BMJ Best Practice

Acute myeloid leukemia

Straight to the point of care

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Summary

Acute myeloid leukemia (AML) is a life-threatening hematologic malignancy that predominantly occurs in older adults.

Many subtypes exist; acute promyelocytic leukemia (APL) may be associated with life-threatening coagulopathy.

Characteristically, abnormal myeloid blasts are present in the bone marrow (and in some cases the peripheral blood and extramedullary tissue) and normal hematopoiesis is reduced.

Workup includes bone marrow aspirate and trephine biopsy. Cytogenetic analysis and molecular genetic testing can inform diagnosis, prognosis, and treatment.

Treatment includes chemotherapy and/or targeted therapies in two main phases: induction and consolidation. Hematopoietic stem cell transplantation and/or maintenance therapy may be used in select patients.

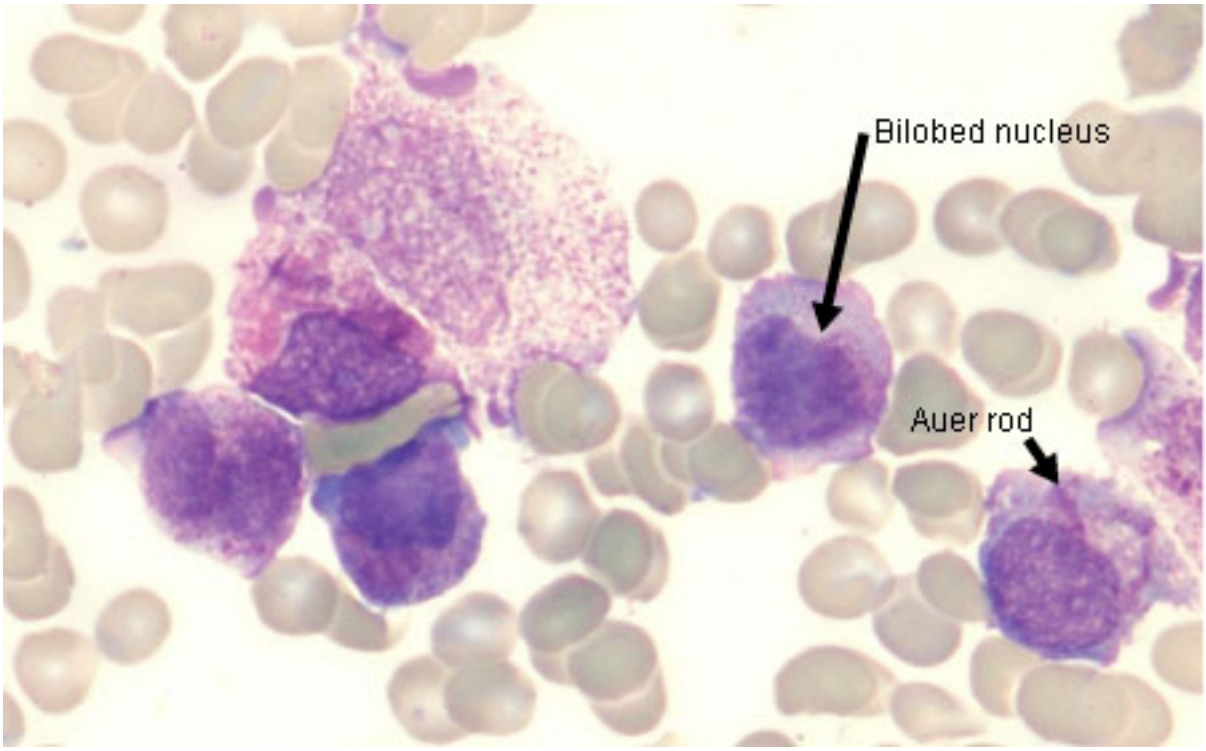
Definition

Acute myeloid leukaemia (AML) is a life-threatening hematologic malignancy caused by clonal expansion of myeloid blasts in the bone marrow, peripheral blood, and/or extramedullary tissues.

AML is a highly heterogeneous disease that can be classified into subtypes based on blast count (in the bone marrow or peripheral blood) and the presence of genetic abnormalities.[1] [2] See Classification .

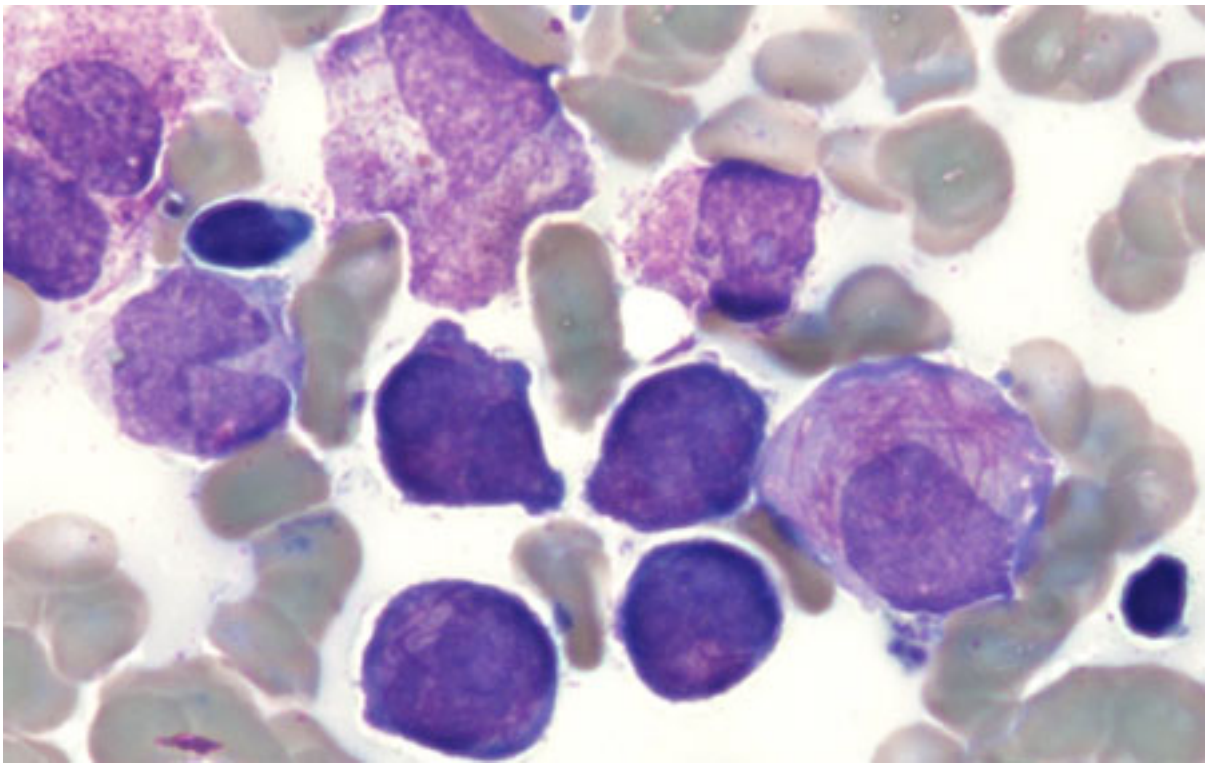
AML may arise de novo, or secondary to a prior treatment, preexisting hematologic disorder (e.g., myelodysplastic syndrome), or germline predisposition.[1] [2]

The acute promyelocytic leukemia (APL) subtype of AML is characterized by a distinctive cytomorphology (hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods), a tendency for coagulopathy (due to thrombocytopenia and disseminated intravascular coagulation), and a specific t(15;17)(q22;q12) cytogenetic abnormality resulting in the PML::RARA fusion gene.



Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods

From the collection of Drs K. Raj and P. Mehta; used with patient consent



Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes, some with bundles of Auer rods

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Epidemiology

In 2024, there will be an estimated 20,800 new cases of AML and 11,220 deaths related to AML in the US.[5]

AML is more common in older adults.[5] In the US, approximately 61% of cases are diagnosed in people ages 65 years or over (2017-2021 data).[5] The median age at diagnosis is 69 years.[5]

AML is more common in men (male to female ratio is approximately 1.5:1).[5]

Etiology

The exact underlying cause of AML is unknown. However, a number of risk factors have been identified.

Exposure to radiation, benzene, or alkylating agents

Cytogenetic abnormalities involving chromosomes 5 and 7 are associated with exposure to radiation, benzene, and alkylating agents (e.g., cyclophosphamide, melphalan, mechlorethamine).[6] [7] AML caused by alkylating agents usually occurs after a latency period of 5-10 years.[6] [7] [8] [9][10]

Treatment with topoisomerase II inhibitors

Cytogenetic abnormalities involving chromosome 11q23 (KMT2A gene) are associated with treatment with topoisomerase II inhibitors (e.g., etoposide, teniposide, and anthracyclines such as doxorubicin). Other cytogenetic abnormalities associated with these agents include chromosomal rearrangements such as t(15;17)(q22;q12), which results in acute promyelocytic leukemia (APL, a subtype of AML), and t(8;21). AML caused by topoisomerase II inhibitors usually occurs after a latency period of 1-5 years.[6] [7] [10] [11]

Previous hematologic disorders

The incidence of AML is increased in patients with previous hematologic disorders, including: aplastic anemia (particularly in the presence of monosomy 7); paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome (MDS), chronic myeloid leukemia, chronic myelomonocytic leukemia, myeloproliferative neoplasms (polycythemia vera, essential thrombocythemia, primary myelofibrosis).[12] [13] [14] [15] [16]

Inherited genetic conditions

Including Bloom syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia, Kostmann syndrome, Li-Fraumeni syndrome, neurofibromatosis, and bone marrow failure syndromes (e.g., Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, severe congenital neutropenia, and Diamond-Blackfan anemia).[1] [2] [17] [18] [19] [20] [21] [22] [23]

Constitutional chromosomal abnormalities

Down syndrome (trisomy 21), Klinefelter syndrome (XXY), and Patau syndrome (trisomy 13) are associated with increased risk of AML.[24] [25] [26] In those with Down syndrome who develop AML, additional unbalanced chromosomal abnormalities such as dup(1q), del(6q), del(7p), dup(7q), +8, +11, and del(16q) are distinctive and may contribute to the pathogenesis.[27]

Environmental exposures

For example, smoking, hair dyes, alcohol, pesticides, diesel fuel, fertilizers, and infectious agents.[28] [29] [30] [31] [32] [33] [34] An increased risk of AML has been reported among abattoir workers, veterinarians, and meat packagers.[35] [36]

Cytogenetic abnormalities

Patients with AML may have a normal karyotype, or cytogenetic abnormalities that are either unbalanced (e.g., due to loss or gain of chromosomes or parts of a chromosome such as 5q, 7q, 11q, 13q, 12p, 17p) or balanced (e.g., due to chromosomal rearrangements affecting genes such as KMT2A at 11q23, RUNX1 at 21q22, RARA at 17q21, CBF-beta at 16q22).[1] [2] [23] Normal karyotype is frequent in de novo AML or MDS.[7]

APL (a subtype of AML) is characterized by a t(15;17)(q22;q12) balanced chromosomal rearrangement, which results in the PML::RARA fusion gene.[23] [37]

Genetic mutations

Patients with AML may have genetic mutations, including TP53, c-KIT, FLT3 (ITD and TKD), CEBPA (basic leucine zipper [bZIP] domain), NPM1, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and ZRSR2.[23] [38]

Genetic abnormalities have been incorporated into classification systems to define specific subtypes of AML, and some have prognostic implications that can guide risk stratification (e.g., TP53 mutation is an adverse-risk genetic abnormality).

See Classification and Criteria .

Pathophysiology

In AML, genetic abnormalities in hematopoietic precursor cells result in the accumulation of myeloid blasts unable to differentiate into mature neutrophils, red blood cells, or platelets. This can lead to bone marrow failure (manifest as anemia, neutropenia, and/or thrombocytopenia), the commonest cause of death in AML. As there is little correlation between blast percentage and cytopenias, secretion of inhibitory substances such as chemokines (rather than physical replacement of normal marrow by the myeloid blasts) is thought to lead to suppression of normal hematopoiesis.[39]

Anemia may lead to pallor, fatigue, dizziness, palpitations, and dyspnoea.

Neutropenia may lead to severe infections by endogenous aerobic gram-positive and gram-negative bacteria, and *Candida* and *Aspergillus* species.[40] Increasing neutrophil counts is a useful predictor of treatment response in AML.

Thrombocytopenia may lead to mucosal bleeding, bruising, ecchymoses, and petechiae.

Leukemic infiltration of the lungs, spleen, liver, lymph nodes, gums, skin, testicles, or central nervous system (CNS) may occur, usually when the white blood cell count (WBC) is >50,000/microliter (>50 × 10^9/L), and blasts are monocytic or express CD56 antigen on their surface.[41]

Leukostasis (symptomatic hyperleukocytosis), a life-threatening complication of AML, may occur if WBC count is extremely elevated (>100,000/microliter [>100 × 10^9/L]). Symptoms of leukostasis include respiratory

distress and altered mental status, caused by leukemia cells impairing microvascular perfusion in pulmonary and CNS tissue, respectively.

Classification

The 5th edition of the World Health Organization (WHO) classification of hematolymphoid tumors: myeloid and histiocytic/dendritic neoplasms[1]

The WHO classification classifies acute myeloid leukemia (AML) based on the presence of AML-defining genetic abnormalities, and by differentiation (i.e., for AML cases lacking defining genetic abnormalities).

AML with defining genetic abnormalities*

- Acute promyelocytic leukemia (APL) with PML::RARA fusion
- AML with RUNX1::RUNX1T1 fusion
- AML with CBFB::MYH11 fusion
- AML with DEK::NUP214 fusion
- AML with RBM15::MRTFA fusion
- AML with BCR::ABL1 fusion
- AML with KMT2A rearrangement
- AML with MECOM rearrangement
- AML with NUP98 rearrangement
- AML with NPM1 mutation
- AML with CEBPA mutation
- AML myelodysplasia-related (defined by cytogenetic abnormalities or somatic mutations**)
- AML with other defined genetic alterations.

*A blast threshold is not required except for "AML with BCR::ABL1 fusion" and "AML with CEBPA mutation," which require ≥20% blasts for diagnosis.

**The presence of 1 or more "AML myelodysplasia-related" defining cytogenetic abnormalities or somatic mutations, and/or a history of myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasms (MPNs; e.g., chronic myelomonocytic leukemia), is required for diagnosing "AML myelodysplasia-related". Defining cytogenetic abnormalities include: complex karyotype (≥3 abnormalities); 5q deletion or loss of 5q due to unbalanced translocation; monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation; 11q deletion; 12p deletion or loss of 12p due to unbalanced translocation; monosomy 13 or 13q deletion; 17p deletion or loss of 17p due to unbalanced translocation; isochromosome 17q; and idic(X)(q13). Defining somatic mutations include: ASXL1; BCOR; EZH2; SF3B1; SRSF2; STAG2; U2AF1; and ZRSR2.

AML defined by differentiation

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute basophilic leukemia
- Acute myelomonocytic leukemia
- Acute monocytic leukemia
- Acute erythroid leukemia

- Acute megakaryoblastic leukemia.

International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias[2]

The ICC classification of acute myeloid leukemia (AML) is hierarchical, whereby AML-defining recurrent genetic abnormalities are prioritized. Diagnostic qualifiers (including prior therapy, antecedent myeloid neoplasms, and germline predisposition) are appended to diagnostic classifications for specific diagnosis.

AML hierarchical classification

- Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/PML::RARA (≥10% blasts required)
- APL with other RARA rearrangements (e.g., IRF2BP2::RARA; NPM1::RARA; ZBTB16::RARA; STAT5B::RARA; STAT3::RARA) (≥10% blasts required)
- AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 (≥10% blasts required)
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 (≥10% blasts required)
- AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A (≥10% blasts required)
- AML with other KMT2A rearrangements (e.g., AFF1::KMT2A; AFDN::KMT2A; MLLT10::KMT2A; TET1::KMT2A; KMT2A::ELL; KMT2A::MLLT1) (≥10% blasts required)
- AML with t(6;9)(p22.3;q34.1)/DEK::NUP214 (≥10% blasts required)
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2; MECOM(EVI1) (≥10% blasts required)
- AML with other MECOM rearrangements (e.g., MECOM::MYC; ETV6::MECOM; MECOM::RUNX1) (≥10% blasts required)
- AML with other rare recurring translocations (≥10% blasts required)
- AML with t(9;22)(q34.1;q11.2)/BCR::ABL1 (≥20% blasts required)
- AML with mutated NPM1 (≥10% blasts required)
- AML with in-frame basic leucine zipper (bZIP) CEBPA mutations (≥10% blasts required)
- AML and myelodysplastic syndrome (MDS)/AML with mutated TP53 (variant allele fraction of ≥10%) (10% to 19% blasts required for MDS/AML; ≥20% blasts required for AML)
- AML and MDS/AML with myelodysplasia-related gene mutations* (10% to 19% blasts required for MDS/AML; ≥20% blasts required for AML)
- AML with myelodysplasia-related cytogenetic abnormalities** (10% to 19% blasts required for MDS/AML; ≥20% blasts required for AML)
- AML not otherwise specified (NOS) (10% to 19% blasts required for MDS/AML; ≥20% blasts required for AML).

