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HOW TO

How to Treat Adult Acute Myeloid Leukemia

An Evolving Paradigm

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Acute myeloid leukemia (AML) is an aggressive hematologic malignancy with a heterogeneous presentation and treatment landscape. Here, we discuss a clinical case and describe the diagnosis and management of AML in adults, with focus on emerging aspects from a cardio-oncology perspective.

CLINICAL CASE

A 76-year-old woman presented with 1 month of progressively worsening fatigue, night sweats, 5-pound weight loss, easy bruising, and gingival bleeding. She was previously healthy but for the past few weeks had spent the majority of her days in bed due to severe malaise. Vital signs were within normal limits. Physical examination revealed diffuse superficial ecchymoses and nontender hepatosplenomegaly. Laboratory evaluation revealed white blood cell count 500 cells/μL, hemoglobin 8.1 g/dL, and platelet count 32,000/m^3. Her Eastern Cooperative Oncology Group performance status was 2.

She underwent bone marrow aspiration. Flow cytometry revealed 30% blasts, and cytogenetics showed normal female karyotype (46, XX [21]) without abnormalities in chromosomal rearrangements. Molecular assays detected mutations in *TET2* and *NRAS*. She was diagnosed with intermediate-risk AML.

HOW DO WE DIAGNOSE AML?

AML must be distinguished from other hematologic malignancies, nutritional deficiencies, infections, medication effects, and other differential diagnoses. Diagnostic testing includes complete blood count with peripheral smear to evaluate for leukemic myeloblasts, electrolytes to screen for tumor lysis syndrome, lactate dehydrogenase, and coagulation profile to evaluate for disseminated intravascular coagulation. Diagnosis is made upon bone marrow biopsy with histochemical staining for cytology, flow cytometry, cytogenetics, and molecular studies (1). Cytogenetic abnormalities inform prognosis, and separate AML into categories as favorable, intermediate, and unfavorable (1).

KEY POINTS

- Diagnosis is made on bone marrow aspiration revealing >20% myeloblasts.
- Cytogenetic abnormalities help risk-stratify patients and guide treatment decisions.

CASE CONTINUED

Discussion was held that, given her older age and poor performance status, she would unlikely tolerate high-intensity induction chemotherapy or stem cell transplantation. She was initiated on therapy with venetoclax plus azacitidine, with goal of achieving

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ABBREVIATIONS AND ACRONYMS

AML = acute myelogenous leukemia

CR = complete remission

EF = ejection fraction

ECG = electrocardiogram

HCT = hematopoietic stem cell transplantation

disease remission, improved symptoms, and life prolongation.

HOW DO WE TREAT AML?

Treatment of AML involves a multidisciplinary team of physicians, nurses, pharmacists, social workers, and others. Treatment decisions depend on the subtype of AML, presence of genetic mutations, and fitness of each individual patient.

ACUTE PROMYELOCYTIC LEUKEMIA TREATMENT. The AML variant acute promyelocytic leukemia is uniquely treated with all-*trans* retinoic acid combined with arsenic trioxide. Along with treatment of acute promyelocytic leukemia, special care must be taken to manage complications including differentiation syndrome, disseminated intravascular coagulation, tumor lysis syndrome, leukostasis, cytopenias, and neutropenic infections. Clinicians should obtain baseline and serial electrocardiograms (ECGs), with attention to QTc prolongation and monitoring for torsades de pointes with arsenic-based therapy.

TRADITIONAL AML TREATMENT. Traditionally, AML is treated with high-dose cytotoxic chemotherapy induction with 7 days of continuous cytosine arabinoside plus 3 days of anthracycline therapy ("7+3"), followed by consolidation with the same drugs in order to maintain a deep remission and prevent relapse. This regimen has yielded a 5-year survival of 20% to 35% in young patients and 10% in older patients (1). Consolidation consists of further intensive chemotherapy or bridge to potentially curative allogeneic hematopoietic stem cell transplantation (HCT), and is guided by patient factors including age, performance status, cytogenetics, and molecular characteristics (1). Patients who achieve negative minimal residual disease detected by flow cytometry and polymerase chain reaction after intensive combination chemotherapy have longer leukemia-free and overall survival.

Allogeneic HCT is the preferred method in fit patients with intermediate or unfavorable prognosis who achieved remission with induction therapy. Relapsed and refractory AML remain difficult conditions to treat, often with salvage chemotherapy followed by plan for allogeneic HCT. Among those who are able to undergo allogeneic HCT, further assessment of age, AML severity, donor type, and comorbidities will determine whether they are eligible for myeloablative conditioning or reduced-intensity conditioning regimens. The higher-intensity regimens often come with a higher rate of cardiovascular toxicities compared with lower regimens, and thus cardiovascular comorbidities must be taken into account.

