Holistic Integrative Oncology

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CACA guidelines for holistic integrative management of adult acute myeloid leukemia

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Abstract

The CACA Guidelines was summarized by Hematology Oncology Committee of China Anti- Cancer Association. This portion of the CACA Guidelines for adult acute myeloid leukemia (AML) not only focuses on diagnosis, the treatment options for younger (age < 60 years) and older (age ≥ 60 years) patients (including non-APL, APL, R/R AML), but also pay attention to the treatment of AML complications, including central nervous system leukemia (CNSL), cardiotoxicity, agranulocytosis and fever, hepatitis B virus reactivation, uric acid nephropathy, bleeding and coagulation disorders, and nursing for patients with AML from the perspective of holistic integrative medicine to enhance the quality of life and treatment effects.

Keywords Acute myeloid leukemia, Diagnosis, Treatment

1 Diagnosis of adult acute myeloid leukemia

1.1 Diagnosis of adult acute myeloid leukemia

The diagnostic criteria for acute myeloid leukemia (AML) are based on the World Health Organization (WHO) 2016 classification criteria for tumors of hematopoietic and lymphoid tissues. Blast cells ≥ 20% in peripheral blood or bone marrow are the necessary for the diagnosis of AML. If patients are confirmed to have recurrent cytogenetic abnormalities including t (8; 21) (q22; q22), inv (16) (p13; q22) or t (16; 16) (p13; q22) and t (15; 17) (q22; q12), they should be diagnosed with AML even when blast cells are < 20% [1].

During clinical reception, history-taking should include age, the past medical history and treatment situation (especially the history of blood diseases or history of tumors), vital organs insufficiency, extramedullary infiltration, and the family history (especially the history of blood diseases or history of tumors), as well as the history of inherited metabolic diseases. For patients suspected of having leukemia, medical examinations should be carried out, while in the diagnosis process, bone marrow cell morphology (cell morphology, cytochemistry and histopathology), immunophenotyping and cytogenetics (karyotypes) should be assessed. When necessary, fluorescence in situ hybridization (FISH) and molecular tests for fusion genes and gene mutations related to leukemia should be conducted. Human leukocyte antigen (HLA) matching may be performed for patients undergoing allogeneic hematopoietic stem cell transplantation.

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1.2 Prognosis and stratification factors of AML

1.2.1 Poor prognosis factors for AML

Age ≥ 60 years old and a history of myelodysplastic syndromes (MDS) or myeloproliferative neoplasm (MPN), treatment-related/secondary AML, hyperleukocytosis ($\geq 100 \times 10^9$/L), central nervous system leukemia (CNSL), or extramedullary infiltration (except for liver, spleen and lymph node involvement), among other factors, are factors indicating a poor prognosis of AML.

1.2.2 Risk rating of cytogenetic/molecular genetic indexes

Genetic prognostic grouping for AML is carried out according to the cytogenetic and molecular genetic abnormalities of AML during diagnosis, as shown in Table 1 [2–8].

1.3 Diagnosis of relapsed or refractory acute myeloid leukemia (R/R AML)

1.3.1 Diagnostic criteria for relapsed AML

Leukemia blast cells ≥ 0.05 in bone marrow or peripheral blood reoccur after complete remission (CR) (except for other reasons including bone marrow regeneration after consolidation chemotherapy), or the occurrence of extramedullary infiltration of leukemia cells are factors for the diagnosis of relapsed AML.

1.3.2 Diagnostic criteria for refractory leukemia

Patients who do not achieve CR after 2 courses of standard treatment regimens, patients who relapse within 12 months following CR; patients who relapse more than 12 months after CR but not CR after re-induction treatment; patients who relapse for 2 or more times, and patients with persistent AML are diagnosed with refractory leukemia.

2 Treatment and nursing of adult acute myeloid leukemia and its complications

For patients with AML (not APL), participation in clinical studies is first recommended. If patients are not able to participate in a clinical study, they should be treated according to the following suggestions.

2.1 Treatment of preliminarily diagnosed AML (not APL)

2.1.1 Treatment for patients with AML < 60 years old

(1) Induction treatment (Table 2)
(2) Monitoring after induction treatment

① Treatment monitoring after induction with a standard dose of Ara-C (Tables 3 and 4):
② Monitoring after induction with a intermediate or high dose of Ara-C (Table 5):

Table 1 Genetic prognostic grouping for AML

Level of prognosis	Cytogenetics	Molecular genetics
Good prognosis	inv (16) (p13; q22) or t (16; 16) (p13; q22) t (8; 21) (q22; q22)	NPM1 mutation without FLT3-ITD mutation or with FLT3-ITD mutation[a] of a low allelic ratio Biallelic mutated CEBPA
Moderate prognosis	Normal karyotypes t (9; 11) (p22; q23) Other abnormalities	inv (16) (p13; q22) or t (16; 16) (p13; q22) with C-kit mutation[b] t (8; 21) (q22; q22) with C-kit mutation[b] NPM1 mutation with FLT3-ITD mutation[a] of a high allelic ratio
Poor prognosis	Monomeric karyotypes Complex karyotypes (≥ 3 chromosome aberrations), without t (8; 21) (q22; q22), inv (16) (p13; q22) or t (16;16) (p13; q22) or t (15; 17) (q22; q12) -5 -7 5q- -17 or abn (17p) 11q23 chromosome translocation, except for t (9; 11) inv (3) (q21; q26.2) or t (3; 3) (q21q26.2) t (6; 9) (p23; q34) t (9; 22) (q34.1; q11.2) t (7; 11) (p15; p15)	TP53 mutation RUNX1 (AML1) mutation[c] ASXL1 mutation[c] FLT3-ITD mutation[a and c] of a high allelic ratio