*Defined by gene mutations including: ASXL1; BCOR; EZH2; RUNX1; SF3B1; SRSF2; STAG2; U2AF1; and ZRSR2.

**Defined by cytogenetic abnormalities including: complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities); del(5q)/t(5q)/add(5q); -7/del(7q); +8; del(12p)/t(12p)/add(12p); i(17q); -17/add(17p)/del(17p); del(20q); and idic(X)(q13) clonal abnormalities.

Diagnostic qualifiers for specific AML or MDS/AML diagnosis

- Therapy-related (prior chemotherapy, radiation therapy, immune interventions)
- Progressing from MDS (MDS should be confirmed by standard diagnostics)
- Progressing from MDS/myeloproliferative neoplasms (MPN) (MDS/MPN should be confirmed by standard diagnostics)

- Germline predisposition.

Case history

Case history #1

A 58-year-old man presents to his primary care physician with increasing tiredness, accompanied by bruising on his legs. He also complains of aching bones. He has no recent history of illness. On examination, he is pyrexial and pale, has bony tenderness over the sternum and tibia, and has petechiae on his legs. There are no palpable lymph nodes. He has crepitations at the left base. The liver and spleen are not palpable.

Other presentations

Other presentations include dizziness, palpitations, and dyspnea, due to anemia. Severe infection and fever may be present due to neutropenia. Mucosal bleeding and ecchymoses may be present due to thrombocytopenia.

Coagulopathies are reasonably common with AML, and disseminated intravascular coagulation (DIC) is common with acute promyelocytic leukemia (APL).

Patients may present with features of extramedullary infiltration, such as hepatosplenomegaly or lymphadenopathy. Less commonly, patients present with gingival enlargement, testicular masses, skin chloromas, cutaneous ulcers, and/or symptoms of meningeal leukemic infiltration (e.g., headache, confusion).

Pulmonary symptoms (e.g., dyspnea) and gastrointestinal symptoms (e.g., severe abdominal pain) due to leukemic infiltration or infection may be present.

An elevated white blood cell count >100,000/microliter (>100 × 10^9/L; hyperleukocytosis) occurs in approximately 5% to 20% of patients with AML, predisposing them to complications such as tumor lysis syndrome, central nervous system involvement, and leukostasis (symptomatic hyperleukocytosis; symptoms include respiratory distress and altered mental status).[3] [4] These are medical emergencies and require immediate treatment.

Approach

AML is a highly heterogeneous disease. The diagnosis of AML requires a multifaceted approach that includes medical history, clinical assessment, and pathologic assessment (including bone marrow and/or peripheral blood).

As AML and acute lymphoblastic leukemia (ALL) are often clinically indistinguishable, confirmation of a myeloid origin of the leukemic cells by immunophenotyping is essential. This may be done on peripheral blood before confirmation from the bone marrow.

History

In all patients, a complete medical history (including family history, if known) is important for diagnosis.

Risk of AML is increased in certain patient groups, including those with a prior history of hematologic disease; previous treatment with chemotherapy; genetic disorders (e.g., inherited chromosomal fragility disorders; bone marrow failure syndromes; chromosomal abnormalities [e.g., trisomy disorders]); age over 65 years; smokers; and prior exposure to radiation or benzene.

The clinical features in the recent history that suggest a diagnosis of AML are related to cytopenia, and include increased fatigue, dizziness, palpitations, fevers, infections, mucosal bleeding (from the gums or nose or menorrhagia in females), gingival enlargement, petechial rash, and bone pain. There may be a history of a skin rash or masses (e.g., skin chloromas). Pulmonary symptoms (e.g., dyspnea) and gastrointestinal symptoms (e.g., severe abdominal pain) due to leukemic infiltration or infection may be present. Neurologic symptoms (e.g., headache, confusion) due to meningeal leukemic infiltration may be present.

Physical examination

Findings may include pallor, ecchymoses, and petechiae. Features of extramedullary leukemic infiltration may be evident (e.g., hepatosplenomegaly, lymphadenopathy, skin and testicular masses). Dental abscess, nasopharyngeal infections, chest signs, or perianal infections may be apparent. Within the skin, leukemia cutis infiltration may be present, and the presence of cutaneous ulcers (e.g., Sweet syndrome or pyoderma gangrenosum) may indicate underlying malignancy. Rarely, an acute abdomen may occur.

Initial laboratory tests

All patients with suspected AML should have the following baseline tests:[23] [38]

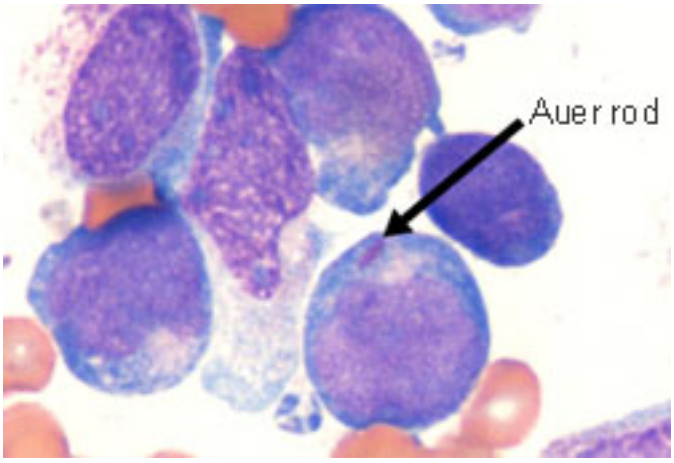
- Complete blood count with differential
- Peripheral blood smear
- Comprehensive metabolic panel (serum electrolytes, renal and liver profiles, serum uric acid, and serum lactate dehydrogenase [LDH])
- Coagulation panel (prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen, and D-dimers).

Laboratory findings

Most patients with AML (including those with acute promyelocytic leukemia [APL], a subtype of AML) have anemia, neutropenia, and/or thrombocytopenia, but blood count can vary greatly.

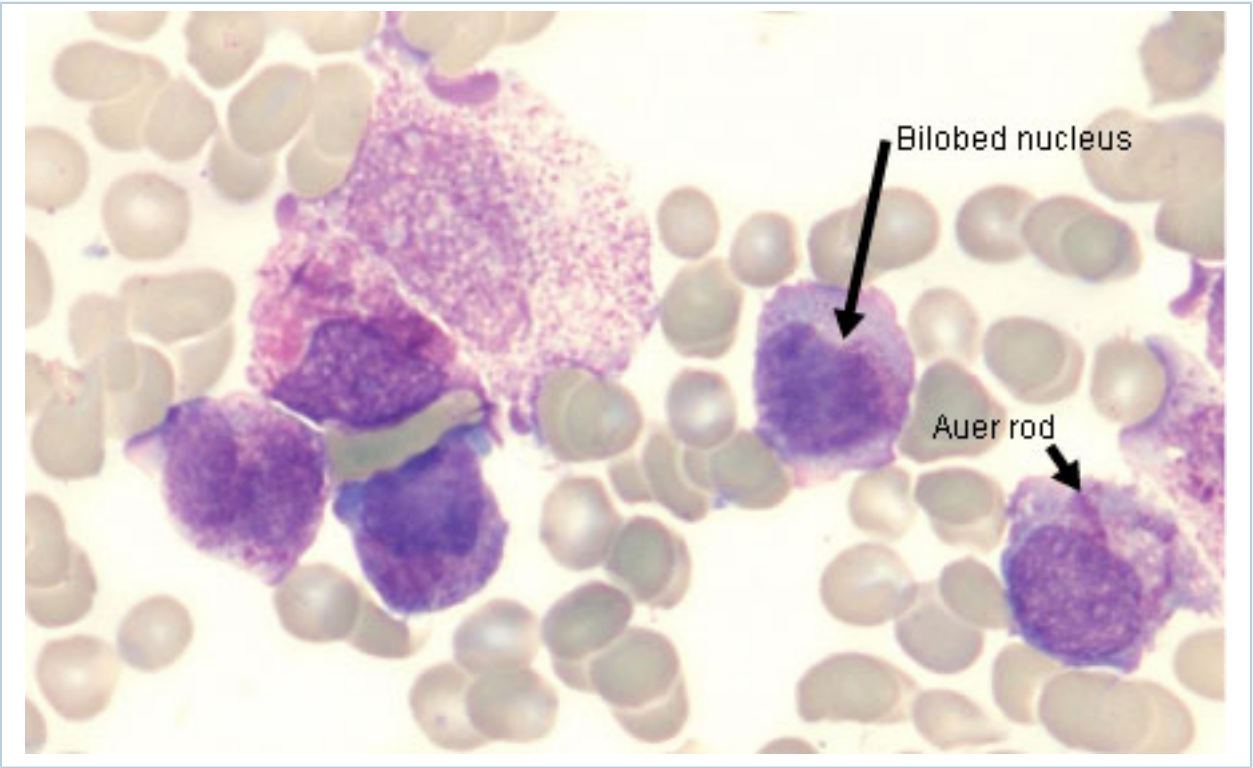
An elevated white blood cell (WBC) count >100,000/microliter (>100 × 10^9/L; hyperleukocytosis) occurs in approximately 5% to 20% of patients with AML, predisposing them to complications such as tumor lysis syndrome (TLS), central nervous system (CNS) involvement, and leukostasis (symptomatic hyperleukocytosis; symptoms include respiratory distress and altered mental status).[3] [4] These are medical emergencies and require immediate treatment. Despite the elevation in WBC count, many patients have severe neutropenia (<500 granulocytes/microliter [<0.5 × 10^9 granulocytes/L]), thus placing them at high risk for serious infections.

In AML, the blood film may show myeloid blasts characterized by Auer rods or Phi bodies. In APL, the blood film will typically show hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods (as well as myeloid blasts). A variant of APL is characterized by hypogranular promyelocytes (absence of Auer rods), but is less common.



Peripheral blood film of a patient with acute myeloid leukemia with maturation showing myeloid blasts with an Auer rod

From the collection of Drs K. Raj and P. Mehta; used with patient consent



Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods

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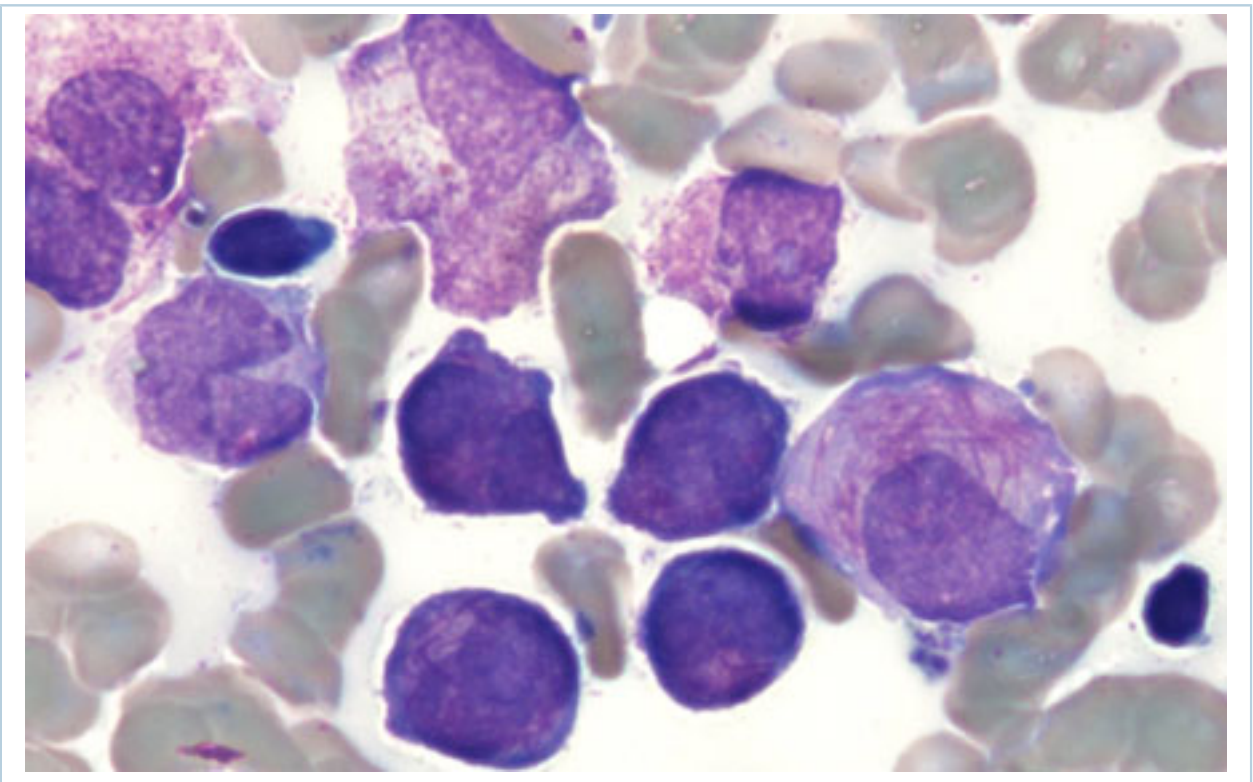

Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes, some with bundles of Auer rods

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Hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, and elevated serum LDH may occur due to TLS, particularly during treatment and if WBC count (tumor burden) is high. This can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. TLS is an oncologic emergency.[51] See Tumor lysis syndrome .

Hypercalcemia may occur due to bony infiltration or ectopic release of a parathyroid hormone-like substance.

The coagulation tests PT and aPTT may be mildly prolonged with normal fibrinogen and D-dimer. If these tests are abnormal (prolonged PT and aPTT, decreased fibrinogen, and/or elevated D-dimer), disseminated intravascular coagulation (DIC) should be suspected and an urgent referral is warranted to commence treatment. Refer to the International Society on Thrombosis and Haemostasis (ISTH) scoring system for DIC.[52] DIC occurs most frequently in APL.

Bone marrow evaluation

The diagnostic workup includes bone marrow aspirate and trephine biopsy analyses. The following tests should be performed.[23] [38]

- Cytomorphology assessment: demonstrates bone marrow hypercellularity and infiltration by myeloid blasts (as well as hypergranular or hypogranular [less common] promyelocytes, in APL). Blast cells are negative for terminal deoxynucleotidyl transferase (TdT) and stain positive for myeloperoxidase.
- Immunophenotyping (using flow cytometry on bone marrow aspirate): identifies cell surface and cytoplasmic markers of myeloid blasts (e.g., CD34, CD33) and establishes lineage.
- Immunohistochemistry (using core biopsy specimen): may be used instead of flow cytometry for immunophenotyping if bone marrow aspirate is unavailable or of poor quality.

If bone marrow specimens are inadequate or unattainable, then peripheral blood can be used for pathologic assessment provided there are sufficient numbers of circulating blasts.

Genetic testing

Cytogenetic analysis (karyotyping and fluorescence in situ hybridization [FISH]) and molecular genetic testing should be performed to inform the diagnosis, prognosis, and treatment.[23] [38]

In AML, the following genetic abnormalities should be investigated due to their association with specific prognoses and treatment targets: RUNX1::RUNX1T1; CBFB::MYH11; MLLT3::KMT2A (or other KMT2A rearrangements); DEK::NUP214; BCR::ABL1; KAT6A::CREBBP; c-KIT; NPM1; FLT3 (ITD and TKD); IDH1; IDH2; CEBPA (basic leucine zipper [bZIP] domain); -5 or del(5q); -7; -17/abn(17p); GATA2; MECOM(EVI1); ASXL1; BCOR; EZH2; RUNX1; SF3B1; SRSF2; STAG2; U2AF1; ZRSR2; and TP53.[23] [38] See Criteria .

Next-generation sequencing panels and multiplex gene panels are recommended for mutational analysis.[23]

APL is characterized by the PML::RARA fusion gene caused by a t(15;17)(q22;q12) balanced chromosomal rearrangement.[23][37]

Definitive diagnosis and classification

AML can be diagnosed and classified according to the latest World Health Organization (WHO) classification (5th Edition, 2022) or the International Consensus Classification (ICC).[1] [2] In both classifications, bone marrow evaluation, genetic testing, and predisposing factors (e.g., prior therapy; antecedent myeloid neoplasms; inherited genetic mutations or syndrome) are required to make a definitive AML diagnosis. However, the classifications differ in how specific subtypes of AML are categorized, and in the blast count threshold requirements for certain subtypes of AML.

The 5th edition of the WHO Classification of Haematolymphoid Tumours no longer requires a blast count threshold of ≥20% for the diagnosis of AML with defining genetic abnormalities (except for BCR::ABL1 fusion and CEBPA mutation).[1] In the ICC classification, however, a blast count of ≥10% is required for diagnosing AML with defining genetic abnormalities (except for BCR::ABL1 fusion where a blast count of ≥20% is required).[2]

See Classification section for further details.

Additional tests

Human leukocyte antigen (HLA) typing should be performed in all patients being considered for an allogeneic stem cell transplant.