MODERN ERA OF AML TREATMENT. In recent years, novel high-intensity induction combinations have been studied in both frontline and salvage settings, including cladribine combined with idarubicin and cytosine arabinoside, as well as fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (1). Further, the combination of liposomal daunorubicin plus cytarabine (CPX-351) has shown improved complete remission (CR), overall survival, lower 30- and 60-day mortality, and better tolerated adverse effects compared with "7+3" in high-risk AML in a phase III trial; it was subsequently approved in 2017 for adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes, with expanded approval for pediatric patients in 2021 (2).

NOVEL TARGETED THERAPY APPROACHES IN AML. Since 2017, advances in the field have led to the development of targeted agents for specific mutations, many of which have received Food and Drug Administration approval and are being studied in ongoing clinical trials. Development of FLT3 (FMS-like tyrosine kinase 3) inhibitors midostaurin and gilteritinib, isocitrate dehydrogenase (*IDH1* and *IDH2*) inhibitors ivosidenib and enasidenib, hypomethylating agents azacitidine and decitabine, B-cell lymphoma 2 (*BCL-2*) inhibitor venetoclax, anti-CD33 antigen-drug conjugate gemtuzumab ozogamicin, and hedgehog inhibitor glasdegib have helped structure individualized therapies for patients with AML (1,2). Black-box warnings for these agents are included in **Table 1**. Clinical trials are ongoing and have demonstrated benefit of maintenance gilteritinib (NCT02997202) and midostaurin (NCT01883362) in patients with FLT3-mutated AML after allogeneic HCT. Future studies will evaluate doublet and triplet combinations of these agents in addition to STAT3 inhibitors, monoclonal antibodies, chimeric antigen receptor T cells, natural killer cells, bispecific T cell engagers, and others for treatment of AML (2).

CONSIDERATION OF AGE AND FITNESS IN THE TREATMENT OF AML. Younger or fit patients are often treated upfront with a triple combination of fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor plus venetoclax (3) or with cladribine combined with idarubicin and cytosine arabinoside plus venetoclax (4) in lieu of traditional "7+3," with the addition of targeted agents as previous for appropriate mutations. Eligible patients should undergo allogeneic HCT in first CR followed by maintenance therapy, or consolidation therapy