Monomeric karyotypes: two or more autosomal monomers, or one autosomal monomer complicated with at least one chromosomal structural abnormality

Modifying gene mutations of DNMT3a and RNA splicing chromatins (SF3B1, U2AF1, SRSF2, ZRSR2, EZH2, BCOR and STAG2) will lead to a poor prognosis if they are not accompanied by t (8; 21) (q22; q22), inv (16) (p13q22) or t (16; 16) (p13; q22) or t (15; 17) (q22; q12) [9, 10]. However, the level of their evidence-based medical evidence cannot be equal to those of TP53, ASXL1, RUNX1 and other mutations. Therefore, they are not used as the basis for risk stratification

[a] The low allelic ratio is < 0.5 while the high allelic ratio is ≥ 0.5. If no FLT3 testing for allelic ratio is performed, positive FLT3-ITD should be treated as a high allele ratio

[b] C-kit D816 has prognostic effects on t (8; 21) (q22; q22), inv (16) (p13; q22) and t (16; 16) (p13; q22), while the other mutation sites have no prognostic effect and are still classified into the good prognosis group

[c] Such abnormalities should not be stratefied as poor markers if they occur with good markers

Table 2 Induction treatment regimens for patients with AML < 60 years old

Classification of chemotherapy regimens	
Conventional induction treatment regimen	A standard dose of Ara-C (100-200 mg/m^2/d) for 7 days, accompanied by IDA of 12 mg/m^2/d for 3 days or DNR of 60-90 mg/m^2/d for 3 days [11–13]
Induction treatment regimen with an intermediate dose of Ara-C	HHT of 2 mg/m^2/d for 7 days, DNR of 40 mg/m^2/d for 3 days, Ara-C of 100 mg/m^2/d for days 1–4 and of 1 g/m^2/q12h for days 5–7 [6, 14]
Other induction treatment regimens	A regimen composed of IA, DA, MA and HA + anthracyclines, such as HAA (HA + aclacinomycin), HAD (HA + DNR)[4]

Refer to the low-dose regimen for aged patients when patients have severe complications

Table 3 Bone marrow examination from day 7 to day 14 after chemotherapy

Residual leukemia cells	Treatment regimen
Residual leukemia cells ≥ 10%	Consider double-induction treatment[a] or watch and wait
Residual leukemia cells < 10%, but without hypoplasia	Perform double-induction treatment[a] or wait for recovery
Residual leukemia cells < 10%, with hypoplasia	Wait for recovery

[a] A standard dose of Ara-C + anthracyclines or anthraquinones (IDA or DNR, Mitox, etc.); a preexcitation regimen with G-CSF (such as GAG regimen: G-CSF + Ara-C + Acla)

(3) Treatment options after CR of AML (Table 6)

The treatment options after the remission of AML should be not only based on the above genetic risk grouping but also dynamically adjusted according to the measurable residual disease (MRD). For patients who are persistently positive for MRD or for whom MRD becomes positive after being negative, especially those who are positive for MRD after consolidation treatment, hematopoietic stem cell transplantation is recommended even if the patients are in the good or intermediate prognosis group. Multiparameter flow cytometry and PCR can be used for the detection of MRD.

2.1.2 Treatment for patients ≥ 60 years old

(1) Induction treatment for patients ≥ 60 years old (Table 7)
(2) Bone marrow monitoring after intensive induction chemotherapy for patients ≥ 60 years old with AML (Table 8)
(3) Treatment options for patients ≥ 60 years old after CR of AML

Table 4 Bone marrow and hemogram examination from day 21 to day 28 (recovery of bone marrow) after chemotherapy

Remission of bone marrow	Treatment regimen
Complete remission	Begin treatment after remission
Proportion of leukemia cells decreased < 60%	Treat according to induction failure
Incomplete remission, but with a proportion of leukemia cells decreased > 60%	Repeat the original regimen for one course of treatment; or chang to a second-line regimen
Residual leukemia cells < 10%, with hypoplasia	Wait for recovery
Residual leukemia cells ≥ 10%, with hypoplasia	Consider further treatment (refer to the double-induction treatment regimen or the treatment regimens chosen for patients with failed induction treatment)

Table 5 Bone marrow and hemogram reexamination from day 21 to day 28 (recovery of bone marrow) after termination of chemotherapy

Remission of bone marrow	Treatment regimen
Complete remission	Begin treatment after remission
Not achieved complete remission with bone marrow recovery	Treat according to induction failure
Residual leukemia cells < 10%, with hypoplasia	Wait for recovery
Residual leukemia cells ≥ 10%, with hypoplasia	Treat according to treatment failure

Table 6 Treatment options for different risk groups after CR of AML

Level of prognosis	Treatment regimen after complete remission
Good prognosis group	Multiple courses of treatment with a high dose of Ara-C[a]
	Others[b]
Intermediate prognosis group	Allogeneic hematopoietic stem cell transplantation[c]
	Multiple courses of treatment with a high dose of Ara-C[a]
	Autologous hematopoietic stem cell transplantation[d]
	Others[b]
Poor prognosis group	Allogeneic hematopoietic stem cell transplantation[c]
	Multiple courses of treatment with a high dose of Ara-C[a]
	Others[b]
Patients not stratified	Refer to the treatment for patients in the intermediate prognosis group Treat as for the poor prognosis group if the white blood cell count ≥ 100×10^9/L during diagnosis

