	<5	Mostly detected in core-binding factor AML (25–30% of cases) Confers unfavorable prognosis in AML with t(8;21); unfavorable effect in AML with inv(16)/t(16;16) less firmly established Tyrosine kinase inhibitors with activity against KIT are in clinical development
NRAS	Approx. 15	Most frequent in cytogenetically normal AML, AML with inv(16)/t(16;16), and AML with inv(3)/t(3;3) Mutant *RAS* may be predictive of sensitivity to cytarabine
DNMT3A	18–22	Early event in leukemogenesis Incidence increases with older age Most frequent in cytogenetically normal AML (30–37% of cases); associated with *NPM1* and *FLT3*-ITD mutations Moderate adverse effect on outcome; possibly limited to the unfavorable ELN molecular subgroup of cytogenetically normal AML Associated with clonal hematopoiesis in healthy elderly persons
ASXL1	5–17	Early event in leukemogenesis Incidence increases with older age Associated with secondary AML evolving from a myelodysplastic syndrome Frequent concurrent mutations (e.g., in *RUNX1*, *SRSF2*, and *IDH2*) *ASXL1* mutations predictive of inferior outcome Associated with clonal hematopoiesis in healthy elderly persons
IDH1 and *IDH2*	*IDH1*, 7–14; *IDH2*, 8–19	Incidence of the $IDH2^{R140}$ mutation increases with older age *IDH1* and *IDH2* mutations most frequent in cytogenetically normal AML (25–30% of cases); association with *NPM1* mutations (except for $IDH2^{R172}$) Prognostic significance dependent on mutational context (*NPM1* and *FLT3*-ITD status) and on type of mutation ($IDH1^{R132}$ and $IDH2^{R172}$ with possible adverse effect, $IDH2^{R140}$ with possible favorable effect) IDH1 and IDH2 inhibitors are in clinical development *IDH1* and *IDH2* mutations may identify patients who are likely to have a response to pharmacologic BCL2 inhibition
TET2	7–25	Early event in leukemogenesis Incidence increases with older age Mutually exclusive of *IDH1* and *IDH2* mutations Prognostic significance is not finally established; in some studies, *TET2* mutations are associated with inferior survival among patients with cytogenetically normal AML or in the favorable ELN subgroup of cytogenetically normal AML Associated with clonal hematopoiesis in healthy elderly persons
KMT2A-PTD	5	Associated with cytogenetically normal AML (5–11% of cases) and trisomy 11 (up to 90% of cases) Possible moderate adverse effect on outcome, but not an independent prognostic factor
	% *of patients*	
TP53	Approx. 8	Incidence increases with older age *TP53* alterations predominantly detected in AML with complex aberrant karyotype (deletions, mutation, or both in 56–78% of cases) Mutations associated with –5 or del(5q), –7 or del(7q), monosomal karyotype, and genomic complexity, among other factors *TP53* mutations confer very poor outcome

* Approx. denotes approximately, BCL2 B-cell CLL–lymphoma 2 protein, ELN European LeukemiaNet, ITD internal tandem duplication, KIT v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homologue, and PTD partial tandem duplication.

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Current stratification of molecular genetic and cytogenetic alterations, according to ELN recommendations

Table 2. Current Stratification of Molecular Genetic and Cytogenetic Alterations, According to ELN Recommendations.*

Risk Profile	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Biallelic mutated *CEBPA* (normal karyotype)
Intermediate-I†	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse‡
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *GATA2–MECOM (EVI1)* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *KMT2A* rearranged –5 or del(5q); –7; abnl(17p); complex karyotype§

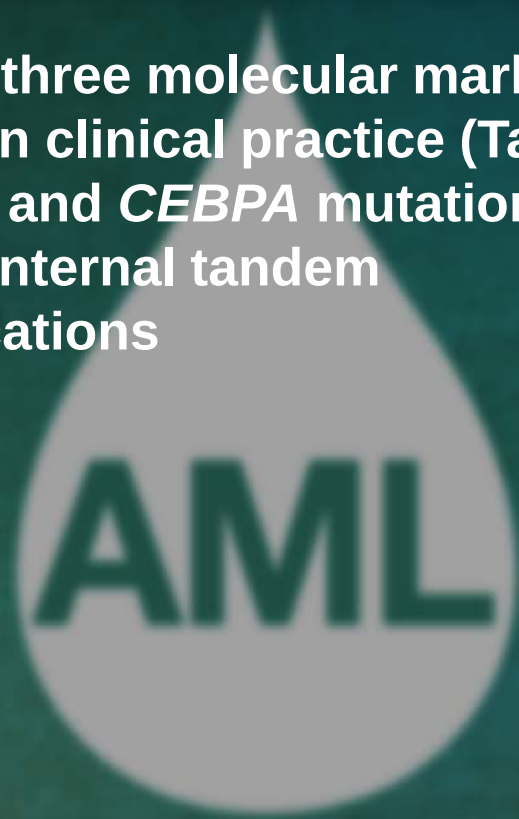
* Three changes were made to the original recommendations reported by Döhner et al.[1] First, cases of AML with mutated *CEBPA* are now restricted to cases with biallelic *CEBPA* mutations.[4] Second, the molecular designation of inv(3)(q21q26.2) or t(3;3)(q21;q26.2) has been changed to *GATA2–MECOM (EVI1)*.[3] Finally, for *MLL*, the official gene symbol *KMT2A* (lysine [K]-specific methyltransferase 2A) has been adopted.