CNS imaging (e.g., brain MRI or CT scan) should be carried out in patients presenting with neurologic signs or symptoms suggesting CNS involvement.[23] [38] A diagnostic lumbar puncture should be carried out if CNS imaging does not identify CNS bleeding, meningeal disease, and a mass lesion, and neurologic signs and symptoms persist. A single dose of intrathecal chemotherapy (e.g., methotrexate or cytarabine) may be considered at the time of diagnostic lumbar puncture. Coagulopathy should be managed before lumbar puncture, particularly in patients with APL.

An FDG-PET/CT scan should be considered in patients with suspected extramedullary disease.[38]

Cardiac function assessment (echocardiogram or multigated acquisition scan) should be performed in patients:

- with a history or symptoms of cardiac disease,
- with prior exposure to cardiotoxic drugs or radiation therapy to the thorax, or
- of older age.[23] [38]

Findings may guide treatment.

Chest x-ray may be performed to identify pneumonia, mediastinal masses, pulmonary infiltrates, or cardiomegaly.

History and exam

Key diagnostic factors

pallor (common)

- Common finding on physical examination due to anemia.

ecchymoses or petechiae (common)

- Common finding on physical examination due to thrombocytopenia.

Other diagnostic factors

fatigue (common)

- Many patients have fatigue. Caused by bone marrow infiltration, anemia, or the action of associated systemic inflammatory cytokines.

dizziness (common)

- Many patients have dizziness. Caused by bone marrow infiltration, anemia, or the action of associated systemic inflammatory cytokines.

palpitations (common)

- Many patients have palpitations. Caused by bone marrow infiltration, anemia, or the action of associated systemic inflammatory cytokines.

dyspnea (common)

- Many patients have dyspnea. Caused by bone marrow infiltration, anemia, pulmonary infection, or the action of associated systemic inflammatory cytokines.

fever and infections (common)

- Many patients present with fever and/or other signs and symptoms of infection due to neutropenia.
- Notable sites of infection include mouth, teeth (dental abscess), nasopharynx, pulmonary, and perianal.[53] [54]

lymphadenopathy (common)

- Common finding on physical examination due to extramedullary leukemic infiltration.
- Enlarged lymph nodes are frequently the initial cause for seeking medical attention by the patient.

hepatosplenomegaly (common)

- Common finding on physical examination due to extramedullary leukemic infiltration.

mucosal bleeding (common)

- Bleeding from the gums or nose or menorrhagia in females may be due to associated thrombocytopenia.

skin and/or testicular mass (uncommon)

- May be present due to extramedullary leukemic infiltration.

skin infiltration (uncommon)

- Leukemia cutis may be present.
- The presence of cutaneous ulcers (e.g., Sweet syndrome or pyoderma gangrenosum) may indicate underlying malignancy.
- Sweet syndrome is characterized by fever, leukocytosis (symptomatic hyperleukocytosis; symptoms include respiratory distress and altered mental status), and tender, erythematous, well-demarcated papules and plaques on skin, which show dense neutrophilic infiltrates.
- Pyoderma gangrenosum is characterized by presence of ulcers on leg, or less commonly the hands. Develops as a consequence of immune dysfunction and may be associated with AML.

gingival enlargement (uncommon)

- Consequence of leukemic infiltration; gingivae bleed easily due to associated thrombocytopenia.

bone pain (uncommon)

- Related to bone marrow infiltration by blast cells.

skin chloromas (uncommon)

- May be present due to extramedullary leukemic infiltration.

abdominal pain (uncommon)

- Severe abdominal pain may be present due to leukemic infiltration or infection.
- Acute abdomen is rarely noted on physical exam.

neurologic symptoms (e.g., headache, confusion) (uncommon)

- May be present due to meningeal leukemic infiltration.

Risk factors

Strong

age over 65 years

- AML is more common in older adults.[5] In the US, approximately 61% of cases are diagnosed in people ages 65 years or over (2017-2021 data).[5] The median age at diagnosis is 69 years in the US.[5]

previous treatment with chemotherapy

- Alkylating agents (e.g., cyclophosphamide, melphalan, mechlorethamine) predispose to AML (latency of 5-10 years), with associated chromosome 5 and 7 abnormalities.[6] [7] [10]
- Topoisomerase II inhibitors (e.g., etoposide, teniposide, and anthracyclines such as doxorubicin) predispose to AML (latency of 1-5 years), with associated chromosome 11q23 (KMT2A gene) abnormalities.[6] [7] [10][11] Other cytogenetic abnormalities associated with these agents include t(15;17)(q22;q12), which results in acute promyelocytic leukemia (APL, a subtype of AML), and t(8;21).

previous hematologic disorders

- The incidence of AML is increased in patients with previous hematologic disorders, including: aplastic anemia (particularly in the presence of monosomy 7); paroxysmal nocturnal hemoglobinuria;

myelodysplastic syndrome (which evolves to AML in approximately 30% of patients); chronic myeloid leukemia (may progress to myeloid blast crisis); chronic myelomonocytic leukemia; and myeloproliferative neoplasms (polycythemia vera, essential thrombocythemia, primary myelofibrosis).[12] [13] [14] [15] [16]

inherited genetic conditions

- Inherited chromosomal fragility disorders and bone marrow failure syndromes are associated with an increased risk for AML.[17] [18] [19]
- These include Bloom syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia, Kostmann syndrome, Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, severe congenital neutropenia, and Diamond-Blackfan anemia.[1] [2][17] [18] [19] [20] [21] [22] [23]
- Familial AML may be due to germline mutations of the tumor suppressor gene TP53 (Li-Fraumeni syndrome) or deletion at the carboxy terminus of CEBPA, which encodes a granulocytic differentiation factor.[42] [43]
- Neurofibromatosis due to abnormalities of the tumor suppressor gene NF1 at chromosome 17q11.2 predisposes to AML, usually in the second decade of life.[44]

constitutional chromosomal abnormalities

- Down syndrome (trisomy 21), Klinefelter syndrome (XXY), and Patau syndrome (trisomy 13) are associated with increased risk of AML.[24] [25] [26]
- In those with Down syndrome who develop AML, additional unbalanced chromosomal abnormalities such as dup(1q), del(6q), del(7p), dup(7q), +8, +11, and del(16q) are distinctive and may contribute to the pathogenesis.[27]

radiation exposure

- Historically, survivors of the atomic bombing of Hiroshima and Nagasaki had an increased incidence of myelodysplastic syndromes and AML.[8] This incidence was highest in those under 20 years of age at the time of exposure.[45]
- Radiation therapy, particularly in combination with alkylating agents (e.g., cyclophosphamide, melphalan), also predisposes to AML.[6] [7] [46]

benzene exposure

- A 2- to 10-fold increase in leukemia, predominantly AML, occurs in painters, printers, petroleum refinery workers, and chemical, rubber, and shoe manufacturing workers exposed to benzene.[47]
- Additional benzene exposure occurs due to smoking or from unleaded gasoline vapors.[48] The risk of leukemogenesis is proportionate to the level of exposure.[49]
- Benzene exposure is associated with a depletion of CD4+ lymphocytes.[50]

Weak

environmental exposures

- Smoking has been found to be associated with the development of AML.[28] [29]
- Use of hair dyes and alcohol consumption has also been linked with AML, but the evidence is weak and inconsistent.[30] [31] [32] [33]
- A 1.1- to 1.4-fold increased risk of AML occurs in agricultural workers. This has been attributed to pesticides, diesel fuel, fertilizers, and infectious agents.[34] Abattoir workers, veterinarians, and meat packagers also have an increased risk.[35] [36]

male sex

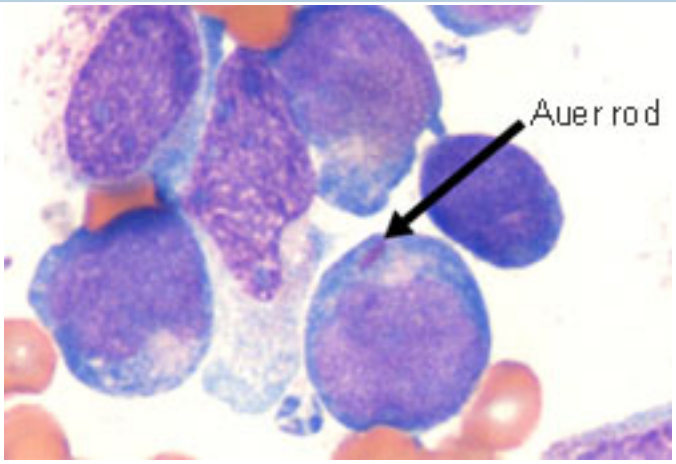
- AML is more common in men, with a male to female ratio of approximately 1.5:1.[5]

Tests

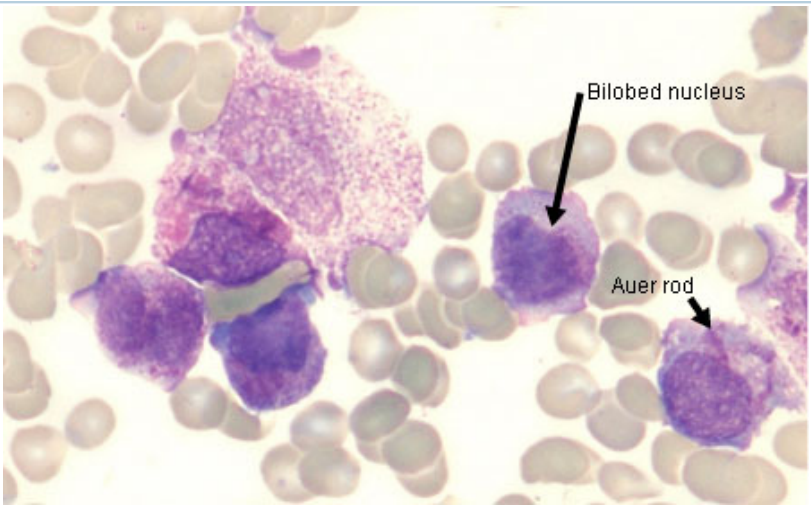
1st test to order

Test	Result
CBC with differential • Most patients with AML or acute promyelocytic leukemia (APL) have anemia, neutropenia, and/or thrombocytopenia, but blood count can vary greatly. • An elevated white blood cell (WBC) count >100,000/microliter (>100 × 10^9/L; hyperleukocytosis) occurs in approximately 5% to 20% of patients with AML, predisposing them to complications such as tumor lysis syndrome, central nervous system involvement, and leukostasis (symptomatic hyperleukocytosis; symptoms include respiratory distress and altered mental status).[3] [4] These are medical emergencies and require immediate treatment. Despite the elevation in WBC count, many patients have severe neutropenia (<500 granulocytes/microliter [<0.5 × 10^9 granulocytes/L]), thus placing them at high risk for serious infections.	**anemia, macrocytosis, leukocytosis, neutropenia, and/or thrombocytopenia**
peripheral blood smear • Blasts are immature cells and are not normally seen in the peripheral blood. • AML is characterized by myeloid blasts with Auer rods or Phi bodies. • Acute promyelocytic leukemia (APL) is characterized by hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods (as well as myeloid blasts). • A variant of APL is characterized by hypogranular promyelocytes (absence of Auer rods), but is less common.	**myeloid blasts on blood film; presence of Auer rods or Phi bodies (in AML); presence of hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods, or hypogranular promyelocytes without Auer rods (in APL)**

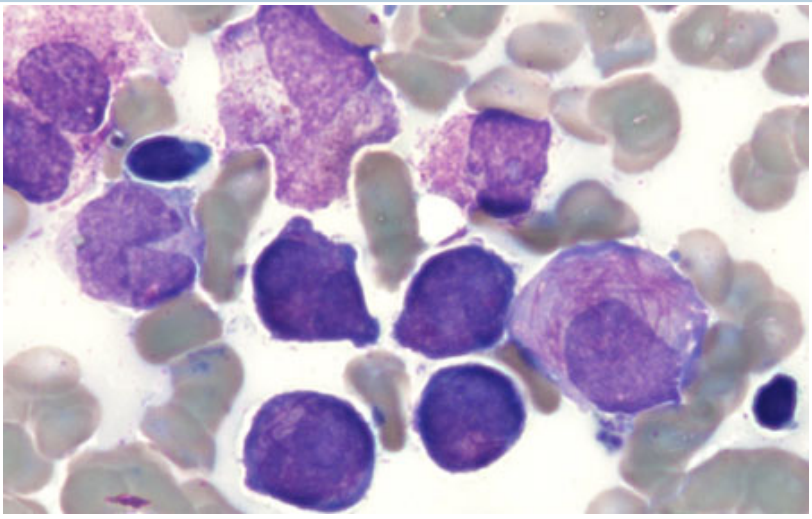
Test	Result



Peripheral blood film of a patient with acute myeloid leukemia with maturation showing myeloid blasts with an Auer rod
From the collection of Drs K. Raj and P. Mehta; used with patient consent

- 

Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods
From the collection of Drs K. Raj and P. Mehta; used with patient consent

Test	Result
 *Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes, some with bundles of Auer rods* *From the collection of Drs K. Raj and P. Mehta; used with patient consent*	
coagulation panel • Ordered as baseline and monitored throughout treatment. • Prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be mildly prolonged with normal fibrinogen and D-dimer. • If these tests are abnormal (prolonged PT and aPTT, decreased fibrinogen, and/or elevated D-dimer), disseminated intravascular coagulation (DIC) should be suspected and an urgent referral is warranted. Refer to the International Society on Thrombosis and Haemostasis (ISTH) scoring system for DIC.[52] • DIC occurs most frequently in acute promyelocytic leukemia (APL). • Severely decreased fibrinogen suggests primary fibrinolysis.	**PT, aPTT, fibrinogen, and/or D-dimer may be normal or abnormal; if abnormal, DIC should be suspected**
serum electrolytes • Ordered as baseline and monitored throughout treatment. • Hyperkalemia, hypocalcemia, and hyperphosphatemia (together with hyperuricemia and elevated serum lactate dehydrogenase) may occur due to tumor lysis syndrome (TLS), particularly during treatment and if white blood cell count (tumor burden) is high. This can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. TLS is an oncologic emergency.[51] See Tumor lysis syndrome . • Hypercalcemia may occur due to bony infiltration or ectopic release of a parathyroid hormone-like substance.	**serum potassium and phosphorus may be elevated; serum calcium may be decreased or elevated**
serum uric acid • Ordered as baseline and monitored throughout treatment. • Hyperuricemia (together with hyperkalemia, hypocalcemia, hyperphosphatemia, and elevated serum lactate dehydrogenase) may occur due to tumor lysis syndrome (TLS), particularly during treatment and if white blood cell count (tumor burden) is high. This can lead to cardiac arrhythmias, seizures, acute renal failure, and	**may be elevated**

Test	Result
death, if untreated. TLS is an oncologic emergency.[51] See Tumor lysis syndrome . • The degree of uric acid elevation may reflect the extent of disease burden and is useful for prognosis.[55]	
serum lactate dehydrogenase (LDH) • Ordered as baseline and monitored throughout treatment. • Elevated serum LDH (together with hyperkalemia, hypocalcemia, hyperphosphatemia, and hyperuricemia) may occur due to tumor lysis syndrome (TLS), particularly during treatment and if white blood cell count (tumor burden) is high. This can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. TLS is an oncologic emergency.[51] See Tumor lysis syndrome . • The degree of LDH elevation may reflect the extent of disease burden and is useful for prognosis.[56]	**may be elevated**
renal function • Ordered as baseline and monitored throughout treatment. • Includes measurement of BUN and creatinine. • Acute renal failure may occur if tumor lysis syndrome (TLS) develops. TLS is an oncologic emergency.[51] See Tumor lysis syndrome .	**may be abnormal if there is renal dysfunction**
liver function tests • Ordered as baseline and monitored throughout treatment. • Includes measurement of total bilirubin, albumin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).	**may be abnormal if there is liver dysfunction**
bone marrow evaluation • Diagnostic workup includes bone marrow aspirate and trephine biopsy analyses.[23] [38] • Cytomorphology assessment demonstrates bone marrow hypercellularity and infiltration by myeloid blasts in AML (as well as hypergranular or hypogranular [less common] promyelocytes in acute promyelocytic leukemia [APL]). Blast cells are negative for terminal deoxynucleotidyl transferase (TdT) and stain positive for myeloperoxidase. • Immunophenotyping (using flow cytometry on bone marrow aspirate) identifies cell surface and cytoplasmic markers of myeloid blasts (e.g., CD34, CD33) and establishes lineage. • Immunohistochemistry (using core biopsy specimen) may be used instead of flow cytometry for immunophenotyping if bone marrow aspirate is unavailable or of poor quality. • Confirmation of a myeloid origin of the leukemic cells by immunophenotyping is essential to differentiate AML and acute lymphoblastic leukemia (ALL), as these are often clinically indistinguishable. • If bone marrow specimens are inadequate or unattainable, then peripheral blood can be used for pathologic assessment provided there are sufficient numbers of circulating blasts.	**bone marrow hypercellularity and infiltration by myeloid blasts; presence of Auer rods or Phi bodies (in AML); presence of hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods, or hypogranular promyelocytes without Auer rods (in APL); positive for cell-surface and cytoplasmic markers for myeloid blasts (e.g., CD34, CD33, myeloperoxidase); negative for TdT**
genetic testing • Cytogenetic analysis (karyotyping and fluorescence in situ hybridization [FISH]) and molecular genetic testing should be performed to inform the diagnosis, prognosis, and treatment.[23] [38] • In AML, the following genetic abnormalities should be investigated due to their association with specific prognoses and treatment targets: RUNX1::RUNX1T1; CBFB::MYH11; MLLT3::KMT2A	**may identify AML-defining genetic abnormalities**