[a] A high dose of Ara-C (3 g/m^2/q12h for 6 doses) for 3–4 courses of treatment [15, 16]

[b] A intermediate or high dose of Ara-C (1-2 g/m^2/q12h for 6 doses); an intermediate or high dose of Ara-C for 2–3 courses of treatment as consolidation therapy, followed by autologous hematopoietic stem cell transplantation [16–19]; standard-dose chemotherapy (Ara-C plus anthracyclines/anthraquinones, HHT, podophyllotoxin analogues, etc.) for ≥ 6 courses cycle of chemotherapy after remission, or consolidation of standard-dose chemotherapy for 3–4 courses, followed by autologous hematopoietic stem cell transplantation [20]

[c] An intermediate or high dose of Ara-C for 1–2 courses during the search for donors during chemotherapy [21]. Depending on the risk of relapse and the hematopoietic recovery after allogeneic hematopoietic stem cell transplantation, FLT3-ITD positive patients can receive FLT3 inhibitors for maintenance treatment, while demethylation drugs can be chosen for the maintenance treatment of FLT3-ITD negative patients

[d] An intermediate or high dose of Ara-C for 2–3 courses, followed by autologous hematopoietic stem cell transplantation [17–19]

[e] An intermediate or high dose of Ara-C for 2–3 courses, or consolidation therapy of standard-dose chemotherapy, followed by autologous hematopoietic stem cell transplantation [17–19]

Table 7 Induction treatment options for patients ≥ 60 years old

Age		
Patients aged 60 to 75 (fit for intensive chemotherapy)	Without poor prognosis factors	Standard-dose chemotherapy[a]
		Low-intensity chemotherapy[b]
	With poor prognosis factors	Low-intensity chemotherapy[b]
		Standard-dose chemotherapy[a]
Patients ≥ 75 years old or < 75 years old, with severe nonhematologic complications or who are unfit for intensive chemotherapy	Low-intensity chemotherapy	
	Supportive treatment	

[a] Standard-dose chemotherapy: Ara-C (100 mg/m^2/d for 7 days) plus IDA (10-12 mg/m^2/d for 3 days) or DNR (45-60 mg/m^2/d for 3 days) [22–25]

[b] Low-intensity chemotherapy: venetoclax (100 mg, d1, 200 mg, d2, 400 mg, d3-28) plus azacitidine (75 mg/m^2/d for 7 days) or decitabine (20 mg/m^2/d for 5 days) [26–28]. For patients with IDH1 mutations, azacitidine (75 mg/m^2/d for 7 days) plus ivosidenib (500 mg, oral, once daily) can be used. Azacitidine (75 mg/m^2/d for 7 days) or decitabine (20 mg/m^2/d for 5 days). Low-dose chemotherapy ± G-CSF (e.g. a low dose of Ara-C as the basic regimen—CAG, CHG, CMG, C-cytarabine, A-aclacinomycin, H-homoharringtonine and M-mitoxantrone); azacitidine or decitabine plus low-dose chemotherapy, etc [29–33]

Table 8 Bone marrow examination from day 21 to day 28 after intensive induction chemotherapy for patients with AML ≥ 60 years old

Remission of bone marrow	Treatment regimen
Complete remission	Begin treatment after remission
Proportion of leukemia cells decreased < 60%	Treat according to induction failure
Proportion of leukemia cells decreased > 60%, but with incomplete remission	Repeat the original regimen for one course of treatment or chang to a second-line regimen
Residual leukemia cells < 10%, with hypoplasia	Wait for recovery
Residual leukemia cells ≥ 10%, with hypoplasia	Treat according to treatment failure

Treatment options after CR through standard-dose induction chemotherapy:

① A standard dose of Ara-C (75-100 mg/m^2/d for 5–7 days) is used as the consolidation and intensification regimen, which can be combined with anthracyclines or anthraquinones (IDA, DNR or Mitox, etc.), HHT, podophyllotoxin analogues. The total cycle of chemotherapy after remission is 4–6 courses.
② 4–6 doses of Ara-C (0.5-2 g/m^2/q12h) for 1–2 courses of treatment for fit patients < 70 years old with normal renal functions (creatinine clearance rate ≥ 70 mL/min) and good prognostic karyotypes or normal karyotypes accompanied by good molecular genetic abnormalities, followed by standard-dose treatment. The total cycle of treatment after remission is 4–6 courses.
③ Allogeneic hematopoietic stem cell transplantation with nonmyeloablative condition for fit patients < 70 years old with normal organ functions, poor prognostic factors and suitable donors [34, 35].
④ Treatment with demethylation drugs (such as azacitidine or decitabine) until the disease progresses.

Treatment options after CR with low-intensity induction chemotherapy: For some patients who can tolerate standard-dose chemotherapy after CR with a good prognosis, the treatment regimen can be changed to intensive chemotherapy. Alternatively, low-intensity treatment regimen may be continued as well.

(4) Maintenance treatment

Demethylation drugs (azacitidine or decitabine) can be used for maintenance treatment after induction and consolidation treatment until the disease progresses [36, 37].

2.2 Treatment of acute promyelocytic leukemia

In recent years, all trans retinoic acid (ATRA) and arsenious oxide have been used for the treatment of acute promyelocytic leukemia (APL) so that APL can be cured without hematopoietic stem cell transplantation (Table 9).