† This category includes all cases of AML with a normal karyotype except for those included in the favorable subgroup; most of these cases are associated with a poor prognosis, but they should be reported separately because of the potential different response to treatment.

‡ Adequate numbers of most abnormalities have not been studied to draw firm conclusions regarding their prognostic significance.

§ A complex karyotype is defined as three or more chromosomal abnormalities in the absence of one of the World Health Organization–designated recurring translocations or inversions — t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), and inv(3)/t(3;3). About two thirds of patients with AML with a complex karyotype have a mutation of *TP53*, a deletion of *TP53*, or both. *TP53* alterations in AML rarely occur outside a complex karyotype.

- Currently three molecular markers are used in clinical practice (Table 2)
  - *NPM1* and *CEBPA* mutations
  - *FLT3* internal tandem duplications



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Current therapy

- General therapeutic strategy in patients with AML has not changed substantially in more than 30 years.

- Induction Therapy:
  - Continuous-infusion cytarabine with an anthracycline → mainstay of induction therapy

- Consolidation Therapy:
  - Conventional chemotherapy as well as allogeneic hematopoietic cell transplantation

- Consolidation with Intensive Chemotherapy:
  - Adults 60 years or younger, preferred regimen is 2 to 4 cycles of intermediate-dose cytarabine (favorable ELN genetic profile and good performance status).

- Allogeneic hematopoietic cell transplantation

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.

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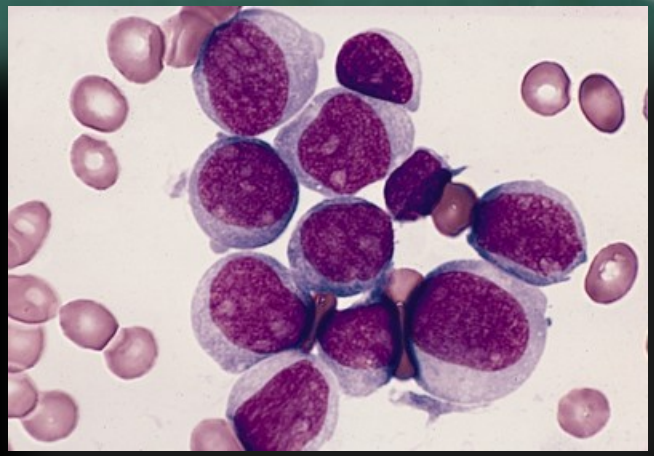
Relapse of AML

- Factors that dictate the risk of relapse:
  - Patient's general health, age, poor health status
  - Biological characteristics of the AML
  - Degree of detectable residual leukemia
  - High-risk cytogenetic and molecular subgroups
  - Therapy-related AML
  - AML after a myelodysplastic syndrome or myeloproliferative neoplasms
  - Hematopoietic cell transplantation after first complete remission



Indications for allogeneic hematopoietic cell transplantation and factors influencing outcome

Table 4. Indications for Allogeneic Hematopoietic-Cell Transplantation and Factors Influencing the Outcome.*