Test	Result
(or other KMT2A rearrangements); DEK::NUP214; BCR::ABL1; KAT6A::CREBBP; c-KIT; NPM1; FLT3 (ITD and TKD); IDH1; IDH2; CEBPA (basic leucine zipper [bZIP] domain); -5 or del(5q); -7; -17/abn(17p); GATA2; MECOM(EVI1); ASXL1; BCOR; EZH2; RUNX1; SF3B1; SRSF2; STAG2; U2AF1; ZRSR2; and TP53.[23] [38] See Criteria . • Next-generation sequencing panels and multiplex gene panels are recommended for mutational analysis.[23] • Acute promyelocytic leukemia (APL, a subtype of AML) is characterized by the PML::RARA fusion gene caused by a t(15;17)(q22;q12) balanced chromosomal rearrangement.[23] [37]	

Other tests to consider

Test	Result
CNS imaging and lumbar puncture • CNS imaging (e.g., brain MRI or CT scan) should be carried out in patients who present with neurologic signs or symptoms suggesting CNS involvement.[23] [38] • A diagnostic lumbar puncture should be carried out if CNS imaging does not identify CNS bleeding, meningeal disease, and a mass lesion, and neurologic signs and symptoms persist. A single dose of intrathecal chemotherapy (e.g., methotrexate or cytarabine) may be considered at the time of diagnostic lumbar puncture. • Coagulopathy should be managed before lumbar puncture, particularly in patients with acute promyelocytic leukemia (APL).	**CNS imaging may show intracranial bleeding, leptomeningeal disease, mass lesion; lumbar puncture may detect malignant cells**
FDG-PET/CT scan • Should be considered in patients with suspected extramedullary disease.[38]	**may show extramedullary lesions**
human leukocyte antigen (HLA) typing • Ordered to assess and match for suitable donor for allogeneic stem cell transplant.	**variable**
chest x-ray • May be performed to identify pneumonia, mediastinal masses, pulmonary infiltrates, or cardiomegaly.	**may show evidence of pneumonia, mediastinal masses, pulmonary infiltrates, cardiomegaly**
echocardiogram • Should be performed to assess cardiac function in patients: with a history or symptoms of cardiac disease; with prior exposure to cardiotoxic drugs or radiation therapy to the thorax; or of older age.[23] [38] • Findings may guide treatment.	**variable**
multigated acquisition scan • Should be performed to assess cardiac function in patients: with a history or symptoms of cardiac disease; with prior exposure to cardiotoxic drugs or radiation therapy to the thorax; or of older age.[23] [38] • Findings may guide treatment.	**variable**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Acute lymphoblastic leukemia (ALL)	• Clinically indistinguishable from AML.	• Bone marrow biopsy and aspirate, peripheral blood smear, and immunophenotyping can establish the diagnosis. • Blast cells in ALL are positive for terminal deoxynucleotidyl transferase (TdT) and lack staining for myeloperoxidase; also demonstrate presence of lymphoid markers.
Biphenotypic leukemia	• Clinically indistinguishable from AML.	• Expression of antigens representing both myeloid and lymphoid leukemia in the leukemic clone suggests biphenotypic leukemia. • The presence of the Philadelphia chromosome (BCR::ABL1 fusion gene) supports a diagnosis of biphenotypic leukemia, but does not exclude Philadelphia chromosome-positive AML.
Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes (MLNE)	• Blast phase MLNE may be clinically indistinguishable from AML.	• Sustained/persistent eosinophilia (or tissue eosinophilia in a target organ) with elevated serum tryptase.[57] • The presence of tyrosine kinase gene fusions (e.g., PDGFRA, PDGFRB, FGFR1, JAK2, ABL1, FLT3). [57]
Myelodysplastic syndrome (MDS)	• History of longstanding anemia and transfusion dependence.	• The distinction between high-risk MDS and AML is based on the numbers of blasts present. However, the estimation of blast counts can be difficult and is subjective. The blood film shows dysplasia in >10% of cells of any lineage, and the bone marrow may show ≤19% blasts. • Micromegakaryocytes and acquired Pelger-Huet (spectacle eye nucleus)

Condition	Differentiating signs / symptoms	Differentiating tests
		• neutrophils are specific for MDS. Associated chromosomal deletions or unbalanced chromosomal abnormalities, particularly of chromosomes 8, 7, and 5, are common. Complex cytogenetic changes may occur. • The presence of dysplasia may suggest that AML has evolved from MDS.
Chronic myeloid leukemia (CML) blast crisis	• There may be a history of preceding CML.	• Blood film may be indistinguishable from AML but may have an excess of basophils and eosinophils. • The presence of the Philadelphia chromosome (BCR::ABL1 fusion gene) supports a diagnosis of CML, but does not exclude Philadelphia chromosome-positive AML. • Typically no other karyotypic abnormalities are present.
Myelofibrosis	• Symptoms (constitutional, bleeding, infections) are less acute. • Moderate to massive splenomegaly is more common.	• Blood film shows teardrop red blood cells and a leukoerythroblastic film. • Bone marrow biopsy shows reticulin fibrosis.
Aplastic anemia	• May have history of medications that cause aplastic anemia, such as chloramphenicol and nonsteroidal anti-inflammatory drugs.	• A negative Coombs test suggests aplastic anemia. • Bone marrow biopsy and aspirate are hypocellular. • Low percentage of blast cells in peripheral blood (<10%). Precursors are morphologically normal. • Patients may have concurrent paroxysmal nocturnal hemoglobinuria clone and evidence of intravascular hemolysis (reticulocytosis, elevated serum lactate dehydrogenase, indirect bilirubin, decreased haptoglobin).
Drug-induced bone marrow failure	• History of using drugs that may cause pancytopenia (e.g., chloramphenicol,	• Bone marrow biopsy and aspirate will be hypocellular,

Condition	Differentiating signs / symptoms	Differentiating tests
	methotrexate, and chemotherapeutic agents). • Cessation of the implicated agent, or administration of an antidote (e.g., folic acid for methotrexate), reverses the pancytopenia.	and no excess of blasts are present. • Peripheral blood smear may be helpful. • Megaloblastic erythropoiesis is seen with methotrexate. • Bone marrow should be reassessed after drug cessation.
Leukemoid reaction	• Recent history of hematopoietic growth factor treatment may be present. • Appropriate treatment (i.e., stopping the growth factor) results in normalization of the blood count.	• Bone marrow biopsy and aspirate, and peripheral blood smear are helpful in differentiating diagnosis. • Bone marrow shows no excess of blasts, but does show mature hematopoietic cells. Increased macrophage activity and toxic granulation of myeloid cell series may be present, suggesting infections; Dohle bodies may also be seen in infections.
Vitamin B12 deficiency	• May have a family history consistent with pernicious anemia. • Paresthesia is an early symptom. • Glossitis and neurologic signs, such as cognitive impairment or subacute combined degeneration (ataxia, decreased vibration sense, muscle weakness, and hyporeflexia), occur with severe deficiency.	• Macrocytic anemia will be present unless there is an associated iron deficiency. • Peripheral blood smear shows megaloblastic changes. • Serum vitamin B12 levels are low.

DIAGNOSIS

Criteria

European LeukemiaNet: risk stratification by genetic abnormality at initial diagnosis[23]

Favorable risk

- t(8;21)(q22;q22.1)/RUNX1::RUNX1T1*
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11*
- Mutated NPM1 without FLT3-ITD**
- Basic leucine zipper (bZIP) in-frame mutated CEBPA

Intermediate risk

- Mutated NPM1 with FLT3-ITD**

- Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions)
- t(9;11)(p21.3;q23.3)/MLLT3::KMT2A
- Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Adverse risk

- t(6;9)(p23.3;q34.1)/DEK::NUP214
- t(v;11q23.3)/KMT2A-rearranged (excluding KMT2A partial tandem duplication)
- t(9;22)(q34.1;q11.2)/BCR::ABL1
- t(8;16)(p11.2;p13.3)/KAT6A::CREBBP
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1)
- t(3q26.2;v)/MECOM(EVI1)-rearranged
- -5 or del(5q); -7; -17/abn(17p)
- Complex karyotype (≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies [or polysomies] without structural abnormalities); monosomal karyotype (presence of ≥2 distinct monosomies [excluding loss of X or Y], or one single autosomal monosomy in combination with at least one structural chromosome abnormality [excluding core-binding factor AML])
- Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2 (these mutations should not be used as adverse prognostic markers if they co-occur with favorable-risk AML subtypes)
- Mutated TP53 (variant allele fraction ≥10%)

*KIT and/or FLT3 mutation does not alter risk categorization

**AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse risk.

European LeukemiaNet: treatment response criteria[23]

Complete remission (CR)

- Bone marrow blasts <5%; absence of circulating blasts; absence of extramedullary disease
- Absolute neutrophil count (ANC) ≥1000/microliter (≥1 × 10^9/L)
- Platelet count ≥100,000/microliter (≥100 × 10^9/L)

CR with partial hematologic recovery (CRh)

- Bone marrow blasts <5%; absence of circulating blasts; absence of extramedullary disease
- ANC ≥500/microliter (≥0.5 × 10^9/L)
- Platelet count ≥50,000/microliter (≥50 × 10^9/L)

CR with incomplete hematologic recovery (CRi)

- All CR criteria except for residual neutropenia (ANC <1000/microliter [<1 × 10^9/L]) or thrombocytopenia (platelet count <100,000/microliter [<100 × 10^9/L])

Morphologic leukemia-free state (MLFS)

- Bone marrow blasts <5%; absence of circulating blasts; absence of extramedullary disease; no hematologic recovery required
- Note: bone marrow should not merely be "aplastic"; bone marrow spicules should be present; ≥200 cells should be enumerated in the aspirate or cellularity should be ≥10% in the biopsy

Partial remission (PR)

- All hematologic criteria of CR
- Decrease of bone marrow blast percentage to 5% to 25%
- Decrease of pretreatment bone marrow blast percentage by ≥50%

No response

- Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS, or PR are categorized as having no response prior to the response landmark. Patients failing to achieve response by the designated landmark are designated as having refractory disease.

Nonevaluable for response

- Includes patients lacking an adequate bone marrow response evaluation (includes those with early death, withdrawal prior to response assessment, or a technically suboptimal bone marrow sample precluding assessment).

CR, CRh, or CRi without measurable (minimal) residual disease (MRD) (CRMRD-, CRhMRD-, or CRiMRD-)

- CR, CRh, or CRi with MRD below a defined threshold for a genetic marker by quantitative polymerase chain reaction (qPCR) or multiparameter flow cytometry.
- Response without MRD should be confirmed with a subsequent assessment at least 4 weeks apart. The date of response without MRD is the first date in which the MRD was below the defined threshold.
- Response with MRD detection at low-level (CRMRD-LL) is included in this category of CR, CRh, or CRi without MRD. CRMRD-LL is currently only defined for NPM1-mutant and core-binding factor AML.

Refractory disease

- No CR, CRh, or CRi at the response landmark.

Relapsed disease (after CR, CRh, or CRi)

- Bone marrow blasts ≥5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease.

MRD relapse (after CR, CRh, or CRi without MRD)

- 1) conversion from MRD negativity to MRD positivity, independent of method; or 2) increase of MRD copy numbers ≥1 log10 between any two positive samples in patients with CRMRD-LL, CRhMRD-LL, or CRiMRD-LL by qPCR.
- The result of 1 or 2 should be rapidly confirmed in a second consecutive sample from the same tissue source.

Screening

There is no role for screening of the asymptomatic population.

Bone marrow failure syndromes

Due to the risk of developing AML and secondary malignancies, patients with inherited bone marrow failure syndromes (e.g., Fanconi anemia, Kostmann syndrome, and Diamond-Blackfan anemia) would benefit from regular complete blood count (CBC) to screen for the development of myelodysplastic syndrome (MDS) or AML.[22]

Aplastic anemia

It is recommended that patients with aplastic anemia be followed up regularly (e.g., with CBC, immunophenotyping) to detect the development of clonal disorders such as paroxysmal nocturnal hemoglobinuria, MDS, or AML.[58] See Aplastic anemia .

Autologous hematopoietic stem cell transplant recipients and patients treated with chemotherapy and/or radiation therapy

These patients are at increased risk for secondary malignancies (including AML). Regular monitoring with CBC and peripheral blood film, and early bone marrow investigation if AML is suspected, is recommended.[59]

Approach

Dose-intense chemotherapy is recommended for patients with AML who are considered fit and healthy enough to tolerate intensive therapy.[23] [38][60] [65] Patients unsuitable for intensive therapy should be considered for low-intensity therapy.

Enrollment in a clinical trial should be considered for all patients, where possible. Clinical trials frequently offer the best management option for patients with AML, particularly those who are older, are unable to tolerate chemotherapy, or have unfavorable disease (e.g., those with TP53 mutations or 17p deletion).[38] [60] [65]

Treatment goals

The early goals of treatment are to achieve complete remission and reduce the risk of relapse. See Criteria for treatment response criteria.

The long-term goal is to improve disease-free survival and overall survival, with minimal long-term adverse effects. For fit younger patients (<60 years of age) who are treated with intensive chemotherapy, the overall goal is disease cure. In older patients, the goal is usually to achieve complete remission that extends survival and quality of life; cure may be possible for a subset of fit older patients.

The goals of treatment should be discussed with the patient in the context of their disease and fitness, and this should inform decision-making and treatment planning throughout the course of treatment.

Treatment phases

Treatment for AML involves using multiagent, dose-intense chemotherapy regimens in two main phases: induction and consolidation. Some patients may undergo allogeneic stem cell transplantation (SCT) or maintenance therapy if complete remission is achieved.

Treatment is guided by the patient's ability to tolerate intensive treatment regimens (e.g., based on age, fitness/performance status, comorbidities), risk stratification (e.g., based on genetic abnormalities), disease biology/subtype, measurable (minimal) residual disease (MRD) assessment, and patient preference/goals.

See Criteria for risk stratification.

Induction therapy for AML

Induction therapy is the first phase of treatment. The aim of induction is to achieve complete remission with low or undetectable MRD.

Patients who are fit and able to tolerate intensive therapy should undergo induction therapy with dose-intense chemotherapy regimens.[23] [38] [60] [65]

The standard intensive induction regimen is:[23] [38] [60]

- Cytarabine for 7 days plus an anthracycline (e.g., daunorubicin, idarubicin) for 3 days (i.e., standard 7+3 regimen)

Alternative intensive induction regimens include:[23] [38] [60]

- Cytarabine for 7 days plus mitoxantrone for 3 days

- Fludarabine plus cytarabine plus granulocyte colony-stimulating factor (G-CSF) plus idarubicin (FLAG-IDA; use with caution in patients ages >60 years)
- Liposomal daunorubicin/cytarabine (also known as CPX-351; a liposome-encapsulated fixed-dose combination of daunorubicin plus cytarabine) for patients with therapy-related AML (tAML) or AML with myelodysplasia-related changes (AML-MRC), particularly those ages >60 years

One or two courses of induction therapy is recommended.[60]

Complete remission rate with standard induction chemotherapy is 70% to 80% in patients <60 years of age.[66] [67] [68] [69] In patients ≥60 years of age, the complete remission rate is lower (60% to 70%).[70] [71] However, complete remission rate varies significantly depending on disease biology.

Patients who do not achieve complete remission following induction therapy are considered to have refractory disease.

Consolidation therapy for AML

The aim of consolidation therapy is to maintain complete remission and reduce the risk of relapse following induction therapy.

Consolidation therapy is guided by risk factors for relapse (e.g., genetic abnormalities, white blood cell [WBC] count at presentation, MRD).

Consolidation regimens usually consist of up to 4 cycles of intermediate-dose or high-dose cytarabine (IDAC or HiDAC) alone or in combination with other chemotherapy drugs (e.g., idarubicin, daunorubicin, mitoxantrone).[38]

Patients with tAML or AML-MRC who received liposomal daunorubicin/cytarabine for induction therapy can also receive this regimen for consolidation therapy (up to 2 cycles).[72] [73] [74]

Measurable (minimal) residual disease (MRD) assessment in AML

MRD assessment (e.g., using molecular genetic testing or flow cytometry) should be performed during and after treatment to assess treatment response (i.e., the presence of leukemic cells in the peripheral blood and/or bone marrow).[23] [75] MRD should also be assessed before allogeneic SCT.[51]

MRD assessment can inform prognosis and treatment planning when combined with standard morphology-based assessment of treatment response. Leukemic cells may persist in patients who achieve morphologic complete remission following treatment; therefore, MRD assessment can determine deeper remission status and improve prognostication and risk stratification.

The European LeukemiaNet has published recommendations for assessing MRD (including frequency and timing) in AML patients.[23] [75]

Stem cell transplantation (SCT) for AML

Patients with intermediate-risk disease and particularly those with adverse-risk disease may be considered for allogeneic SCT (with reduced-intensity conditioning for older patients) following one or more cycles of consolidation chemotherapy, if they are fit and able to tolerate SCT.[51] [76] [77] These patients may also proceed directly to transplant if a suitable donor is available at first complete remission (i.e., in lieu of consolidation chemotherapy).