2.3 Treatment of relapsed or refractory AML

Examinations of chromosomes and molecular abberations (such as next-generation sequencing, RNA sequencing) should be carried out for relapsed or refractory AML(R/R AML) to assess the disease status and choose the appropriate regimens or clinical trials Early relapse refers to relapse within 12 months after remission, while late relapse refers to the relapse more than 12 months after remission (Tables 10 and 11).

2.4 Treatment of complications in patients with AML

2.4.1 Treatment of CNSL

The incidence of CNSL in AML is usually less than 3%. It is recommended by the National Comprehensive Cancer Network (NCCN) that lumbar puncture shouldn't be routinely performed for patients without CNS symptoms at initial diagnosis. Lumbar puncture and intrathecal injection (Ara-C 40-50 mg and/or MTX 5-15 mg + dexamethasone5-10 mg) for patients with CR in CNSL screening (Table 12). Four times of intrathecal injection are recommended in case of no CNSL. Intrathecal injection of chemotherapeutic drugs twice a week until the CSF is normal, and subsequently once a week for 4–6 weeks.

2.4.2 Treatment of cardiotoxicity in AML

Clinical observations and studies have shown that cardiotoxicity caused by anthracyclines is generally progressive as well as irreversible and the heart may suffer damage after the first use of anthracyclines. Thus, early monitoring and prevention in advance are particularly important.

Classification of cardiotoxicity caused by anthracyclines The cardiotoxicity caused by anthracyclines can be divided into acute, chronic and delayed according to the time of onset [51, 52] (Table 13).

Diagnosis Drug cardiotoxicity refers to one or more of the following, but does not include subclinical cardiovascular injury occurring early in the use of chemotherapeutic drugs [53](Table 14).

Treatment Symptomatic treatment for routine heart failure due to cardiotoxicity involves a combination of three drug types: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and β-receptor blockers.

Cardioprotective agents include coenzyme Q10, levocarnitine, N-acetylcysteine, antioxidants (vitamin C and vitamin E) and other iron chelating agents (such as desferrioxamine and EDTA).

2.4.3 Treatment of agranulocytosis and fever in AML

Diagnosis of agranulocytosis and fever in AML Agranulocytosis refers to an absolute neutrophil count (ANC) < 0.5×10^9/L in peripheral blood while serious agranulocytosis refers to an ANC < 0.1×10^9/L. Fever refers to a single oral temperature ≥ 38.3℃ (axillary

Table 9 Treatment options for APL

Preliminarily diagnosed WBC ≤ 10 × 109/L		
Treatment regimen with ATRA + arsenic-trioxide [38–40]	Induction treatment	ATRA plus arsenic-trioxide or compound realgar natural indigo tablets until complete remission (CR)[a]
	Consolidation treatment	ATRA for 7 courses. Arsenic-trioxide or compound realgar natural indigo tablets for 4 courses[b]
	Maintenance treatment	Every 3 months for a cycle. Month 1: ATRA for 2 weeks with an interval for 2 weeks; Month 2 and Month 3: arsenic-trioxide or compound realgar natural indigo tablets for 2 weeks with an interval for 2 weeks[a], repeating for 3 cycles
ATRA + arsenic-trioxide + other chemotherapy regimens [41]	Induction treatment	Same as the induction treatment[a] in the treatment regimen with ATRA + arsenic-trioxide; anthracyclines or anthraquinones used for the control of leucocytosis
	Consolidation treatment	HA regimen, MA regimen, DA regimen and IA regimen[c]
	Maintenance treatment	Same as the maintenance treatment in the treatment regimen with ATRA + arsenic-trioxide, repeating for 8 cycles
ATRA + other chemotherapy regimens (arsenic-trioxide intolerance or arsenic-trioxide-free drugs)	Induction treatment	ATRA until CR and ATRA plus DNR or IDA for Days 2, 4, 6 and 8[a]
	Consolidation treatment	ATRA for 14d plus DNR or IDA for 3d with an interval for 28d as a course of treatment with a total of 2 courses[a]
	Maintenance treatment	Every 3 months for a cycle: Days 1–14: ATRA; Days 15–90: 6-MP; MTX once a week for a total of 11 times, with 8 cycles[a]
Newly diagnosed WBC > 10 × 10^9/L		
ATRA + arsenic-trioxide + induction chemotherapy, consolidation chemotherapy and maintenance treatment alternatively combined with ATRA/arsenicals [38]	Induction treatment	ATRA plus arsenic-trioxide or compound realgar natural indigo tablets until CR; ATRA plus DNR or IDA for Days 1-3[a]
	Consolidation treatment	HA regimen, MA regimen, DA regimen and IA regimen[c]
	Maintenance treatment	Same as the maintenance treatment in the treatment regimen with ATRA + arsenic-trioxide for newly diagnosed WBC ≤ 10 × 10^9/L, repeating for 8 cycles
ATRA + arsenicals + induction chemotherapy, consolidation with ATRA + arsenic-trioxide and maintenance treatment with ATRA/6-MP/MTX [42]	Induction treatment	ATRA (Days 1–36) + arsenic-trioxide (Days 9–36) + IDA (Days 2, 4, 6 and 8)[a]
	Consolidation treatment	① ATRA (Days 1–28) + arsenic-trioxide (Days 1–2); ② ATRA (Days 1–7, 15–21 and 29–35) + arsenolite (Days 1–5, 8–12, 15–19, 22–26 and 29–33)
	Maintenance treatment	Same as the maintenance treatment in the treatment regimen with ATRA + arsenic-trioxide for newly diagnosed WBC ≤ 10 × 10^9/L