TABLE 1 Treatment Regimens and Novel Targeted Agents for Patients With AML

Regimen/Agent	Indication	Toxicity/Adverse Events	Cardiovascular Toxicity
Traditional therapy			
7+3	Intensive induction/salvage	Febrile neutropenia, tumor lysis syndrome	Anthracycline-associated cardiomyopathy, pericarditis
Modern era/nontraditional induction therapy			
CPX-351	Newly diagnosed t-AML, AML-MRC (FDA approval August 2017)	Tumor lysis syndrome, febrile neutropenia	Anthracycline-associated cardiomyopathy, edema, arrhythmia, hypo/hypertension, chest pain
FLAG-IDA (alone or in combination with venetoclax)	Intensive induction/salvage regimen for AML (combination therapy clinical trial, NCT03214562)	Febrile neutropenia, bacteremia, pneumonia, sepsis	Anthracycline-associated cardiomyopathy, edema
CLIA (alone or in combination with venetoclax)	Intensive induction/salvage regimen for AML (combination therapy clinical trial, NCT02115295) (7)	Febrile neutropenia, infection, alanine aminotransferase elevations	Anthracycline-associated cardiomyopathy, edema
Novel targeted agents			
Midostaurin	Newly diagnosed FLT3 ITD/TKD-mutated AML (FDA approval April 2017)	Embryofetal toxicity	QTc prolongation, edema, hypotension, risk of heart failure development (6%), pericardial effusion
Gilteritinib	Relapsed/Refractory FLT3 ITD/TKD-mutated AML (FDA approval November 2018)	Differentiation syndrome, PRES, pancreatitis	QTc prolongation, risk of heart failure development (4%), edema, hypotension, pericardial effusion, myocarditis, pericarditis
Ivosidenib	Adults ≥75 with AML and IDH1 mutation, and relapsed/refractory AML with IDH1 mutation (FDA approval July 2018)	Differentiation syndrome, fatigue, rarely PRES and Guillain-Barré syndrome	QTc prolongation, edema, hypotension, chest pain, ventricular fibrillation (<1%)
Enasidenib	Relapsed/Refractory *IDH2*-mutated AML (FDA approval August 2017)	Differentiation syndrome, diarrhea, nausea	Does not prolong QTc, pulmonary edema
GO	Patients with CD33+ expressing leukemic blasts	Hepatotoxicity, severe/fatal hepatic sinusoidal obstruction syndrome (black box warning)	QTc prolongation, cardiotoxicity, tachycardia
Regimens in older or medically unfit patients			
HMA (azacitidine/decitabine) plus venetoclax	Frontline induction in medically unfit/patients older than 65 y	Cytopenias, febrile neutropenia, gastrointestinal upset, fatigue, edema Avoid in patients with liver disease, kidney disease, or taking CYP3A inhibitor medication	Chest pain, edema, atrial fibrillation (<5%), cardiomyopathy, (<5%), hyper/hypotension
HMA monotherapy (azacitidine or decitabine)	Patients eligible for HMA but not candidates for venetoclax or ivosidenib	Cytopenias, febrile neutropenia	Chest pain, atrial fibrillation (<5%), cardiomyopathy, (<5%), hyper/hypotension
LoDAC plus venetoclax	Patients who are not eligible for HMA-based therapy and do not have targetable mutation	Neutropenia, thrombocytopenia, febrile neutropenia	Edema, chest pain, pericarditis
LoDAC plus glasdegib	Patients who are not eligible for HMA-based therapy and do not have targetable mutation	Nausea, vomiting, diarrhea Glasdegib is potentially teratogenic, and should be avoided in patients taking CYP3A4 inhibitor/inducer medications	QTc prolongation, ventricular fibrillation/tachycardia, edema, chest pain, pericarditis Patients taking glasdegib should get ECG 1 week after starting therapy, and monthly ×2 to monitor QTc prolongation
Oral Azacitidine	Maintenance therapy in patients with AML who achieved CR1 but were unable to undergo HCT (8)	Nausea/vomiting, diarrhea, febrile neutropenia, embryofetal toxicity, pneumonia	Chest pain, atrial fibrillation (<5%), cardiomyopathy, (<5%), hyper/hypotension
Future directions/clinical trials			
HMA (azacitidine/decitabine) plus ivosidenib	Newly diagnosed AML with mutant IDH1 (ongoing RCT: AGILE [NCT03173248])	Cytopenias, differentiation syndrome	Chest pain, atrial fibrillation (<5%), cardiomyopathy, (<5%), hyper/hypotension, QTc prolongation, edema, hypotension, chest pain, ventricular fibrillation (<1%)
Azacitidine plus gilteritinib	Newly diagnosed AML with mutant FLT3 (currently restricted to clinical trial only)	Gilteritinib associated with differentiation syndrome, pancreatitis	QTc prolongation (gilteritinib), chest pain, atrial fibrillation (<5%), cardiomyopathy, (<5%), hyper/hypotension
Decitabine plus bortezomib	Newly diagnosed AML (without FLT3 mutation or favorable-risk cytogenetics) (NCT01420926)	Febrile neutropenia	Chest pain, atrial fibrillation (<5%), cardiomyopathy, (<5%), hyper/hypotension, pulmonary edema (<1%)

AML = acute myelogenous leukemia; AML-MRC = acute myelogenous leukemia with myelodysplasia-related changes; CLIA = cladribine combined with idarubicin and cytosine arabinoside; CR1 = first complete remission; ECG = electrocardiogram; FDA = Food and Drug Administration; FLAG-IDA = fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor; FLT3 = FMS-like tyrosine kinase 3; GO = gemtuzumab ozogamicin; HCT = hematopoietic stem cell transplantation; HMA = hypomethylating agent; ITD = internal tandem duplication; LoDAC = low-dose cytarabine; PRES = posterior reversible encephalopathy syndrome; RCT = randomized controlled trial; t-AML = therapy-related acute myelogenous leukemia; TKD = tyrosine kinase domain.

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followed by maintenance therapy when applicable. Oral azacitidine maintenance therapy has been shown to improve overall and relapse-free survival in older patients who achieved remission after chemotherapy but were unable to undergo HCT, and was recently approved by the Food and Drug Administration for AML maintenance (5).

Older or medically unfit patients (Eastern Cooperative Oncology Group performance status ≥3) may be treated with less intensive therapies, which have less toxicity but a lower degree of achieving CR. The treatment goal in this group becomes to achieve a remission that improves symptoms, quality of life, independence from transfusions, and overall survival. Regimens such as low-dose cytarabine, gemtuzumab ozogamicin, venetoclax plus low-dose cytarabine (6), and hypomethylating agents plus venetoclax have been approved for therapy in "medically unfit" adults with AML (7). Therapeutic options and novel targeted agents for use in patients with AML are listed in **Table 1**.

KEY POINTS

- The goal of induction therapy is to induce remission, followed by consolidation with chemotherapy or allogeneic HCT with curative intent.
- Several targetable agents for specific mutations have improved the treatment landscape of AML.
- AML and its treatment is associated with significant toxicities that require close monitoring.
- We suggest referring all patients with AML to a major center to consider a clinical trial approach if possible.