Allogeneic SCT may be considered in patients with favorable-risk disease with persistent MRD if a suitable donor is available.[23] [51]

Autologous SCT is an alternative to allogeneic SCT in select patients (e.g., those with intermediate-risk disease who are MRD negative) if a donor is not available, but is not commonly performed.[23] [60][78] [79]

Targeted therapies for AML

Targeted therapies can be considered for patients with certain biologic markers and genetic abnormalities.

CD33-positive AML

Patients with CD33-positive AML and favorable- or intermediate-risk disease can be treated with gemtuzumab ozogamicin (an anti-CD33 monoclonal antibody conjugated with the cytotoxic agent calicheamicin) in combination with induction and consolidation chemotherapy.[80] [81][82] [83] Important adverse effects associated with gemtuzumab ozogamicin include hypersensitivity reactions, hepatotoxicity (veno-occlusive disease), and myelotoxicity.

FLT3-mutated AML

Patients with FLT3-mutated AML can be treated with the oral tyrosine kinase inhibitors midostaurin (for FLT3-ITD-mutated or FLT3-TKD-mutated) or quizartinib (for FLT3-ITD-mutated only) in combination with standard intensive induction and consolidation chemotherapy.[84] [85] [86] Quizartinib is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

Maintenance therapy for AML

Maintenance therapy with oral azacitidine (single agent) may be considered for patients with complete remission after intensive induction chemotherapy (with or without complete blood count recovery), but who are not candidates for intensive consolidation therapy (including SCT).[87]

Maintenance therapy with oral azacitidine should not replace consolidation therapy.

FLT3-mutated AML: maintenance therapy post-consolidation chemotherapy

Patients with FLT3-mutated AML who achieve complete remission with midostaurin or quizartinib (in combination with standard induction and consolidation chemotherapy) may continue these agents as monotherapy for maintenance therapy post-consolidation chemotherapy.[84][85][86]

FLT3-mutated AML: maintenance therapy posttransplant

Several oral tyrosine kinase inhibitors can be considered for post-allogeneic SCT maintenance therapy in patients with FLT3-mutated AML. These include:[38] [85] [86][88] [89] [90]

- Sorafenib (for FLT3-ITD-mutated only)
- Gilteritinib (for FLT3-ITD-mutated or FLT3-TKD-mutated, particularly if patients are MRD-positive before or after SCT)
- Midostaurin (for FLT3-ITD-mutated or FLT3-TKD-mutated)
- Quizartinib (for FLT3-ITD-mutated only)

The role of maintenance therapy in the posttransplant setting is still evolving.

Treatment for patients with AML who are not suitable for standard intensive chemotherapy

Low-intensity therapy should be considered for newly diagnosed patients who are not suitable for standard intensive chemotherapy (e.g., due to age, frailty, comorbidities). Options include:

- Venetoclax (a BCL-2 inhibitor) is approved for use in combination with a hypomethylating agent (decitabine or azacitidine) or low-dose subcutaneous cytarabine (LDAraC) for patients with newly diagnosed AML ages 75 years or older, or who are unsuitable for intensive induction chemotherapy due to comorbidities.[91] [92] [93] [94] [95] Tumor lysis syndrome (TLS) has been uncommonly reported in patients with AML treated with venetoclax.[96] See Management approach (Supportive care for AML and APL).
- Glasdegib (a Hedgehog pathway inhibitor) is approved for use in combination with LDAraC for patients ages ≥75 years who are unsuitable for standard induction chemotherapy.[97] [98] [99]
- Ivosidenib (an IDH1 inhibitor) is approved in the US for use as monotherapy or in combination with azacitidine for patients with newly diagnosed IDH1-mutated AML who are ages 75 years or older, or who are unsuitable for intensive induction chemotherapy due to comorbidities.[100] [101] Life-threatening differentiation syndrome has been reported in patients receiving ivosidenib. See Management approach (Supportive care for AML and APL).
- Enasidenib (an IDH2 inhibitor) may be used as monotherapy or in combination with azacitidine for patients with newly diagnosed IDH2-mutated AML who are unsuitable for intensive induction chemotherapy.[102] [103] [104] The US Food and Drug Administration (FDA) has issued a warning regarding differentiation syndrome associated with enasidenib.[105] Differentiation syndrome has reportedly occurred as early as 10 days and up to 5 months after starting treatment. See Management approach (Supportive care for AML and APL).
- Gemtuzumab ozogamicin (single agent) may be used for patients with CD33-positive AML who are not suitable for standard induction chemotherapy.[106]

Patients should continue low-intensity therapy until disease progression or intolerance. SCT may be an option in select patients who respond to low-intensity therapy. If eligible and a suitable donor is available, patients should undergo allogeneic SCT (with reduced-intensity conditioning) at first remission.[38] [60]

AML with TP53 mutations or 17p deletion

Patients with TP53 mutations or 17p deletion are typically unresponsive to standard intensive chemotherapy and the prognosis is poor.[107] A clinical trial is recommended for these patients.[38] If a clinical trial is not available, low-intensity therapy (e.g., venetoclax plus decitabine) and allogeneic SCT (if eligible and a suitable donor is available) can be considered.[95]

Relapsed or refractory#AML

Patients with relapsed or refractory disease have a poor prognosis.[108]

There is no standard salvage regimen for relapsed or refractory disease. Where possible, patients should be offered enrollment in a clinical trial.

At relapse, all patients should undergo molecular re-evaluation to identify targets (actionable genes) for salvage therapy, which may have emerged since diagnosis (due to clonal evolution) or were not detected at diagnosis.[23]

Relapse after first complete remission occurs in approximately 50% of patients who have received standard induction therapy, usually in the first year following treatment. Approximately 40% to 60% of

relapsed patients achieve a second complete remission with intensive salvage chemotherapy (e.g., IDAC or HiDAC with or without an anthracycline or mitoxantrone), although duration of remission is usually limited.[109]

Patients unsuitable for intensive salvage chemotherapy can be considered for low-intensity salvage therapy, which should be continued until disease progression or intolerance. Options include:

- Venetoclax combined with a hypomethylating agent (azacitidine or decitabine) or LDAraC.[110] [111]
- Gilteritinib (an oral kinase inhibitor) for patients with FLT3-mutated AML.[112] Gilteritinib has been associated with differentiation syndrome.
- Ivosidenib for patients with IDH1-mutated AML.[113]
- Olutasidenib for patients with IDH1-mutated AML.[114] [115] Olutasidenib has been associated with differentiation syndrome.
- Enasidenib for patients with IDH2-mutated AML.[102]
- Gemtuzumab ozogamicin (single agent) for patients with CD33-positive AML.[116]

Important predictors of response to salvage therapy are age, genetic abnormalities, duration of first remission, and history of previous SCT.[117] [118] [119]

Patients who achieve a second complete remission with intensive salvage therapy should undergo allogeneic SCT to reduce the risk of relapse, if they are eligible and a suitable donor is available.[38] [60] [108]

Patients who are unable to tolerate salvage therapy or who decline further treatment should be offered best supportive care and/or palliative care.

Reinduction therapy (with chemotherapy) may be considered for all patients with relapse following long remission (i.e., ≥12 months following induction therapy).[38] [60]

Management of acute promyelocytic leukemia (APL)

APL is a subtype of AML (characterized by the presence of the PML::RARA fusion gene) that requires urgent treatment to prevent very early death caused by coagulopathy.[38] [60] [61] Treatment should commence as soon as APL is suspected (i.e., before confirmation by genetic testing).

Patients with APL are managed in three treatment phases: induction, consolidation, and maintenance.

Treatment is based on whether patients are non-high risk (defined as WBC count ≤10,000/microliter [≤10 × 10^9/L] at presentation) or high risk (defined as WBC count >10,000/microliter [>10 × 10^9/L] at presentation).[38] [60] [61]

Once a treatment regimen and protocol have been decided, it should be adhered to in its entirety from induction to consolidation and maintenance (barring major complication or inadequate response).[38]

Induction therapy for APL

Induction regimens for non-high-risk APL include:[38] [61]

- All-trans-retinoic acid (ATRA; also known as tretinoin) plus arsenic trioxide (standard of care)
- ATRA plus idarubicin or gemtuzumab ozogamicin; considered only if arsenic trioxide is not available or contraindicated

Induction regimens for high-risk APL include:[38] [61]

- ATRA plus arsenic trioxide plus an anthracycline (idarubicin or daunorubicin)
- ATRA plus arsenic trioxide plus gemtuzumab ozogamicin (single dose)
- ATRA plus anthracycline-based chemotherapy (e.g., idarubicin; or daunorubicin plus cytarabine)

ATRA and arsenic trioxide can cause differentiation syndrome, which can be life-threatening if not treated promptly. Arsenic trioxide can also prolong QT interval and cause electrolyte abnormalities. See Management approach (Supportive care for AML and APL).

Induction therapy should continue until complete remission is achieved, after which consolidation therapy should be given.[61] Complete remission following ATRA-based induction therapy is achieved in most (>90%) patients.[120]

Consolidation therapy for APL

Consolidation regimens for APL are usually similar to induction regimens (e.g., ATRA plus arsenic trioxide [for non-high-risk APL]; ATRA plus arsenic trioxide plus chemotherapy [for high-risk APL]).[38] [61]

Maintenance therapy for APL

Maintenance therapy may be considered for patients with high-risk APL, but it is not required for non-high-risk patients.[60][61]

Maintenance regimens for APL usually consist of ATRA plus mercaptopurine and methotrexate for 1 to 2 years.[121] [122] [123] With close MRD monitoring post-consolidation, the role of maintenance therapy is now being challenged.[124] [125] In some countries, such as the UK, maintenance therapy for APL is no longer used.

Measurable (minimal) residual disease (MRD) assessment in APL

MRD assessment (to detect the PML::RARA fusion transcript) should be carried out following consolidation therapy to evaluate treatment response (i.e., molecular remission) and guide subsequent treatment.[60] [61]

Patients with high-risk APL should undergo long-term MRD monitoring (e.g., every 3 months for 2 years following treatment) due to the increased risk of relapse.[38] [60] [61] Long-term MRD monitoring is not required for non-high-risk patients in molecular remission following consolidation therapy.

Relapsed or refractory APL

Patients with relapsed or refractory APL should be considered for salvage therapy to achieve molecular remission (i.e., MRD negativity).

Salvage therapy should be based on previous treatment and whether relapse occurs early or late (definitions vary, but most relapses occur <2 years).[38] [60] [61] Patients who relapse early following treatment comprising ATRA plus arsenic trioxide can be treated with ATRA plus chemotherapy, or single-agent gemtuzumab ozogamicin.[38] [61] Patients who relapse early following treatment with ATRA plus chemotherapy (without arsenic trioxide) can be treated with arsenic trioxide-containing regimens (e.g., ATRA plus arsenic trioxide).[38] [61] Retreatment with the previous regimen may be considered if relapse occurs late.

Patients with relapsed or refractory disease should be referred to a transplant center. An autologous SCT (if MRD negative) or allogeneic SCT (if MRD positive or refractory disease) should be arranged.[38]

[61] Patients not eligible for SCT may be continued on salvage therapy or enrolled in a clinical trial (if available).

Central nervous system (CNS) involvement in AML and APL

CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[23] [38]

A screening lumbar puncture (in patients without neurologic signs and symptoms) should be considered at first remission before consolidation therapy in patients at high-risk for CNS disease; for example, those with any of the following:[38]

- WBC count >40,000/microliter (>40 × 10^9/L)
- Monocytic lineage
- Mixed-phenotype acute leukemia
- Extramedullary disease
- FLT3 mutations
- High-risk APL

If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

Supportive care for AML and APL

Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

Patients with AML who are unsuitable for or decline standard- or low-intensive chemotherapy should be offered best supportive care.[38] [126]

Electrolyte abnormalities

- Correction of electrolyte abnormalities is important before and during treatment (particularly for patients with APL who are treated with arsenic trioxide).
- Patients should be commenced on hydration (e.g., intravenous fluids).

Tumor lysis syndrome (TLS)

- An oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment (including chemotherapy and targeted agents e.g., venetoclax) or spontaneously (rare), particularly if WBC count (tumor burden) is high.
- TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. See Tumor lysis syndrome .
- TLS associated with venetoclax may occur as early as 6 to 8 hours following the first dose in patients with AML.[96] TLS risk assessment should be carried out before administering venetoclax, and guidance on TLS prophylaxis, laboratory monitoring, dose titration, and drug interactions should be strictly adhered to during treatment with venetoclax.[38] [96]

Differentiation syndrome

- Treatments for AML (e.g., ivosidenib, enasidenib, olutasidenib, gilteritinib) and APL (e.g., ATRA, arsenic trioxide) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128]
- Differentiation syndrome is characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated WBC count (>10,000/microliter [>10 × 10^9/L]). Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the treatment causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]

Hyperleukocytosis

- Generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor.
- In AML patients with hyperleukocytosis, hydroxyurea is recommended for leukoreduction.[23] [38] It is recommended that WBC count is lowered to <25,000/microliter (<25 × 10^9/L), particularly before initiating treatment with hypomethylating agents and venetoclax.[23] [38]
- In APL patients, hydroxyurea should be considered to manage high WBC count during treatment with ATRA and arsenic trioxide (particularly if differentiation syndrome occurs).[38] [61]
- Urgent leukapheresis may be considered in patients with AML who are symptomatic and have a very high WBC count; however, this is not recommended in patients with APL because leukapheresis may worsen coagulopathy.[38] [61]

Anemia and thrombocytopenia

- Red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] During the acute phase of APL, patients are at particular risk of significant coagulopathy.
- Packed red blood cell transfusion is recommended to keep hematocrit >25%.
- Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in patients with APL or those with significant bleeding.[38] [61]
- Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in patients with APL or those with significant bleeding.

Infections and febrile neutropenia

- During acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129]
- Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
newly diagnosed AML: suitable for intensive chemotherapy		
	1st	intensive induction therapy
	plus	supportive care
■ with CD33-positive AML	plus	gemtuzumab ozogamicin
■ with FLT3-mutant AML	plus	midostaurin or quizartinib
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate
newly diagnosed AML: not suitable for intensive chemotherapy		
	1st	low-intensity therapy
	plus	supportive care
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate
newly diagnosed non-high-risk acute promyelocytic leukemia (APL)		
	1st	induction therapy
	plus	supportive care
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate
newly diagnosed high-risk acute promyelocytic leukemia (APL)		
	1st	induction therapy
	plus	supportive care
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate

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Ongoing (summary)

complete remission: AML		
	1st	consolidation therapy
	plus	supportive care
	adjunct	stem cell transplantation
■ with CD33-positive AML	plus	gemtuzumab ozogamicin
■ with FLT3-mutant AML	plus	midostaurin or quizartinib
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate
■ eligible for maintenance therapy	adjunct	maintenance therapy
complete remission: acute promyelocytic leukemia (APL)		
	1st	consolidation therapy
	plus	supportive care
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate
■ with high-risk APL	adjunct	maintenance therapy
relapsed or refractory AML		
	1st	salvage therapy, reinduction therapy, or clinical trial
	plus	supportive care
	adjunct	stem cell transplantation
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate
relapsed or refractory acute promyelocytic leukemia (APL)		
	1st	salvage therapy + stem cell transplantation or clinical trial
	plus	supportive care
■ with CNS involvement	plus	intrathecal cytarabine or methotrexate

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

newly diagnosed AML: suitable for intensive chemotherapy

1st **intensive induction therapy**

Primary options

» cytarabine

--AND--

» daunorubicin
-or-
» idarubicin

Secondary options

» cytarabine
-and-
» mitoxantrone

OR

» fludarabine
-and-
» cytarabine
-and-
» filgrastim (G-CSF)
-and-
» idarubicin

OR

» daunorubicin/cytarabine liposomal

» Induction therapy is the first phase of treatment. The aim of induction is to achieve complete remission with low or undetectable measurable (minimal) residual disease (MRD). See Criteria .

» Patients who are fit and able to tolerate intensive therapy should undergo induction therapy with dose-intense chemotherapy regimens.[23] [38] [60] [65]

» The standard intensive induction regimen is cytarabine for 7 days plus an anthracycline (e.g., daunorubicin, idarubicin) for 3 days (i.e., standard 7+3 regimen).[23] [38] [60]

» Alternative intensive induction regimens include: cytarabine for 7 days plus mitoxantrone

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for 3 days; fludarabine plus cytarabine plus granulocyte colony-stimulating factor (G-CSF) plus idarubicin (FLAG-IDA; use with caution in patients ages >60 years); and liposomal daunorubicin/cytarabine (also known as CPX-351; a liposome-encapsulated fixed-dose combination of cytarabine plus daunorubicin) for patients with therapy-related AML (tAML) or AML with myelodysplasia-related changes (AML-MRC), particularly those ages >60 years.[23] [38] [60]

» One or two courses of induction therapy is recommended.[60]

» Complete remission rate with standard induction chemotherapy is 70% to 80% in patients <60 years of age.[66] [67] [68] [69] In patients ≥60 years of age, the complete remission rate is lower (60% to 70%).[70] [71] However, complete remission rate varies significantly depending on disease biology.