[a] Drug dose: ATRA of 25 mg/m^2/d; arsenic trioxide of 0.16 mg/m^2/d; compound realgar natural indigo tablets of 60 mg/m^2/d; DNR of 45 mg/m^2/d; IDA of 8 mg/m^2/d; 6-MP of 50-90 mg/m^2/d;MTX of 5-15 mg/m^2/d

[b] ATRA of 25 mg/m^2/d for 2 weeks with an interval for 2 weeks as a course of treatment. Arsenic-trioxide of 0.16 mg/m^2/d or compound realgar natural indigo tablets of 60 mg/m^2/d for 4 weeks with an interval for 4 weeks as a course of treatment

[c] HA regimen: HHT of 2 mg/m^2/d for Days 1–7; Ara-C of 100 mg/m^2/d for Days 1–5. MA regimen: MIT of 6-8 mg/m^2/d for Days 1–3; Ara-C of 100 mg/m^2/d for Days 1–5. DA regimen: DNR of 40 mg/m^2/d for Days 1–3; Ara-C of 100 mg/m^2/d for Days 1–5. IA regimen: IDA of 8 mg/m^2/d for Days 1–3; Ara-C of 100 mg/m^2/d for Days 1–5

temperature ≥ 38.0℃), or oral temperature ≥ 38.0℃ (axillary temperature ≥ 37.7℃) for more than 1 h.

Treatment of agranulocytosis and fever in AML Initial empiric treatment with antibiotics should be administered as soon as possible, the principle of which is to cover the most common and virulent pathogens that can quickly lead to serious complications or threats to life. The epidemiology of infection in the region, the hospital and the department must be taken into account to cover drug-resistance bacteria until accurate etiological results are obtained. Gram-negative bacteria are the main cause of infection in agranulocytosis.

In patients with an ANC ≥ 0.5 × 10^9/L with stable defervescence for 48 h after empiric treatment with antibiotics for agranulocytosis with fever of unknown origin, antibiotics can be discontinued; if the ANC continues to be < 0.5 × 10^9/L, antibiotics can be discontinued after 7 days of defervescence. In patients in whom the ANC is still < 0.5 × 10^9/L and empiric antibiotics are discontinued, fluoroquinolones can be adopted for preventive treatment [54].

2.4.4 Prevention of AML hepatitis B virus reactivation

Hepatitis B virus (HBV) reactivation is fairly common in patients with solid tumors and hematological

Table 10 Treatment principles of R/R AML

Age	Treatment recommendations	
Patients < 60 years old	Those with early relapse	Clinical trials (highly recommended)
		Targeted drug treatment
		Salvage chemotherapy, followed by HSCT with identical sibling or unrelated donors after CR
		Direct allogeneic hematopoietic stem cell transplantation
	Those with late relapse	Repeating the initially effective induction chemotherapy regimen and considering allo-HSCT after remission
		Clinical trials
		Targeted drug treatment
		Salvage chemotherapy, followed by HSCT with identical sibling or unrelated donors after CR
	Those with refractory AML	Same as those with early relapse
Patients ≥ 60 years old	Those with early relapse	Clinical trials(highly recommended)
		Treatment with new drugs (including targeted and untargeted drugs)
		Optimal supportive treatment
		Salvage chemotherapy and allo-HSCT for fit patients after CR
	Those with late relapse	Clinical trials (highly recommended)
		Repeating the initially effective induction chemotherapy regimen
		Treatment with new drugs (including targeted and untargeted drugs)
		Salvage chemotherapy and allo-HSCT for fit patients after CR
		Optimal supportive treatment (for patients untolerate or unwilling to treatment)
	Those with refractory AML	Same as those with early relapse

malignancies undergoing conventional chemotherapy and may cause serious complications.

High-risk factors for AML HBV reactivation High-risk factors for AML HBV reactivation include treatment with anthracyclines; hormonotherapy with prednisone at a dosage greater than or equivalent to 10-20 mg daily for more than 4 weeks; monoclonal antibody treatment, such as rituximab, obinutuzumab and alemtuzumab; and a history of breast cancer or lymphoma.

Examination Examinations following HBV reactivation should look for improvements in routine blood and biochemical parameters as well as HBsAg, anti-HBc, anti-HBs and HBV-DNA. It is recommended to monitor HBV DNA and ALT every 3 months, and monthly monitor after the withdrawal of antiviral treatment [55].

Treatment For patients with a history of hepatitis B, lamivudine, entecavir or nucleotide analogs should be used in antiviral treatment while they are receiving immunosuppressant treatment [55, 56]. Antiviral treatment can be discontinued after one year of immunosuppressant withdrawal [55]. Moreover, regular examinations of HBV-DNA and ALT are required.

2.4.5 Prevention and treatment of uric acid nephropathy

Chemotherapy-induced destruction of leukemia cells (especially in patients with hyperleukocytosis) will easily lead to uric acid nephropathy. Notably, for hydration and alkalization, allopurinol may be used to inhibit the formation of uric acid.

2.4.6 Correction of bleeding and coagulation disorders

The bleeding time and coagulation time should be closely monitored in patients with leukemia, and coagulation factor supplementation should be provided when necessary to correct any bleeding or coagulation disorders.