Indications for Allogeneic Hematopoietic-Cell Transplantation
Patients 16 to 60–65 yr
First complete remission (in general excluding ELN favorable-risk AML)
Other high-risk clinical features (e.g., therapy-related AML; secondary AML following a preceding myelodysplastic syndrome or myeloproliferative neoplasm)
Persisting minimal residual disease detectable by means of a quantitative real-time PCR assay or multicolor flow cytometry
Primary induction failure: alternative or investigational regimens to achieve complete remission followed by allografting
Second or higher complete remission; first relapse; satisfactory outcome with delay of hematopoietic-cell transplantation requires prompt attainment of second complete remission without major infectious or other condition that compromises later hematopoietic-cell transplantation
Patients >60–65 yr
Patients younger than 75 yr of age who are physically able to undergo transplantation, with careful consideration of coexisting conditions and patient goals; clinical and biologic indications similar to those for younger patients
Factors Influencing the Outcome of Allogeneic Hematopoietic-Cell Transplantation
Disease status
First complete remission best, with more relapses seen after hematopoietic-cell transplantation in patients with advanced complete remission, primary induction failure, or relapse
Increased risk of relapse if longer time to first complete remission or first relapse within 12 mo
Persisting minimal residual disease
Increased risk of relapse with minimal residual disease before hematopoietic-cell transplantation; uncertain whether added therapy to reduce minimal residual disease improves survival, since minimal residual disease may indicate resistant AML
High-risk genetic factors
Increased risk of relapse with high-risk cytogenetic or molecular phenotype
Risk of relapse may be overcome with allogeneic hematopoietic-cell transplantation in some groups, yet high-risk features still lead to higher rates of relapse after allografting
Age and performance status
Modest effect of age on treatment-related mortality among selected patients
Performance status or Hematopoietic Cell Transplantation Comorbidity Index predictive of treatment-related death
Lower risk of relapse with allogeneic hematopoietic-cell transplantation, yet published results of studies involving older patients with AML are limited and selected
Geriatric or frailty indexes may help to identify candidates for hematopoietic-cell transplantation
Despite clear indications, too few older patients with AML undergo hematopoietic-cell transplantation
Reduced-intensity conditioning regimen
Suitable for older or sicker patients who have major coexisting conditions
Lower rate of early treatment-related death with reduced-intensity conditioning, but similar rate of later treatment-related death due to acute or chronic GVHD
Increased risk of relapse with reduced-intensity conditioning
Similar survival with myeloablative hematopoietic-cell transplantation and hematopoietic-cell transplantation with reduced-intensity conditioning among older patients and those with coexisting conditions
Graft source and graft-versus-leukemia effect
Increased risk of GVHD (particularly chronic) with use of filgrastim-mobilized PBSCs
Similar potency of graft-versus-leukemia effect with sibling or unrelated-donor hematopoietic-cell transplantation
Higher treatment-related mortality, but potent graft-versus-leukemia effect with hematopoietic-cell transplantation with umbilical-cord blood
GVHD (acute, chronic, or both) associated with lower risk of relapse
Added antileukemic therapies (under study)
Cytomegalovirus reactivation–associated immune antileukemic activity
Post-transplantation maintenance therapy
Donor lymphocyte infusions: preemptive, or therapeutic for persisting minimal residual disease or relapse
Antigen-directed T cells, antibodies, or antileukemic vaccines

* Allogeneic hematopoietic-cell transplantation can be performed in patients who are physically able to undergo the therapy and who have no major coexisting conditions. GVHD denotes graft-versus-host disease, PBSCs peripheral-blood stem cells, and PCR polymerase chain reaction.

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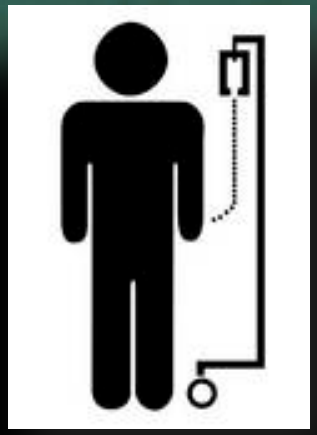
Treatment for patients who are ineligible for intensive therapy

- For older patients, or when transplant is not available, treatments include:
  - Supportive care (including hydroxyurea)
  - Low-dose cytarabine
  - Hypomethylating agents decitabine and azacitidine.

- Factors:
  - Patient's age
  - General health
  - Specific coexisting conditions
  - Disease features
  - Patient's wishes



Selected newer agents in clinical development for the treatment of AML

Table 5. Selected Newer Agents in Clinical Development for the Treatment of AML.*