» Patients who do not achieve complete remission following induction therapy are considered to have refractory disease.

» The long-term treatment goal is to improve disease-free survival and overall survival, with minimal long-term adverse effects. For fit younger patients who are treated with intensive chemotherapy, the overall goal is disease cure. In older patients, the goal is usually to achieve complete remission that extends survival and quality of life; cure may be possible for a subset of fit older patients.

» The goals of treatment should be discussed with the patient in the context of their disease and fitness, and this should inform decision-making and treatment planning throughout the course of treatment.

» Enrollment in a clinical trial should be considered for all patients, where possible.

» MRD assessment should be performed during and after treatment to assess treatment response and inform prognosis and treatment planning. The European LeukemiaNet has published recommendations for assessing MRD (including frequency and timing) in AML.[23] [75]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Acute

Treatment recommended for ALL patients in selected patient group

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Patients with AML who are unsuitable for or decline standard- or low-intensive chemotherapy should be offered best supportive care.[38] [126]

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment. Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment with chemotherapy or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. See Tumor lysis syndrome .

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor. In AML patients, hydroxyurea is recommended for leukoreduction.[23] [38] It is recommended that WBC count is lowered to <25,000/microliter (<25 × 10^9/L). Urgent leukapheresis may be considered in patients with AML (not including APL) who are symptomatic and have a very high WBC count.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in those with significant bleeding.

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» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

with CD33-positive AML **plus** **gemtuzumab ozogamicin**

Treatment recommended for ALL patients in selected patient group

Primary options

» gemtuzumab ozogamicin

» Patients with CD33-positive AML and favorable- or intermediate-risk disease can be treated with gemtuzumab ozogamicin (an anti-CD33 monoclonal antibody conjugated with the cytotoxic agent calicheamicin) in combination with induction and consolidation chemotherapy.[80] [81][82] [83]

» Important adverse effects associated with gemtuzumab ozogamicin include hypersensitivity reactions, hepatotoxicity (veno-occlusive disease), and myelotoxicity.

» See local specialist protocol for dosing guidelines.

with FLT3-mutant AML **plus** **midostaurin or quizartinib**

Treatment recommended for ALL patients in selected patient group

Primary options

» midostaurin

OR

» quizartinib

» Patients with FLT3-mutated AML can be treated with the oral tyrosine kinase inhibitors midostaurin (for FLT3-ITD-mutated or FLT3-TKD-mutated) or quizartinib (for FLT3-ITD-mutated only) in combination with standard intensive induction and consolidation chemotherapy.[84] [85] [86]

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» Quizartinib is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

» See local specialist protocol for dosing guidelines.

with CNS involvement **plus** **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» A screening lumbar puncture (in patients without neurologic signs and symptoms) should be considered at first remission (before consolidation) in patients at high-risk for CNS disease (e.g., those with white blood cell [WBC] count >40,000/microliter [>40 × 10^9/L], monocytic lineage, mixed-phenotype acute leukemia, extramedullary disease, or FLT3 mutations).[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

newly diagnosed AML: not suitable for intensive chemotherapy

1st **low-intensity therapy**

Primary options

» venetoclax

--AND--

» decitabine
-or-
» azacitidine
-or-
» cytarabine

OR

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» glasdegib
-and-
» cytarabine

OR

» ivosidenib

OR

» ivosidenib
-and-
» azacitidine

OR

» enasidenib

OR

» enasidenib
-and-
» azacitidine

OR

» gemtuzumab ozogamicin

» Low-intensity therapy should be considered for newly diagnosed patients who are not suitable for standard intensive chemotherapy (e.g., due to age, frailty, comorbidities).

» Options include: venetoclax; glasdegib; ivosidenib; enasidenib; and gemtuzumab ozogamicin.

» Venetoclax (a BCL-2 inhibitor) is approved for use in combination with a hypomethylating agent (decitabine or azacitidine) or low-dose subcutaneous cytarabine (LDAraC) for patients with newly diagnosed AML ages 75 years or older, or who are unsuitable for intensive induction chemotherapy due to comorbidities.[91] [92] [93] [94] [95] Tumor lysis syndrome (TLS) has been uncommonly reported in patients with AML treated with venetoclax.[96]

» Glasdegib (a Hedgehog pathway inhibitor) is approved for use in combination with LDAraC for patients ages 75 years or older who are unsuitable for standard induction chemotherapy.[97] [98] [99]

» Ivosidenib (an IDH1 inhibitor) is approved in the US for use as monotherapy or in

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combination with azacitidine for patients with newly diagnosed IDH1-mutated AML who are ages 75 years or older, or who are unsuitable for intensive induction chemotherapy due to comorbidities.[100] [101] Life-threatening differentiation syndrome has been reported in patients receiving ivosidenib.

» Enasidenib (an IDH2 inhibitor) may be used as monotherapy or in combination with azacitidine for patients with newly diagnosed IDH2-mutated AML who are unsuitable for intensive induction chemotherapy.[102] [103] [104] The US Food and Drug Administration (FDA) has issued a warning regarding differentiation syndrome associated with enasidenib.[105] Differentiation syndrome has reportedly occurred as early as 10 days and up to 5 months after starting treatment.

» Gemtuzumab ozogamicin (single agent) may be used for patients with CD33-positive AML who are not suitable for standard induction chemotherapy.[106]

» Patients should continue low-intensity therapy until disease progression or intolerance.

» Stem cell transplantation (SCT) may be an option in select patients who respond to low-intensity therapy. If eligible and a suitable donor is available, patients should undergo allogeneic SCT (with reduced-intensity conditioning) at first remission.[38] [60]

» Patients with TP53 mutations or 17p deletion are typically unresponsive to standard intensive chemotherapy and the prognosis is poor.[107] A clinical trial is recommended for these patients.[38] If a clinical trial is not available, low-intensity therapy (e.g., venetoclax plus decitabine) and allogeneic SCT (if eligible and a suitable donor is available) can be considered.[95]

» The goals of treatment should be discussed with the patient in the context of their disease and fitness, and this should inform decision-making and treatment planning throughout the course of treatment.

» In older patients, the treatment goal is usually to achieve complete remission that extends survival and quality of life.

» Enrollment in a clinical trial should be considered for all patients, where possible.

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» Measurable (minimal) residual disease (MRD) assessment should be performed during and after treatment to assess treatment response and inform prognosis and treatment planning. The European LeukemiaNet has published recommendations for assessing MRD (including frequency and timing) in AML.[23] [75]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Patients with AML who are unsuitable for or decline standard- or low-intensive chemotherapy should be offered best supportive care.[38] [126]

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment. Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. TLS associated with venetoclax may occur as early as 6 to 8 hours following the first dose in patients with AML.[96] TLS risk assessment should be carried out before administering venetoclax, and guidance on TLS prophylaxis, laboratory monitoring, dose titration, and drug interactions should be strictly adhered to during treatment with venetoclax.[38] [96] See Tumor lysis syndrome .

» Differentiation syndrome: treatments for AML (e.g., ivosidenib, enasidenib) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128] Differentiation syndrome is

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characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated WBC count (>10,000/microliter [>10 × 10^9/L]). Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the treatment causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor. In AML patients, hydroxyurea is recommended for leukoreduction.[23] [38] It is recommended that WBC count is lowered to <25,000/microliter (<25 × 10^9/L), particularly before initiating treatment with hypomethylating agents and venetoclax.[23] [38] Urgent leukapheresis may be considered in patients with AML (not including APL) who are symptomatic and have a very high WBC count.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in those with significant bleeding.

» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

with CNS involvement **plus** **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

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» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

newly diagnosed non-high-risk acute promyelocytic leukemia (APL)

1st **induction therapy**

Primary options

» tretinoin
-and-
» arsenic trioxide

Secondary options

» tretinoin
-and-
» idarubicin

OR

» tretinoin
-and-
» gemtuzumab ozogamicin

» APL is a subtype of AML (characterized by the presence of the PML::RARA fusion gene) that requires urgent treatment to prevent very early death caused by coagulopathy.[38] [60] [61]

» Treatment should commence as soon as APL is suspected (i.e., before confirmation by genetic testing).

» Patients with APL are managed in three treatment phases: induction, consolidation, and maintenance.

» Treatment is based on whether patients are non-high risk (defined as white blood cell [WBC] count ≤10,000/microliter [≤10 × 10^9/L] at presentation) or high risk (defined as

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WBC count >10,000/microliter [>10 × 10^9/L] at presentation).[38] [60] [61]

» Once a treatment regimen and protocol have been decided, it should be adhered to in its entirety from induction to consolidation and maintenance (barring major complication or inadequate response).[38]

» Induction regimens for non-high-risk APL include:[38] [61]

» All-trans-retinoic acid (ATRA; also known as tretinoin) plus arsenic trioxide (standard of care); or

» ATRA plus idarubicin or gemtuzumab ozogamicin; considered only if arsenic trioxide is not available or contraindicated.

» Induction therapy should continue until complete remission is achieved, after which consolidation therapy should be given.[61] Complete remission following ATRA-based induction therapy is achieved in most (>90%) patients.[120]

» ATRA and arsenic trioxide can cause differentiation syndrome, which can be life-threatening if not treated promptly. Arsenic trioxide can also prolong QT interval and cause electrolyte abnormalities.

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment (particularly for patients with APL who are treated with arsenic trioxide). Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac

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arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. See Tumor lysis syndrome .

» Differentiation syndrome: treatments for APL (e.g., ATRA, arsenic trioxide) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128] Differentiation syndrome is characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated WBC (>10,000/microliter [>10 × 10^9/L]). Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the treatment causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor. In APL patients, hydroxyurea should be considered to manage high WBC count during treatment with ATRA and arsenic trioxide (particularly if differentiation syndrome occurs).[38] [61] Leukapheresis is not recommended for patients with APL because it may worsen coagulopathy.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] During the acute phase of APL, patients are at particular risk of significant coagulopathy. Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in patients with APL or those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in patients with APL or those with significant bleeding.

» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients

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should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

with CNS involvement **plus** **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

newly diagnosed high-risk acute promyelocytic leukemia (APL)

1st **induction therapy**

Primary options

» tretinoin
--AND--
» arsenic trioxide
--AND--
» idarubicin
-or-
» daunorubicin

OR

» tretinoin
-and-
» arsenic trioxide
-and-
» gemtuzumab ozogamicin

Secondary options

» tretinoin

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-and-
» idarubicin

OR

» tretinoin
-and-
» daunorubicin
-and-
» cytarabine

» APL is a subtype of AML (characterized by the presence of the PML::RARA fusion gene) that requires urgent treatment to prevent very early death caused by coagulopathy.[38] [60] [61]

» Treatment should commence as soon as APL is suspected (i.e., before confirmation by genetic testing).

» Patients with APL are managed in three treatment phases: induction, consolidation, and maintenance.

» Treatment is based on whether patients are non-high risk (defined as white blood cell [WBC] count ≤10,000/microliter [≤10 × 10^9/L] at presentation) or high risk (defined as WBC count >10,000/microliter [>10 × 10^9/L] at presentation).[38] [60] [61]

» Once a treatment regimen and protocol have been decided, it should be adhered to in its entirety from induction to consolidation and maintenance (barring major complication or inadequate response).[38]

» Induction regimens for high-risk APL include:[38] [61]

» All-trans-retinoic acid (ATRA; also known as tretinoin) plus arsenic trioxide plus an anthracycline (idarubicin or daunorubicin); or

» ATRA plus arsenic trioxide plus gemtuzumab ozogamicin (single dose); or

» ATRA plus anthracycline-based chemotherapy (e.g., idarubicin; or daunorubicin plus cytarabine).

» Induction therapy should continue until complete remission is achieved, after which consolidation therapy should be given.[61] Complete remission following ATRA-based induction therapy is achieved in most (>90%) patients.[120]

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» ATRA and arsenic trioxide can cause differentiation syndrome, which can be life-threatening if not treated promptly. Arsenic trioxide can also prolong QT interval and cause electrolyte abnormalities.

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment (particularly for patients with APL who are treated with arsenic trioxide). Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. See Tumor lysis syndrome .

» Differentiation syndrome: treatments for APL (e.g., ATRA, arsenic trioxide) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128] Differentiation syndrome is characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated WBC count (>10,000/microliter [>10 × 10^9/L]). Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the treatment causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L)

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and is considered a poor prognostic factor. In APL patients, hydroxyurea should be considered to manage high WBC count during treatment with ATRA and arsenic trioxide (particularly if differentiation syndrome occurs).[38] [61] Leukapheresis is not recommended for patients with APL because it may worsen coagulopathy.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] During the acute phase of APL, patients are at particular risk of significant coagulopathy. Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in patients with APL or those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in patients with APL or those with significant bleeding.

» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

with CNS involvement **plus** **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» A screening lumbar puncture (in patients without neurologic signs and symptoms) should be considered at first remission (before

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consolidation) in patients at high-risk for CNS disease (e.g., those with high-risk AML).[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

Ongoing

complete remission: AML

1st **consolidation therapy**

Primary options

» cytarabine

OR

» cytarabine

--AND--

» idarubicin
-or-
» daunorubicin
-or-
» mitoxantrone

OR

» daunorubicin/cytarabine liposomal

» The aim of consolidation therapy is to maintain complete remission and reduce the risk of relapse following induction therapy.

» Consolidation therapy is guided by risk factors for relapse (e.g., genetic abnormalities, white blood cell count at presentation, measurable [minimal] residual disease [MRD]).

» Consolidation regimens usually consist of up to 4 cycles of intermediate-dose or high-dose cytarabine (IDAC or HiDAC) alone or in combination with other chemotherapy drugs (e.g., idarubicin, daunorubicin, mitoxantrone).[38]

» Patients with therapy-related AML (tAML) or AML with myelodysplasia-related changes (AML-MRC) who received liposomal daunorubicin/cytarabine (also known as CPX-351) for induction therapy can also receive this regimen for consolidation therapy (up to 2 cycles).[72] [73] [74]

» MRD assessment should be performed during and after treatment to assess treatment response and inform prognosis and treatment planning. The European LeukemiaNet has published recommendations for assessing MRD (including frequency and timing) in AML.[23] [75]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Ongoing

Treatment recommended for ALL patients in selected patient group

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Patients with AML who are unsuitable for or decline standard- or low-intensive chemotherapy should be offered best supportive care.[38] [126]

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment. Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. See Tumor lysis syndrome .

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor. In AML patients, hydroxyurea is recommended for leukoreduction.[23] [38] It is recommended that WBC count is lowered to <25,000/microliter (<25 × 10^9/L). Urgent leukapheresis may be considered in patients with AML (not including APL) who are symptomatic and have a very high WBC count.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in those with significant bleeding.

Ongoing

» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

adjunct **stem cell transplantation**

Treatment recommended for SOME patients in selected patient group

» Patients with intermediate-risk disease and particularly those with adverse-risk disease may be considered for allogeneic stem cell transplantation (SCT; with reduced-intensity conditioning for older patients) following one or more cycles of consolidation chemotherapy, if they are fit and able to tolerate SCT.[38] [76] [77] These patients may also proceed directly to transplant if a suitable donor is available at first complete remission (i.e., in lieu of consolidation chemotherapy).

» Allogeneic SCT may be considered in patients with favorable-risk disease with persistent MRD if a suitable donor is available.[23] [38]

» Autologous SCT is an alternative to allogeneic SCT in select patients (e.g. those with intermediate-risk disease who are MRD negative) if a donor is not available, but is not commonly performed.[23] [60] [78] [79]

with CD33-positive AML **plus** **gemtuzumab ozogamicin**

Treatment recommended for ALL patients in selected patient group

Primary options

» gemtuzumab ozogamicin

» Patients with CD33-positive AML and favorable- or intermediate-risk disease can be treated with gemtuzumab ozogamicin (an anti-CD33 monoclonal antibody conjugated with the cytotoxic agent calicheamicin) in combination with induction and consolidation chemotherapy. [80] [81][82] [83]

» Important adverse effects associated with gemtuzumab ozogamicin include hypersensitivity reactions, hepatotoxicity (veno-occlusive disease), and myelotoxicity.

Ongoing

» See local specialist protocol for dosing guidelines.

with FLT3-mutant AML **plus** **midostaurin or quizartinib**

Treatment recommended for ALL patients in selected patient group

Primary options

» midostaurin

OR

» quizartinib

» Patients with FLT3-mutated AML can be treated with the oral tyrosine kinase inhibitors midostaurin (for FLT3-ITD-mutated or FLT3-TKD-mutated) or quizartinib (for FLT3-ITD-mutated only) in combination with standard intensive induction and consolidation chemotherapy.[84] [85] [86]

» Quizartinib is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

» See local specialist protocol for dosing guidelines.

with CNS involvement **plus** **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» A screening lumbar puncture (in patients without neurologic signs and symptoms) should be considered at first remission (before consolidation) in patients at high-risk for CNS disease (e.g., those with white blood cell [WBC] count >40,000/microliter [>40 × 10^9/L], monocytic lineage, mixed-phenotype acute leukemia, extramedullary disease, or FLT3 mutations).[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two

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times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

eligible for maintenance therapy — **adjunct** — **maintenance therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» azacitidine

OR

» midostaurin

OR

» quizartinib

OR

» sorafenib

OR

» gilteritinib

» Maintenance therapy with oral azacitidine (single agent) may be considered for patients with complete remission after intensive induction chemotherapy (with or without complete blood count recovery), but who are not candidates for intensive consolidation therapy (including stem cell transplantation [SCT]).[87]

» Maintenance therapy with oral azacitidine should not replace consolidation therapy.