2.5 Nursing for patients with AML

Before chemotherapy, patients should be educated regarding their treatment regimens and any adverse events and common complications. During agranulocytosis, patients are required to stay in laminar air-flow wards that are regularly and periodically disinfected and kept clean with reduced visitation. Patients are advised to wear medical masks, eat clean food, and prevent oral and perianal infection. The importance of recurrence prevention should be explained during the

Table 11 Treatment regimens of relapsed or refractory AML

Treatment regimens		
Targeted treatment ± demethylation drugs	FLT3-ITD mutation	Gilteritinib[a]
		Sorafenib + demethylation drugs (azacitidine or decitabine)[b]
	FLT3-TKD mutation	Gilteritinib[a]
	IDH1 mutation	Ivosidenib, plus demethylation drugs[c]
	IDH2 mutation	Enasidenib, plus demethylation drugs[d]
Combination chemotherapy	Intensive chemotherapy regimen (for fit patients)	CLAG ± IDA/Mitox regimen[e]
		A high dose of cytarabine ± anthracyclines[f]
		FLAG ± IDA regimen[g]
		HAA (HAD) regimen[h]
		EA ± Mitox regimen[i]
		CAG regimen[j]
	Non-intensive chemotherapy regimen (for unfit patients)	Demethylation drugs (azacitidine and decitabine)[k]
		A low-dose of Ara-C[l]
		Venetoclax + demethylation drugs/ a low-dose of Ara-C[m]
Allogeneic hematopoietic stem cell transplantation	Allogeneic hematopoietic stem cell transplantation should be carried out as soon as possible if permitted	
Immunotherapy	CAR-T immunotherapy, etc	

Venetoclax plus demethylation drugs: venetoclax: 100 mg for Day 1, 200 mg for Day 2 and 400 mg from Day 3 to Day 28; demethylation drugs: azacitidine of 75 mg/m^2 for Days 1–7; decitabine of 25 mg/m^2 for Days 1–5. Venetoclax plus a low dose of Ara-C: venetoclax: 100 mg for Day 1, 200 mg for Day 2, 400 mg for Day 3 and 600 mg from Day 4 to Day 28; Ara-C: 10 mg/m [2], subcutaneous, q12h, d1-10 [43–45]

[a] Gilteritinib: a therapeutic dose of 120 mg/day [46, 47]. Clinical tirals of gilteritinib have shown that patients who didn't reach CR after one course of standard-dose induction treatment benefited from gilteritinib monotherapy as well. Thus, treatment with gilteritinib is recommended for patients without CR after one course of standard-dose induction treatment

[b] Sorafenib + demethylation drugs (azacitidine or decitabine): sorafenib of 200 mg, Bid; azacitidine of 75 mg/m^2 for Days 1–7 or decitabine of 20 mg/m^2 for Days 1–5

[c] Ivosidenib of 500 mg qd, plus demethylation drugs as appropriate. Same as above for doses of demethylation drugs [48, 49]

[d] Enasidenib of 100 mg qd, plus demethylation drugs as appropriate. Same as above for doses of demethylation drugs [50]

[e] CLAG ± IDA/Mitox regimen: Cladribine (Cla), Ara-C and G-CSF with or without IDA/Mitox; Cla of 5 mg/m^2, d1-5; Ara-C of 1-2 g/m^2, 4 h after Cla, d1-5, intravenous infusion for 3 h; G-CSF of 300 μg/m^2, d0-5 (stopping when WBC > 20 × 10^9/L); IDA of 10-12 mg/m^2, d1-3, or Mitox of 10-12 mg/m^2, d1-3

[f] A high dose of cytarabine ± anthracyclines: Ara-C of 1-3 g/m^2, q12h, d1, 3 and 5; plus DNR of 45 mg/m^2 or IDA of 10 mg/m^2, d2, 4 and 6, or Ara-C (not exposed to high dose of ARA-C) of 3 g/m^2, q12h, d1-3

[g] FLAG ± IDA regimen: Flu, Ara-C, G-CSF ± IDA; Flu of 30 mg/m^2, d1-5; Ara-C 1-2 g/m^2, 4 h after Flu, d1-5, intravenous infusion for 3 h; G-CSF of 300 μg/m^2, d0-5; IDA of 10-12 mg/m^2, d1-3

[h] HAA (HAD) regimen: HHT, Ara-C, Acla or DNR: HHT of 2 mg/m^2, d1-7 (or HHT of 4 mg/m^2, administration in two separate doses, d1-3); Ara-C of 100-200 mg/m^2, d1-7; Acla of 20 mg/d, d1-7 (or DNR of 45 mg/m^2/d, d1-3)

[i] EA ± Mitox regimen: VP16, Ara-C ± Mitox: VP16 of 100 mg/m^2, d1-5; Ara-C of 100-150 mg/m^2, d1-7; ± Mitox of 10 mg/m^2, d1-5

[j] CAG regimen: Acla, Ara-C + G-CSF regimen: G-CSF of 150U/m^2, q12h, d0-14; Acla of 20 mg/d, d1-4; Ara-C of 10 mg/m^2, subcutaneous, q12h, d1-4

[k] Demethylation drugs: azacitidine of 75 mg/m^2, d1-7, 28 days for a course of treatment, until there is disease deterioration or serious adverse events; decitabine of 20 mg/m^2, d1-5, 28 days for a course of treatment, until there is disease deterioration or serious adverse events

[l] A low dose of Ara-C: Ara-C of 10 mg/m^2, subcutaneous, q12h, d1-14

[m] Venetoclax + demethylation drugs/ a low-dose of Ara-C

period of remission. Regular follow-up by phone to ask about patient's psychological states after hospital discharge is necessary. Patients should be advised repeatedly to have more meals a day but less food at each meal, with a light diet consisting of digestible food, ensuring the intake of protein, vitamins and energy, and to eat plenty of fresh vegetables and fruits. Eating greasy, raw, cold, spicy or stimulating food is forbidden. Moreover, it is important to prevent getting cold and to maintain a good mood as well as mental health.