Drug Class and Action	Agent	Trial-Registration Number†	Reference
Epigenetic modifiers			
Hypomethylating agents	Decitabine (Dacogen)‡		Kantarjian et al.[57]
	Azacitidine (Vidaza)‡		Dombret et al.[58]
	Oral azacitidine (CC-486)¶	NCT01757535	
	Guadecitabine (SGI-110)¶	NCT02348489	Issa et al.[45]
IDH1 inhibitor	AG-120	NCT02074839	
IDH2 inhibitor	AG-221	NCT01915498	Stein et al.[41]
DOT1L inhibitor	EPZ-5676	NCT01684150	
Bromodomain inhibitors	OTX015	NCT01713582	Dombret et al.[42]
	GSK525762	NCT01943851	
LSD1 (also called KDM1A inhibitor)	GSK2879552	NCT02177812	
Histone deacetylase inhibitors	Vorinostat¶	NCT01802333	
	Panobinostat	NCT01242774	
	Pracinostat	NCT01912274	
	Valproic acid¶	NCT00151255	
Tyrosine kinase inhibitors			
FLT3 inhibitors			
First-generation	Midostaurin¶	NCT00651261; NCT01477606	
	Sunitinib	NCT00783653	
	Sorafenib¶	NCT00373373, NCT00893373	Röllig et al.[43]
Second-generation	Quizartinib¶	NCT02039726	
	Crenolanib¶	NCT01657682; NCT02298166	
	ASP2215	NCT02014558	
KIT inhibitors	Dasatinib¶	NCT02013648; NCT01238211	
	Midostaurin	NCT01830361	
Cell-cycle and signaling inhibitors			
MDM2 inhibitor	Idasanutlin (RG-7388)	NCT01773408	
PLK inhibitor	Volasertib¶	NCT01721876	
Aurora kinase inhibitors	Barasertib¶	NCT00952588	
	Alisertib	NCT01779843	
Cyclin-dependent kinase inhibitors	Alvocidib¶	NCT01413880	
	Palbociclib	NCT02310243	
Phosphatidylinositol 3-kinase inhibitor	Rigosertib	NCT01926587	
PIM kinase inhibitor	LGH447	NCT02078609	
Hedgehog-pathway inhibitors	Vismodegib	NCT01880437	
	PF-04449913	NCT01546038	
mTor inhibitors	Everolimus	NCT01154439	
	Temsirolimus	NCT01611116	
Nuclear export inhibitor			
XPO1 (also called CRM1) inhibitor	Selinexor¶ (KPT-330)	NCT02088541	Etchin et al.[44]
Antibody-based therapies			
Antibody–drug conjugates	Gemtuzumab ozogamicin (anti-CD33 and calicheamicin)‡	NCT00893399	
	SGN-CD33A (anti-CD33 and pyrrolobenzodiazepine dimer)	NCT01902329	
Bispecific antibodies	AMG 330 (anti-CD33 and CD3; bispecific T-cell engager)	NCT02520427	
	MGD006 (anti-CD123 and CD3; dual-affinity retargeting molecule)	NCT02152956	
Stem-cell targeting	Anti-CD123 antibody (CSL362)	NCT01632852	
	SL-401 (diphtheria toxin interleukin-3 fusion protein against CD123)	NCT02270463	
CXCR4 targeting	BMS-936564	NCT02305563	
Immune checkpoint blockade	Ipilimumab	NCT01757639; NCT01822509	
Chimeric antigen receptor T cells	CART-123 (anti-CD123 chimeric antigen receptor T cells)	NCT02159495	
Cytotoxic agents			
Quinolone derivative	Vosaroxin¶	NCT01191801	Ravandi et al.[46]
New drug formulation	CPX-351¶	NCT01696084	Lancet et al.[47]
Nucleoside analogues	Sapacitabine¶	NCT01303796	
	Clofarabine¶	ISRCTN 11036523	
	Cladribine¶	NCT02044796; NCT02115295	
Other agents			
B-cell CLL–lymphoma 2 protein inhibitor	Venetoclax (ABT-199/GDC-0199)	NCT01994837	
Immunomodulatory drug	Lenalidomide¶	NTR4376	
Aminopeptidase inhibitor	Tosedostat	NCT00780598; NTR2477	
Retinoic acid	All-*trans* retinoic acid¶	NCT00131242; ISRCTN88373119	
CXCR4 antagonist	Plerixafor	NCT00906945	
E-selectin antagonist	GMI-1271	NCT02306291	
Homoharringtonine derivative	Omacetaxine¶	ChiCTR-TRC-06000054	

* CRM1 denotes chromosome region maintenance 1, CXCR4 chemokine (C-X-C motif) receptor 4, KDM1A lysine (K)-specific demethylase 1A, LSD1 lysine-specific demethylase 1, E3 ubiquitin protein ligase, mTOR mechanistic target of rapamycin, PI3K phosphatidylinositol 3-kinase, PIM1 oncogene PIM1, PLK polo-like kinase, and XPO1 exportin 1.
† Chinese Clinical Trial Registry numbers begin with ChiCTR-TRC, ClinicalTrials.gov numbers begin with NCT, Current Controlled Trial numbers begin with ISRCTN, and Netherlands Trial Register numbers begin with NTR.
‡ This agent is approved by the EMA, but not by the FDA, for patients 65 years of age or older who have newly diagnosed de novo 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.
¶ This agent is under investigation in randomized, phase 2 or phase 3 clinical trials.
‖ In 2000, this drug was granted accelerated approval by the FDA for the use of this treatment as a single agent in patients older than 60 years of age who had AML in first relapse and who did not meet criteria for intensive treatment. In 2010, it was withdrawn from the U.S. market because of a negative postapproval study (Southwest Oncology Group trial S0106).[48]

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

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