» Patients with FLT3-mutated AML who achieve complete remission with midostaurin or quizartinib (in combination with standard induction and consolidation chemotherapy) may continue these agents as monotherapy for maintenance therapy post-consolidation chemotherapy.[84] [85] [86] Use of midostaurin for maintenance therapy is off-label.

» Several oral kinase inhibitors can be considered for post-allogeneic SCT maintenance therapy in patients with FLT3-mutated AML. These include: sorafenib (for FLT3-ITD-mutated only); gilteritinib (for FLT3-ITD-mutated or FLT3-TKD-mutated, particularly if patients are

Ongoing

measurable [minimal] residual disease [MRD]-positive before or after SCT); midostaurin (for FLT3-ITD-mutated or FLT3-TKD-mutated); and quizartinib (for FLT3-ITD-mutated only).[38] [85] [86] [88] [89][90]

» The role of maintenance therapy in the posttransplant setting is still evolving.

» See local specialist protocol for dosing guidelines.

complete remission: acute promyelocytic leukemia (APL)

1st **consolidation therapy**

» Consolidation regimens for APL are usually similar to induction regimens (e.g., all-trans-retinoic acid [ATRA; also known as tretinoin] plus arsenic trioxide [for non-high-risk APL]; ATRA plus arsenic trioxide plus chemotherapy [for high-risk APL]).[38][61]

» Measurable (minimal) residual disease (MRD) assessment (to detect the PML::RARA fusion transcript) should be carried out following consolidation therapy to evaluate treatment response and guide subsequent treatment. [60] [61] Patients with high-risk APL should undergo long-term MRD monitoring (e.g., every 3 months for 2 years following treatment) due to the increased risk of relapse.[38] [60] [61] Long-term MRD monitoring is not required for non-high-risk patients in molecular remission following consolidation therapy.

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment (particularly for patients with APL who are treated with arsenic trioxide). Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated

Ongoing

serum lactate dehydrogenase, which can occur following treatment or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. See Tumor lysis syndrome .

» Differentiation syndrome: treatments for APL (e.g., ATRA, arsenic trioxide) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128] Differentiation syndrome is characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated WBC (>10,000/microliter [>10 × 10^9/L]). Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the treatment causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor. In APL patients, hydroxyurea should be considered to manage high WBC count during treatment with ATRA and arsenic trioxide (particularly if differentiation syndrome occurs).[38] [61] Leukapheresis is not recommended for patients with APL because it may worsen coagulopathy.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] During the acute phase of APL, patients are at particular risk of significant coagulopathy. Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in patients with APL or those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in patients with APL or those with significant bleeding.

Ongoing

» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

with CNS involvement **plus** **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

with high-risk APL **adjunct** **maintenance therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» tretinoin
-and-
» mercaptopurine
-and-
» methotrexate

» Maintenance therapy may be considered for patients with high-risk APL, but it is not required for non-high-risk patients.[60] [61]

» Maintenance regimens for APL usually consist of ATRA plus mercaptopurine and methotrexate for 1 to 2 years.[121] [122] [123]

» With close measurable (minimal) residual disease (MRD) monitoring post-consolidation,

Ongoing

the role of maintenance therapy is now being challenged.[124] [125] In some countries, such as the UK, maintenance therapy for APL is no longer used.

» See local specialist protocol for dosing guidelines.

relapsed or refractory AML

1st **salvage therapy, reinduction therapy, or clinical trial**

Primary options

» cytarabine

OR

» cytarabine
--AND--
» daunorubicin
-or-
» idarubicin
-or-
» mitoxantrone

OR

» venetoclax
--AND--
» azacitidine
-or-
» decitabine
-or-
» cytarabine

OR

» gilteritinib

OR

» ivosidenib

OR

» olutasidenib

OR

» enasidenib

OR

Ongoing

» gemtuzumab ozogamicin

» Patients with relapsed or refractory AML have a poor prognosis.[108]

» There is no standard salvage regimen for relapsed or refractory AML. Where possible, patients should be offered enrollment in a clinical trial.

» At relapse, all patients should undergo molecular re-evaluation to identify targets (actionable genes) for salvage therapy, which may have emerged since diagnosis (due to clonal evolution) or were not detected at diagnosis.[23]

» Relapse after first complete remission occurs in approximately 50% of patients who have received standard induction therapy, usually in the first year following treatment. Approximately 40% to 60% of relapsed patients achieve a second complete remission with intensive salvage chemotherapy (e.g., intermediate-dose cytarabine [IDAC] or high-dose cytarabine [HiDAC] with or without an anthracycline or mitoxantrone), although duration of remission is usually limited.[109]

» Patients unsuitable for intensive salvage chemotherapy can be considered for low-intensity salvage therapy, which should be continued until disease progression or intolerance. Options include: venetoclax combined with a hypomethylating agent (azacitidine or decitabine) or low-dose subcutaneous cytarabine (LDAraC); gilteritinib (an oral kinase inhibitor) for patients with FLT3-mutated AML; ivosidenib (an IDH1 inhibitor) for patients with IDH1-mutated AML; olutasidenib (an IDH1 inhibitor) for patients with IDH1-mutated AML; enasidenib (an IDH2 inhibitor) for patients with IDH2-mutated AML; and gemtuzumab ozogamicin (single agent) for patients with CD33-positive AML.[102][110] [111] [112] [113][114] [115][116]

» Important predictors of response to salvage therapy are age, genetic abnormalities, duration of first remission, and history of previous stem cell transplantation (SCT).[117] [118] [119]

» Patients who are unable to tolerate salvage therapy or who decline further treatment should be offered best supportive care and/or palliative care.

Ongoing

» Reinduction therapy (with chemotherapy) may be considered for all patients with relapse following long remission (i.e., ≥12 months following induction therapy).[38] [60]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Patients with AML who are unsuitable for or decline standard- or low-intensive chemotherapy should be offered best supportive care.[38] [126]

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment. Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. TLS associated with venetoclax may occur as early as 6 to 8 hours following the first dose in patients with AML.[96] TLS risk assessment should be carried out before administering venetoclax, and guidance on TLS prophylaxis, laboratory monitoring, dose titration, and drug interactions should be strictly adhered to during treatment with venetoclax.[38] [96] See Tumor lysis syndrome .

» Differentiation syndrome: treatments for AML (e.g., ivosidenib, enasidenib, olutasidenib, gilteritinib) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128] Differentiation syndrome is characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated WBC count (>10,000/

Ongoing

microliter [>10 × 10^9/L]). Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the treatment causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor. In AML patients, hydroxyurea is recommended for leukoreduction.[23] [38] It is recommended that WBC count is lowered to <25,000/microliter (<25 × 10^9/L), particularly before initiating treatment with hypomethylating agents and venetoclax.[23] [38] Urgent leukapheresis may be considered in patients with AML (not including APL) who are symptomatic and have a very high WBC count.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in those with significant bleeding.

» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

adjunct **stem cell transplantation**

Treatment recommended for SOME patients in selected patient group

» Patients who achieve second remission with intensive salvage chemotherapy should undergo allogeneic stem cell transplantation to reduce the risk of relapse, if they are eligible and a suitable donor is available.[38] [60] [108]

MANAGEMENT

Ongoing

with CNS involvement | **plus** | **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

relapsed or refractory acute promyelocytic leukemia (APL)

1st | **salvage therapy + stem cell transplantation or clinical trial**

Primary options

» tretinoin
-and-
» idarubicin

OR

» tretinoin
-and-
» daunorubicin
-and-
» cytarabine

OR

» gemtuzumab ozogamicin

OR

» tretinoin
-and-
» arsenic trioxide

OR

Ongoing

» tretinoin

--AND--

» arsenic trioxide

--AND--

» idarubicin

-or-

» daunorubicin

OR

» tretinoin

-and-

» arsenic trioxide

-and-

» gemtuzumab ozogamicin

» Patients with relapsed or refractory APL should be considered for salvage therapy to achieve molecular remission (i.e., measurable [minimal] residual disease [MRD] negativity).

» Salvage therapy should be based on previous treatment and whether relapse occurs early or late (definitions vary, but most relapses occur <2 years).[38] [60] [61] Patients who relapse early following treatment comprising all-trans-retinoic acid (ATRA; also known as tretinoin) plus arsenic trioxide can be treated with ATRA plus chemotherapy, or single-agent gemtuzumab ozogamicin.[38][61] Patients who relapse early following treatment with ATRA plus chemotherapy (without arsenic trioxide) can be treated with arsenic trioxide-containing regimens (e.g., ATRA plus arsenic trioxide).[38] [61] Retreatment with the previous regimen may be considered if relapse occurs late.

» Patients with relapsed or refractory disease should be referred to a stem cell transplantation (SCT) center and, depending on the MRD status following salvage therapy, an autologous SCT (if MRD negative) or allogeneic SCT (if MRD positive or refractory disease) should be arranged.[38][61]

» Patients not eligible for SCT may be continued on salvage therapy or enrolled in a clinical trial (if available).

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

MANAGEMENT

Ongoing

» Consider supportive care measures for all patients, at all stages of treatment, to prevent or manage complications.

» Electrolyte abnormalities: correction of electrolyte abnormalities is important before and during treatment (particularly for patients with APL who are treated with arsenic trioxide). Patients should be commenced on hydration (e.g., intravenous fluids).

» Tumor lysis syndrome (TLS): an oncologic emergency. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. See Tumor lysis syndrome .

» Differentiation syndrome: treatments for APL (e.g., ATRA, arsenic trioxide) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128] Differentiation syndrome is characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated WBC count (>10,000/microliter [>10 × 10^9/L]). Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the treatment causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]

» Hyperleukocytosis: generally defined as a WBC count >100,000/microliter (>100 × 10^9/L) and is considered a poor prognostic factor. In APL patients, hydroxyurea should be considered to manage high WBC count during treatment with ATRA and arsenic trioxide (particularly if differentiation syndrome occurs).[38] [61] Leukapheresis is not recommended for patients with APL because it may worsen coagulopathy.[38] [61]

» Anemia and thrombocytopenia: red blood cell and platelet transfusions may be required depending on symptoms and blood counts.[126] During the acute phase of APL,

Ongoing

patients are at particular risk of significant coagulopathy. Packed red blood cell transfusion is recommended to keep hematocrit >25%. Platelets should be prophylactically transfused once platelet count is <10,000/microliter (<10 × 10^9/L).[23] [38] Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in patients with APL or those with significant bleeding.[38] [61] Activated partial thromboplastin time (aPTT) and fibrinogen levels should be normalized by infusions of fresh frozen plasma and cryoprecipitate in patients with APL or those with significant bleeding.

» Infections and febrile neutropenia: during acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents. See Febrile neutropenia .

with CNS involvement **plus** **intrathecal cytarabine or methotrexate**

Treatment recommended for ALL patients in selected patient group

Primary options

» cytarabine

OR

» methotrexate

» CNS imaging and lumbar puncture should be carried out in patients with neurologic signs and symptoms suggesting CNS involvement.[38]

» If CNS disease is confirmed, intrathecal cytarabine or methotrexate should be given two times per week until the cerebrospinal fluid is clear and weekly thereafter for a further 4 to 6 weeks.[38]

» See local specialist protocol for dosing guidelines.

MANAGEMENT

Emerging

Decitabine/cedazuridine

Decitabine/cedazuridine (oral fixed-dose combination) is approved in Europe for patients with newly diagnosed AML who are ineligible for standard induction chemotherapy. In a phase 3 study, decitabine/cedazuridine demonstrated pharmacokinetic equivalence to standard intravenous decitabine in AML patients not suitable for standard induction chemotherapy.[130]

Cladribine

A purine nucleoside analog, one small phase 2 trial concluded that a cladribine-containing lower-intensity regimen was effective in older or unfit patients with newly diagnosed AML.[131] In one phase 3 study, patients with untreated AML demonstrated improved survival with cladribine combined with standard induction therapy (daunorubicin and cytarabine) compared with those who received standard induction therapy alone.[132] Cladribine combined with standard induction therapy also improved survival in a phase 2 randomized trial of older patients (median age 66 years) with AML.[133] Phase 3 randomized controlled trials assessing the role of cladribine in the management of AML are continuing to recruit.[134]

Sorafenib plus azacitidine for newly diagnosed or relapsed FLT3-mutated AML

Sorafenib is an oral kinase inhibitor. In one small phase 1/2 study (n=27) of patients with newly diagnosed FLT3-mutated AML who were unsuitable for standard chemotherapy, a response rate of 78% (26% with complete response) was achieved with sorafenib plus azacitidine.[135] In a phase 2 study of patients with relapsed FLT3-ITD mutated AML, a response rate of 46% (16% with complete response) was achieved with sorafenib plus azacitidine.[136]

Quizartinib for relapsed or refractory FLT3-mutated AML

Quizartinib is a potent oral kinase inhibitor. In an open-label phase 3 study of patients with relapsed or refractory FLT3-ITD-positive AML, quizartinib improved survival compared with salvage chemotherapy.[137]

Guadecitabine

Guadecitabine is a second-generation hypomethylating agent. It is formulated as a dinucleotide of the drug decitabine with deoxyguanosine, which increases the half-life of decitabine.[138] In a phase 3 study of patients with untreated AML who were unsuitable for intensive chemotherapy, guadecitabine did not demonstrate improved survival compared with a preselected treatment (e.g., azacitidine, decitabine, or low-dose cytarabine).[139] Clinical trials investigating its use in patients with relapsed or refractory AML are ongoing.[140]

Clofarabine

Clofarabine is a second-generation purine nucleoside analog. Findings from one study suggested that clofarabine with cytarabine during remission induction could potentially reduce the need for anthracycline and etoposide in pediatric patients with AML, and may reduce rates of cardiomyopathy and treatment-related cancer.[141] In a phase 3 study of older patients with AML who were unsuitable for intensive chemotherapy, clofarabine improved remission and overall response rates compared with low-dose cytarabine, but did not improve survival.[142] Patients receiving clofarabine were at increased risk of myelotoxicity and required more supportive care.[142]

Crenolanib

Crenolanib is an oral benzimidazole type I tyrosine kinase inhibitor. It selectively and potently inhibits signaling of wild-type and mutant isoforms of class III receptor tyrosine kinases FLT3 and PDGFR-alpha/

beta. Crenolanib is currently being evaluated in phase 3 studies of adult patients with FLT3-mutated AML.[143] The EMA has granted orphan drug designation to crenolanib for the treatment of AML.

Flotetuzumab

Flotetuzumab is a dual-affinity retargeting (DART) antibody-based molecule that recognizes CD123 with CD3. The primary mechanism of action of flotetuzumab is believed to be its ability to redirect T lymphocytes to kill CD123-expressing cells. Leukemic stem cells are characterized by high levels of CD123 expression. Flotetuzumab is currently being evaluated in phase 1/2 studies of patients with relapsed or refractory AML.[144] The FDA has granted orphan drug status to flotetuzumab.

Gilteritinib plus venetoclax and azacitidine

In a phase 1/2 study, the addition of gilteritinib (an oral kinase inhibitor) to venetoclax plus azacitidine resulted in a high rate of complete remission/complete remission with incomplete hematologic recovery (96%) and a deep FLT3 molecular response in patients with newly diagnosed FLT3-mutated AML.[145]

Patient discussions

Patients should be advised to present to their physician immediately if they develop any signs of infection or fever.

Hospitalization may be required to deal with complications, particularly neutropenic fever.

Monitoring

Monitoring

Patients with AML should be closely monitored for recurrence of the disease and development of complications.