3 Follow-up of adult AML

Monitoring MRD through real-time PCR (RT-PCR) and flow cytometry can provide an early warning of relapse so that effective measures can be taken as soon as possible. Patients with persistently negative MRD are expected to reach disease-free survival for a long period of time and even be cured. Thus, MRD must be regularly monitored. It is recommended to examine MRD during and after consolidation treatment. MRD should

Table 12 Treatment of CNSL

CT/MRI for patients with nervous system symptoms	Lumbar puncture without intracranial/ spinal tumor	Normal CSF	Observation
		Leukemia cells found in CSF	Intrathecal injection of chemotherapeutic drugs (twice a week) until the CSF is normal, and subsequently once a week for 4–6 weeks
	Patients with intracranial/ spinal tumors or increased intracranial pressure	Radiotherapy, followed by intrathecal injection of drugs (twice a week) until the CSF is normal, and subsequently once a week for 4–6 weeks	
Patients without nervous system symptoms	Leukemia cells in CSF when lumbar puncture isperformed after CR1	Intrathecal injection of chemotherapeutic drugs twice a week until the CSF is normal, and subsequently once a week for 4–6 weeks. CSF reexamination after treatment if HD-Ara-C treatment is received	
	Normal findings of lumbar puncture after CR1	Lumbar puncture and intrathecal injection for patients with CR in CNSL screening. Four times of intrathecal injection are recommended in case of no CNSL	

Table 13 Classification of cardiotoxicity caused by anthracyclines

Acute	Occurring within hours or days after administration and commonly presenting as an intracardiac conduction disturbance and arrhythmia, rarely presenting as pericarditis and acute left heart failure
Chronic	Occurring within one year of chemotherapy and presenting as left ventricular dysfunction, which may eventually lead to heart failure
Delayed	Occurring years after chemotherapy and presenting as heart failure, cardiomyopathy and arrhythmia

Table 14 Cardiotoxic manifestations caused by anthracyclines

Cardiomyopathy with decreased LVEF, manifesting as overall functions degradation or significant reduction in ventricular septal motion
Congestive heart failure (CHF) -related symptoms
CHF-related signs, such as the third heart sound gallop, tachycardia or both
LVEF decreased by at least 5% from the baseline to the absolute value < 55%, accompanied by symptoms or signs of CHF; or LVEF decreased by at least 10% to the absolute value < 55%, not accompanied by symptoms or signs

be monitored once every 3 months within 2 years after consolidation treatment [57, 58].

Authors' contributions

Professor Hui Wei conceived the manuscript under the valuable advice and guidance of Professor Jianxiang Wang. Members of Hematology Oncology Committee of China Anti- Cancer Association. drafted and approved the manuscript for publication. The author(s) read and approved the final manuscript.

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Consent for publication

Consent for publication bas been obtained from all authors of this manuscript.

Competing interests

The authors have no conflicts of interest to declare.

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References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
2. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47.