HOW DO WE MANAGE CARDIOVASCULAR RISK FACTORS IN THE TREATMENT OF AML?

Important cardiovascular evaluation in AML includes an ECG to note baseline QTc interval and screen for arrhythmias, as well as an echocardiogram to evaluate for baseline cardiac ejection fraction (EF), valvular, or wall motion abnormalities. For patients with cardiovascular risk factors including age >65 years, tobacco smoking history, hypertension, diabetes mellitus, and heart failure, cardiology consultation and risk factor modification is prudent.

CARDIO-ONCOLOGY CONSIDERATIONS. Typical induction regimens for AML involve anthracycline therapy, which is associated with cardiotoxicity; patients with comorbid heart failure may be unable to tolerate these regimens. Anthracyclines should be avoided in patients with baseline left ventricular EF <40%, patients with heart failure and EF between 40% and 50%, and patients with myeloid sarcoma (8). Patients with mild pre-existing left ventricular dysfunction (EF 40%-50%) may be candidates to receive dexrazoxane to prevent anthracycline-mediated cardiotoxicity (8). Patients with impaired cardiac function but who are otherwise medically fit for intensive induction therapy should receive cytarabine-based regimens either alone or in combination with other nonanthracycline agents. The decision to pursue anthracycline-based therapy can be individualized; however, weighing risks and benefits in discussion between the patient, oncologist, and cardiologist is critical. Many of the novel targeted agents in AML come with associated cardiac toxicity of QTc prolongation; thus, it is prudent to monitor baseline and monthly ECGs after starting therapy. Patients with AML and comorbid heart failure should receive guideline-directed medical therapy for heart failure in addition to antineoplastic therapy.

Patients with AML often require multiple blood product transfusions and high volumes of intravenous crystalloid fluids (1). Therefore, patients with AML and coexisting cardiac dysfunction should be monitored with close attention to volume status and development of pulmonary edema during therapy. Patients with underlying cardiomyopathy should follow closely with an experienced cardiologist to manage volume status and titrate neurohumoral blocking medications (8,9). Further, sepsis is common in patients with AML. Physicians should remain vigilant to note hypotension, sinus tachycardia and tachyarrhythmias, and the occasional phenomenon of stress-induced cardiomyopathy. With early recognition and treatment of life-threatening conditions such as sepsis, a large majority of patients with AML who require admission to an intensive care unit will survive and return home with relatively preserved functional status and ability to continue cancer-directed therapy (10). With stress-induced cardiomyopathy, it is prudent to ensure follow-up with a cardiologist to repeat echocardiogram after acute illness to evaluate for EF recovery, and determine ability to continue chemotherapy.

Rarely, AML may cause pericardial disease either via direct infiltration or via chemotherapy toxicity, or from opportunistic infections. Patients may be asymptomatic, or present with chest pain, dyspnea, or tachycardia, and in severe cases, with cardiac tamponade or shock. In addition to history and physical examination, diagnostic tools include an ECG, chest radiographs, and echocardiography. Ultimately, pericardiocentesis may be required for diagnostic and therapeutic purposes, especially in

patients who develop hemodynamic compromise or tamponade physiology.

Future directions involve the study of dexrazoxane as a potential cardioprotective agent in patients with normal EF who are undergoing blood cancer-directed therapy (NCT03589729). We hope that as we enter this era of targeted therapy for hematologic malignancies, we will develop a better understanding and ability to prevent the toxicities of targeted agents employed for treatment of AML.

KEY POINTS

- All patients with newly-diagnosed AML should undergo testing with an ECG to evaluate for arrhythmias and QTc prolongation, and echocardiogram to assess EF and overall cardiac function.
- Patients with baseline cardiac dysfunction or heart failure may not be eligible for anthracycline-based therapy.
- Cardiac function and volume status must be closely monitored during induction therapy.
- Several targeted agents are associated with QTc prolongation that require ECG monitoring.
- Dexrazoxane may play a role in the future of cardiac prevention for hematologic malignancies undergoing cytotoxic chemotherapy regimens.
- Close collaboration with a multidisciplinary cardio-oncology team is paramount, especially in the era of evolving novel agents with new toxicities and monitoring schemas.

CONCLUSIONS

AML is an aggressive hematologic malignancy with heterogeneous classification and treatment options. It is prudent to consider patient age, fitness, underlying mutations, and karyotype alterations when generating treatment regimens. We strongly recommend that all patients with AML, whether frontline or relapsed or refractory, be immediately referred to a major academic center if possible to consider clinical trial-based therapy, stem cell consultation, and multidisciplinary care approach. Special attention must be paid to underlying cardiovascular risk factors, as AML and many of its treatments have cardiovascular implications.

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