For patients with an AML-defining genetic abnormality detected at diagnosis, testing for the abnormality should be repeated during and after completion of treatment to monitor for residual disease.[23] For patients without such abnormalities, regular routine complete blood count to detect any cytopenias is recommended.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
tumor lysis syndrome (TLS)	**short term**	**high**
An oncologic emergency requiring immediate management. TLS is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and/or elevated serum lactate dehydrogenase, which can occur following treatment (including chemotherapy and targeted agents e.g., venetoclax) or spontaneously (rare), particularly if white blood cell (WBC) count (tumor burden) is high. TLS can lead to cardiac arrhythmias, seizures, acute renal failure, and death, if untreated. Vigorous hydration (with intravenous fluids), phosphate-binding agents, and hypouricemic agents (e.g., allopurinol or rasburicase) should be used to prevent or treat TLS. TLS associated with venetoclax may occur as early as 6 to 8 hours following the first dose in patients with AML.[96] TLS risk assessment should be carried out before administering venetoclax, and guidance on TLS prophylaxis, laboratory monitoring, dose titration, and drug interactions should be strictly adhered to during treatment with venetoclax.[38] [96]		
leukostasis (symptomatic hyperleukocytosis)	**short term**	**high**
A life-threatening complication that may occur if white blood cell (WBC) count is extremely elevated (>100,000/microliter [>100 × 10^9/L]). Symptoms of leukostasis include respiratory distress and altered mental status, caused by leukemia cells impairing microvascular perfusion in pulmonary and central nervous system tissue, respectively. In AML patients with hyperleukocytosis, hydroxyurea is recommended for leukoreduction.[23] [38] It is recommended that WBC count is lowered to <25,000/microliter (<25 × 10^9/L), particularly before initiating treatment with hypomethylating agents and venetoclax.[23] [38] In APL patients, hydroxyurea should be considered to manage high WBC count during treatment with all-trans-retinoic acid (ATRA; also known as tretinoin) and arsenic trioxide (particularly if differentiation syndrome occurs).[38] [61] Urgent leukapheresis may be considered in a symptomatic patient with AML and a very high WBC count; however, this is not recommended in patients with acute promyelocytic leukemia (APL) because leukapheresis may worsen coagulopathy.[38]		
neutropenia	**short term**	**high**
Consequence of bone marrow infiltration by leukemic cells and of adverse effects of treatment. Growth factors such as granulocyte-colony stimulating factor have been shown to shorten the duration of neutropenia and reduce the risk of all-cause mortality in AML.[155] [156]		
pancytopenia	**short term**	**high**
Consequence of bone marrow infiltration by leukemic cells and of adverse effects of treatment.		

Complications	Timeframe	Likelihood
Platelets should be prophylactically transfused once the thrombocyte count is <10,000/microliter (<10 × 10^9/L). Platelet count needs to be maintained at >50,000/microliter (>50 × 10^9/L) in patients with APL or those with significant bleeding.[38] [61] Packed red blood cell transfusion is recommended to keep hematocrit >25%.		
infections and febrile neutropenia	**short term**	**high**
Most infections are caused by gram-negative bacteria, gram-positive bacteria (mostly staphylococci), and, less commonly, invasive fungal and viral infections. During acute illness and chemotherapy, all patients should receive antibiotic prophylaxis (e.g., a fluoroquinolone) to reduce the risk of infection and febrile neutropenia.[129] Patients should also receive antifungal prophylaxis with a mold-active antifungal agent (e.g., posaconazole).[129] Other measures to reduce the risk of febrile neutropenia such as body hygiene, germ-reduced food, and reverse isolation or high-efficiency particulate air filtration are indicated. Patients presenting with febrile illness need to be investigated and treated appropriately and promptly with antibiotics or anti-infective agents.		
disseminated intravascular coagulation (DIC)	**short term**	**medium**
DIC is frequently present at diagnosis or occurs soon after acute promyelocytic leukemia (APL) patients commence chemotherapy. It occurs less commonly with monocytic AML. Requires emergency management. If left untreated, it results in high-risk of hemorrhagic death. The induction of tumor cell differentiation with all-trans-retinoic acid (ATRA; also known as tretinoin) and supportive therapy with appropriate blood products can lead to a rapid reversal of the coagulopathy.		
central nervous system (CNS) leukemia	**short term**	**low**
AML rarely involves the CNS in adult patients, but may be more common in pediatric AML patients. Incidence of CNS leukemia has decreased since the incorporation of cytarabine.[157] Patients at high-risk for CNS disease include those with elevated white blood cell (WBC) count (>40,000/microliter [>40 × 10^9/L]), monocytic lineage, mixed-phenotype acute leukemia, extramedullary disease, FLT3 mutations, or high-risk acute promyelocytic leukemia (APL).[38] Morphologic and flow cytometric examination of the cerebrospinal fluid confirms the diagnosis. Treated with intrathecal cytarabine or methotrexate.		
differentiation syndrome	**short term**	**low**
Treatments for AML (e.g., ivosidenib, enasidenib, olutasidenib, gilteritinib) and acute promyelocytic leukemia (APL; e.g., all-trans-retinoic acid [ATRA; also known as tretinoin], arsenic trioxide) can cause differentiation syndrome, which can be life-threatening if not treated promptly.[105] [115] [127] [128] Differentiation syndrome is characterized by fever, fluid retention, respiratory distress, pulmonary infiltrates, pulmonary or pericardial effusion, and an elevated white blood cell (WBC) count (>10,000/microliter [>10 × 10^9/L]).		

FOLLOW UP

Complications	Timeframe	Likelihood
Patients should be monitored for hypoxia, pulmonary infiltrates, and pleural effusion. Patients with differentiation syndrome should be promptly treated with dexamethasone.[61] In severe cases, the drug causing differentiation syndrome may be temporarily discontinued until symptoms resolve.[61]		
delayed therapy-related complications	**long term**	**low**
Long-term complications of chemotherapy include myelodysplasia, secondary malignancies, endocrine dysfunction (mainly hypothyroidism), and cardiomyopathy. Investigations are instigated on suspicion. Infertility may be an issue for younger patients treated for AML, and they should be referred to specialized fertility/assisted conception units.		

Prognosis

The 5-year survival rate of patients with AML is 31.9% (based on US data, 2014-2020).[5]

Younger (<60 years of age) and healthier patients

The overall cure rate for patients between 18 and 60 years of age with AML is 35% to 40%.[148] However, cure rate will vary depending on the presence or absence of certain prognostic markers, including cytogenetic abnormalities and genetic mutations.[23] [117] [149]

Population-based statistics from the US Surveillance, Epidemiology, and End Results Program (2014-2020) report 5-year relative (from the time of diagnosis) of 63.7% among patients ages <50 years.[150]

Older (≥60 years of age) patients

The overall outlook for older patients is poorer than that of younger patients. This is based on the higher prevalence of unfavorable cytogenetics, antecedent myelodysplasia in older patients, a higher incidence of multidrug resistance, and an increased frequency of coexistent medical conditions that affect the ability to tolerate intensive treatment.[151] [152]

Population-based statistics from the US Surveillance, Epidemiology, and End Results Program (2014-2020) report 5-year relative survival from the time of diagnosis of:[150]

- 38.9% for patients ages 50 to 64 years, and
- 11.2% for patients ages >65 years.

Prognosis according to risk and age

For favorable-risk patients (according to the 2022 European LeukemiaNet [ELN] risk groups), 5-year overall survival is:[153]

- 54.6% for all patients
- 62.2% for patients ages <60 years
- 40.6% for patients ages ≥60 years.

For intermediate-risk patients (according to the 2022 ELN risk groups), 5-year overall survival is:[153]

- 34.2% for all patients
- 44.2% for patients ages <60 years
- 19.4% for patients ages ≥60 years.

For adverse-risk patients (according to the 2022 ELN risk groups), 5-year overall survival is:[153]

- 14.8% for all patients
- 25.1% for patients ages <60 years
- 7.6% for patients ages ≥60 years.

Acute promyelocytic leukemia (APL)

The cure rates for APL with current treatment protocols exceed 80%.[154] The aim of current trials is to determine schedules that offer maximum cure rates with minimal toxicities.

Diagnostic guidelines

International

NCCN guidelines: acute myeloid leukemia (https://www.nccn.org/guidelines/category_1) [38]

Published by: National Comprehensive Cancer Network **Last published:** 2024

Diagnosis and management of AML in adults (https://ashpublications.org/blood/article/140/12/1345/485817/Diagnosis-and-management-of-AML-in-adults-2022) [23]

Published by: European LeukemiaNet **Last published:** 2022

Acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines) [60]

Published by: European Society for Medical Oncology **Last published:** 2020

Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet (https://ashpublications.org/blood/article/133/15/1630/273295/Management-of-acute-promyelocytic-leukemia-updated) [61]

Published by: European LeukemiaNet **Last published:** 2019

Recommendations for laboratory testing of UK patients with acute myeloid leukaemia (https://b-s-h.org.uk/guidelines) [62]

Published by: British Society for Haematology **Last published:** 2023

Management of older patients with frailty and acute myeloid leukaemia: a British Society for Haematology good practice paper#(https://b-s-h.org.uk/guidelines) [63]

Published by: British Society for Haematology **Last published:** 2022

Guidelines for the diagnosis and management of acute myeloid leukaemia in pregnancy (https://b-s-h.org.uk/guidelines) [64]

Published by: British Society for Haematology **Last published:** 2015

Treatment guidelines

International

NCCN guidelines: acute myeloid leukemia (https://www.nccn.org/guidelines/category_1) [38]

Published by: National Comprehensive Cancer Network **Last published:** 2024

American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults (https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines) [65]

Published by: American Society of Hematology **Last published:** 2020

Diagnosis and management of AML in adults (https://ashpublications.org/blood/article/140/12/1345/485817/Diagnosis-and-management-of-AML-in-adults-2022) [23]

Published by: European LeukemiaNet **Last published:** 2022

Acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines) [60]

Published by: European Society for Medical Oncology **Last published:** 2020

Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukemia patients with FLT3-internal tandem duplication (https://haematologica.org/article/view/9426) [146]

Published by: Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation **Last published:** 2020

Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet (https://ashpublications.org/blood/article/133/15/1630/273295/Management-of-acute-promyelocytic-leukemia-updated) [61]

Published by: European LeukemiaNet **Last published:** 2019

European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia (https://academic.oup.com/jac/article/73/12/3221/5063539) [147]

Published by: European Conference on Infections in Leukaemia **Last published:** 2018

Management of older patients with frailty and acute myeloid leukaemia: a British Society for Haematology good practice paper (https://b-s-h.org.uk/guidelines) [63]

Published by: British Society for Haematology **Last published:** 2022

International

Guidelines for the diagnosis and management of acute myeloid leukaemia in pregnancy (https://b-s-h.org.uk/guidelines) [64]

Published by: British Society for Haematology **Last published:** 2015

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- National Cancer Comprehensive Network. NCCN guidelines: acute myeloid leukemia [internet publication]. Full text (https://www.nccn.org/guidelines/category_1)
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Images

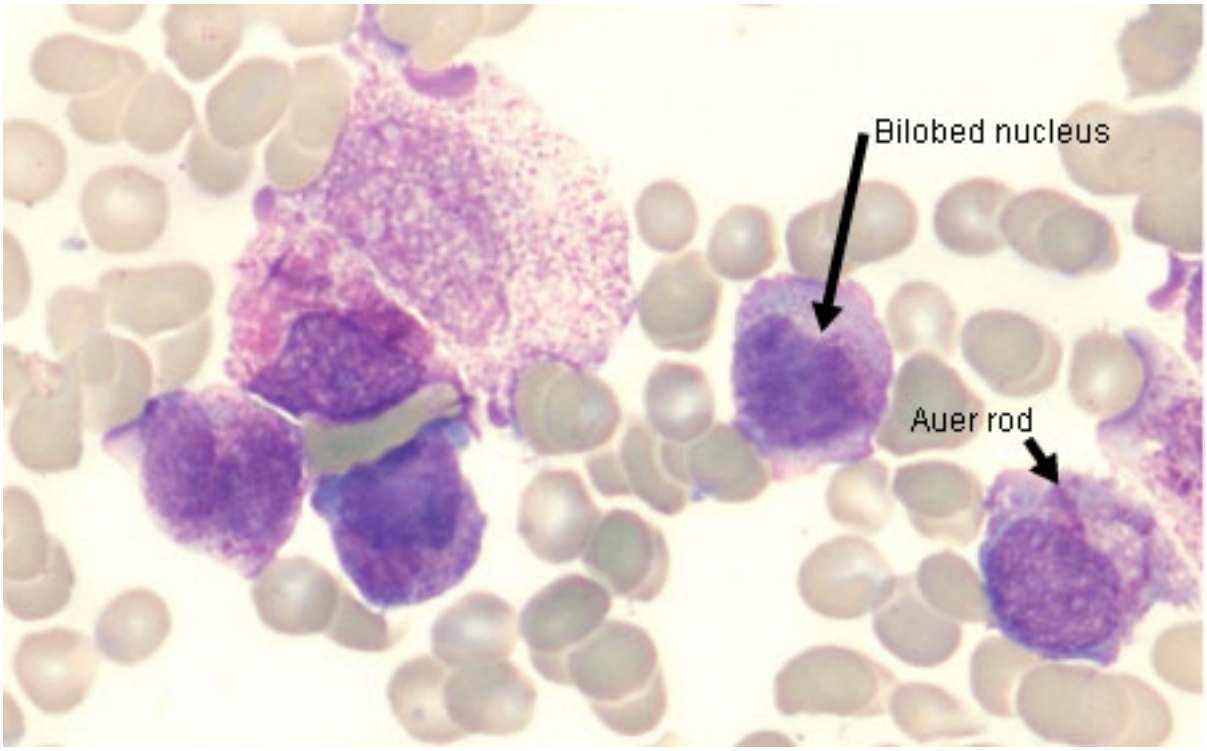

Figure 1: Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes with bilobed nuclei and bundles of Auer rods

From the collection of Drs K. Raj and P. Mehta; used with patient consent

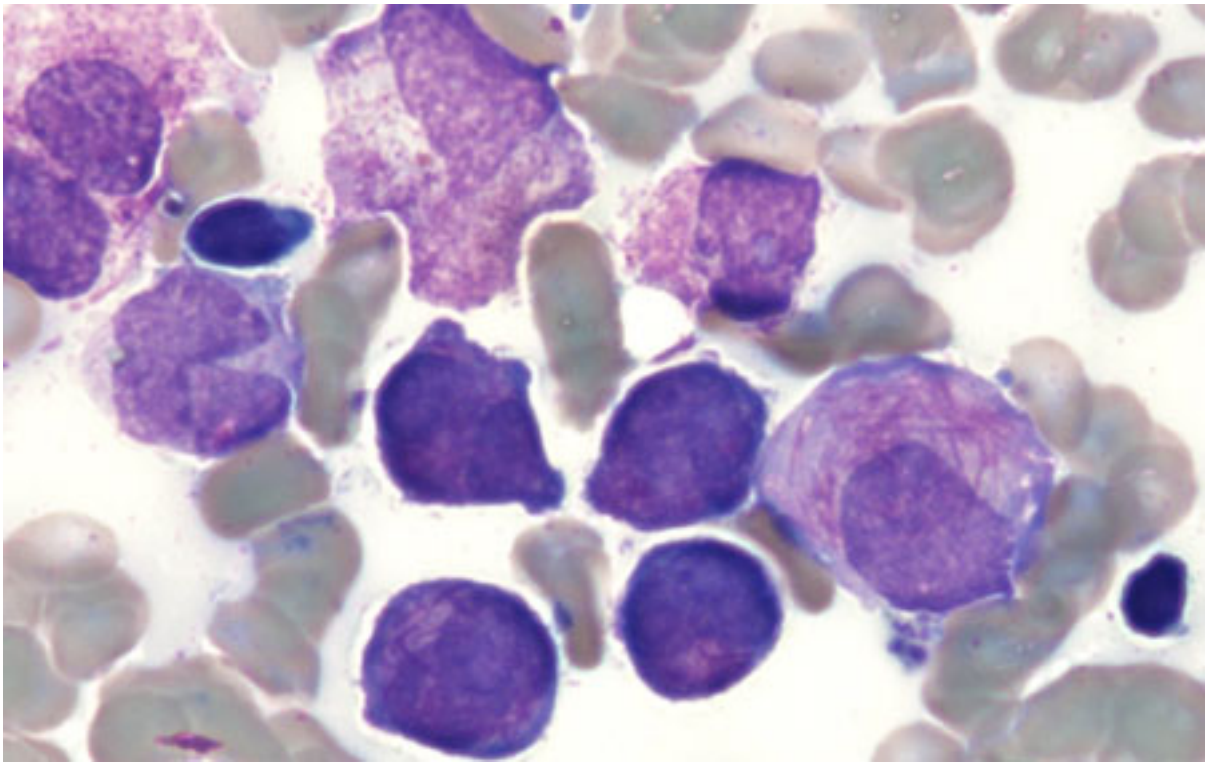

Figure 2: Peripheral blood film of a patient with acute promyelocytic leukemia showing hypergranular promyelocytes, some with bundles of Auer rods

From the collection of Drs K. Raj and P. Mehta; used with patient consent

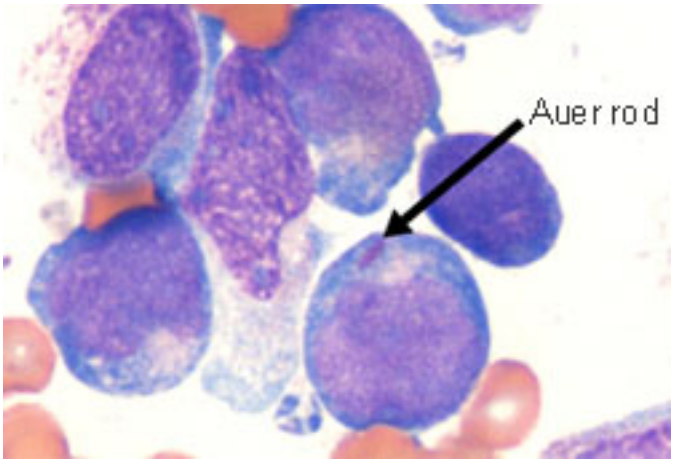

Figure 3: Peripheral blood film of a patient with acute myeloid leukemia with maturation showing myeloid blasts with an Auer rod

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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