3. Mi Y, Xue Y, Yu W, et al. Therapeutic experience of adult acute myeloid leukemia in a single institution of China and its relationship with chromosome karyotype. Leuk Lymphoma. 2008;49(3):524–30.
4. Jin J, Wang J-X, Chen F-F, et al. Homoharringtonine-based induction regimens for patients with de-novo acute myeloid leukaemia: a multicentre, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2013;14(7):599–608.
5. Wei H, Zhou C, Lin D, et al. Benefit of intermediate-dose cytarabine containing induction in molecular subgroups of acute myeloid leukemia. Haematologica. 2020;106(5):1491–5.
6. Wei H, Wang Y, Gale RP, et al. Randomized trial of intermediate-dose Cytarabine in induction and consolidation therapy in adults with acute myeloid leukemia. Clin Cancer Res. 2020;26(13):3154–61.
7. Wei S, Wang S, Qiu S, et al. Clinical and laboratory studies of 17 patients with acute myeloidleukemia harboring t(7;11)(p15;p15) translocation. Leuk Res. 2013;37(9):1010–5.
8. Wei H, Zhou C, Liu B, et al. The prognostic factors in acute myeloid leukaemia with double-mutated CCAAT/enhancer-binding protein alpha (CEBPAdm). Br J Haematol. 2022;197(4):442–51.
9. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. N Engl J Med. 2016;374(23):2209–21.
10. Gale RE, Lamb K, Allen C, et al. Simpson's Paradox and the Impact of Different DNMT3A Mutations on Outcome in Younger Adults With Acute Myeloid Leukemia. J Clin Oncol. 2015;33(18):2072–83.
11. Fernandez HFSZ, Yao X, Litzow MR, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med. 2009;361(13):1249–59.
12. Ohtake S, Miyawaki S, Fujita H, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. Blood. 2011;117(8):2358–65.
13. Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m2 vs 60 mg/m2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. Blood. 2015;125(25):3878–85.
14. Liu J, Mi Y, Fu M, et al. Intensive induction chemotherapy with regimen containing intermediate dose cytarabine in the treatment of de novo acute myeloid leukemia. Am J Hematol. 2009;84(7):422–7.
15. Mayer RJDR, Schiffer CA, Berg DT, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. N Engl J Med. 1994;331(14):896–903.
16. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. J Clin Oncol. 2013;31(27):3360–8.
17. Cornelissen JJ, Versluis J, Passweg JR, et al. Comparative therapeutic value of post-remission approaches in patients with acute myeloid leukemia aged 40–60 years. Leukemia. 2015;29(5):1041–50.
18. Zittoun RAMF, Willemze R, de Witte T, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. N Engl J Med. 1995;332(4):217–23.
19. Cassileth PAHD, Appelbaum FR, Lazarus HM, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. N Engl J Med. 1998;339(23):1649–56.
20. Mi Y, Bian S, Xue Y, et al. Preliminary study on postremission therapy courses in acute myeloid leukemia. Zhonghua xue ye xue za zhi. 2001;22(10):520–3.
21. Koreth JSR, Kopecky KJ, Honda S, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009;301(22):2349–61.
22. Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol. 2010;28(5):808–14.
23. Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood. 2007;109(12):5129–35.
24. Gardin C, Chevret S, Pautas C, et al. Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. J Clin Oncol. 2013;31(3):321–7.
25. Lowenberg BOG, van Putten W, Schouten HC, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009;361(13):1235–48.
26. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018;19(2):216–28.
27. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7–17.
28. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617–29.
29. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood. 2015;126(3):291–9.
30. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2010;28(4):562–9.
31. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol. 2012;30(21):2670–7.
32. Qian SX, Li JY, Tian T, et al. Effect of low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor priming (CAG regimen) on the outcome of elderly patients with acute myeloid leukemia. Leuk Res. 2007;31(10):1383–8.
33. Li JCY, Zhu Y, Zhou J, et al. Efficacy and safety of decitabine in combination with G-CSF, low-dose cytarabine and aclarubicin in newly diagnosed elderly patients with acute myeloid leukemia. Oncotarget. 2015;6(8):6448–58.
34. Storb R. Can reduced-intensity allogeneic transplantation cure older adults with AML? Best Pract Res Clin Haematol. 2007;20(1):85–90.
35. Versluis J, Hazenberg CLE, Passweg JR, et al. Post-remission treatment with allogeneic stem cell transplantation in patients aged 60 years and older with acute myeloid leukaemia: a time-dependent analysis. Lancet Haematol. 2015;2(10):e427–36.
36. Huls G, Chitu DA, Havelange V, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. Blood. 2019;133(13):1457–64.
37. Wei AH, Dohner H, Pocock C, et al. Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med. 2020;383(26):2526–37.
38. Lo- Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369(2):111–21.
39. Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all- trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a andomised, controlled, phase 3 trial. Lancet Oncol. 2015;16(13):1295–305.
40. Zhu HH, Wu DP, Du X, et al. Oral arsenic plus retinoic acidversus intravenous arsenic plus retinoic acid for non- high risk acute promyelocytic leukemia—a multi- center RCT. Blood. 2017;130(Suppl 1):641.
41. Zhu HH, Wu DP, Jin J, et al. Oral tetra- arsenic tetra- sulfide formula versus intravenous arsenic trioxide as first- line treatment of acute promyelocytic leukemia: a multicenter randomized controlled trial. J Clin Oncol. 2013;31(33):4215–21.
42. Iland HJ, Collins M, Bradstock K, et al. Use of arsenic trioxide in remission induction and consolidation therapy for acute promyelocytic leukaemia in the Australasian Leukaemia and Lymphoma Group (ALLG) APML4 study: a non- randomised phase 2 trial. Lancet Haematol. 2015;2(9):e357-366.
43. Ram R, Amit O, Zuckerman T, et al. Venetoclax in patients with acute myeloid leukemia refractory to hypomethylating agents-a multicenter historical prospective study. Ann Hematol. 2019;98(8):1927–32.

44. Aldoss IYD, Aribi A, Ali H, Sandhu K, Al Malki MM, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. Haematologica. 2018;103(9):e404–7.
45. Lou Y, Shao L, Mao L, et al. Efficacy and predictive factors of venetoclax combined with azacitidine as salvage therapy in advanced acute myeloid leukemia patients: A multicenter retrospective study. Leuk Res. 2020;91:106317.
46. Perl AE, Altman JK, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1–2 study. Lancet Oncol. 2017;18(8):1061–75.
47. Perl AEMG, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381:1728–40.
48. DiNardo CD, Stein EM, de Botton S, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. N Engl J Med. 2018;378(25):2386–98.
49. DiNardo CDSA, Stein EM, et al. Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia. J Clin Oncol. 2021;39(1):57–65.
50. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722–31.
51. Barry EAJ, Scully RE, et al. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. Expert Opin Pharmacother. 2007;8:1039–58.
52. Cvetkovi´c RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. Drugs. 2005;65:1005–24.
53. Seidman AHC, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20:1215–21.
54. Chinese Society of Hematology, Chinese Medical Association, Chinese Medical Doctor Association, Hematology Branch. Chinese guidelines for the clinical application of antibacterial drugs for agranulocytosis with fever (2020). Zhonghua xue ye xue za zhi. 2020;41(12):969–78.
55. Mallet V, van Bömmel F, Doerig C, et al. Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation: recommendations of the 5th European Conference on Infections in Leukaemia (ECIL-5). Lancet Infect Dis. 2016;16(5):606–17.
56. Sandherr M, Hentrich M, von Lilienfeld-Toal M, et al. Antiviral prophylaxis in patients with solid tumours and haematological malignancies–update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Ann Hematol. 2015;94(9):1441–50.
57. Schuurhuis GJHM, Freeman S, Bene MC, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018;131(12):1275–91.
58. Wei H, Liu X, Wang Y, et al. The Optimized Clinical Application of Minimal Residual Disease in Acute Myeloid Leukemia with RUNX1-RUNX1T1. Exp Hematol. 2021;96:63–72.

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