*Section A-Research paper*

# Brief Overview about Acute Myeloid Leukemia

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## Abstract

**Background:** Leukemia is a heterogeneous group of hematologic malignancies that arise from the dysfunctional proliferation of developing leukocytes. It is classified as either acute or chronic based on the rapidity of proliferation and as myelocytic or lymphocytic based on the cell of origin. Treatment depends on the type of leukemia but generally involves chemotherapy. Multiple genetic and environmental risk factors are identified in the development of leukemia. According to the Surveillance, Epidemiology, and End Results (SEER) database, there are 61,090 estimated new cases of leukemia in 2021, accounting for 3.2% of all new cancer cases, making leukemia the 10th most common cancer in the United States. This activity describes the evaluation and management of leukemia and reviews the role of the interprofessional team in improving care for patients with this condition. Acute myeloid leukemia (AML) is the most common leukemia among the adult population and accounts for about 80% of all cases. It is characterized by clonal expansion of immature "blast cells" in the peripheral blood and bone marrow resulting in ineffective erythropoiesis and bone marrow failure. With recent advancements in the management guidelines, the cure rates have increased up to 15% in patients older than 60 years and about 40% in patients below 60 years of age. Despite advancements in therapeutic regimens, the prognosis remains very poor in the elderly population. This activity examines when this condition should be considered in the differential diagnosis and how to evaluate it properly. This activity highlights the role of the interprofessional team in caring for patients with this condition.

**Keywords:** Acute Myeloid Leukemia

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## Introduction

The production of abnormal leukocytes defines leukemia as either a primary or secondary process. They can be classified as acute or chronic based on the rapidity of proliferation and myeloid or lymphoid based on the cell of origin. Predominant subtypes are acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), involving the myeloid lineage; acute lymphoblastic leukemia (ALL); and chronic lymphocytic leukemia (CLL), involving the lymphoid chain. Other less common variants, such as mature B-cell and T-cell leukemias, and NK cell-related leukemias, to name a few, arise from mature white blood cells. However, with the advent of next-generation sequencing (NGS) and the identification of various biomarkers, the World Health Organization (WHO) classification was updated in 2016, bringing multiple changes to the traditional classification for acute leukemias and myeloid neoplasms.[1] GLOBOCAN, a global observatory for cancer trends, showed a global incidence of 474,519 cases, with 67,784 in North America. The Age-Standardized Rates are around 11 per 100,000, with a mortality rate of approximately 3.2.[2]

Many genetic risk factors have been identified, such as Klinefelter and Down syndromes, ataxia telangiectasia, Bloom syndrome, and telomeropathies such as Fanconi anemia, dyskeratosis congenita, and Shwachman-Diamond syndrome; germline mutations in RUNX1, CEBPA, to name a few. Viral infections associated with Epstein Barr virus, human T-lymphotropic virus, ionizing radiation exposure, radiation therapy, environmental exposure with benzene, smoking history, history of chemotherapy with alkylating agents, and topoisomerase II agents have also been implicated in the development of acute leukemias. Symptoms are nonspecific and can include fever, fatigue, weight loss, bone pain, bruising, or bleeding. Definitive diagnoses often require bone marrow biopsy, the results of which help the hematologists and stem cell transplant physicians regarding the selection of treatment options ranging from chemotherapy to allogeneic stem cell transplantation. The prognosis is variable depending on the leukemia subtype in question.
**Acute vs. chronic myeloid leukemia:** Blasts, which are immature and dysfunctional cells, normally make up 1% to 5% of marrow cells. Acute leukemias are characterized by greater than 20% blasts in the peripheral blood smear or on bone marrow leading to a more rapid onset of symptoms. In contrast, chronic leukemia has less than 20% blasts with a relatively chronic onset of symptoms. The accelerated/blast phase is a transformation of chronic myeloid leukemia into an acute phase with a significantly higher degree of blasts.[1][3][4]

Acute myeloid leukemia (AML) is the most common leukemia among the adult population and accounts for about 80% of all cases. It is characterized by clonal expansion of immature “blast cells” in the peripheral blood and bone marrow resulting in ineffective erythropoiesis and bone marrow failure. With recent advancements in the management guidelines, the cure rates have increased up to 15% in patients older than 60 years and about 40% in patients below 60 years of age. Despite advancements in therapeutic regimens, the prognosis remains very poor in the elderly population.[1][2][3]
Depending upon the etiology, genetics, immune-phenotype, and morphology, there are different classification systems for AML.[4][5]
The most common risk factor for AML is myelodysplastic syndrome. Other hematological disorders that increase the risk of AML include myelofibrosis and aplastic anemia.
Several congenital disorders like Down syndrome and Bloom syndrome also increase the risk of AML, which tends to present in the early 20s.
Environmental exposures like radiation, tobacco smoke and benzene are also risk factors for AML
Finally, previous exposure to chemotherapeutic agents is also a risk factor for AML.

**Epidemiology**

The number of new cases among men and women per year is about 4.2 per 100,000 population. The incidence is over 20,000 cases per year in the United States. The average age at the time of diagnosis is about 65 years. It is more prevalent among non-Hispanic whites. Males have more predominance compared to females, with a ratio of 5:3.

**Pathophysiology**

AML is characterized by mutations of the genes involved in hematopoiesis. These mutations result in a clonal expansion of undifferentiated myeloid precursors (blasts) in the peripheral blood and bone marrow resulting in ineffective erythropoiesis and bone marrow failure. Recent studies also revealed that it could arise from a series of recurrent hematopoietic stem cell genetic alterations which get accumulated with age. In most cases, AML appears as *de novo* in a previously healthy person. The exact cause of genetic mutations is unclear, but few risk factors include exposure to radiation, chemotherapeutic agents, and smoking. AML can also evolve from myeloproliferative disorders (MPD), myelodysplastic syndrome (MDS), paroxysmal nocturnal hemoglobinuria, and aplastic anemia. Familial causes of genetic mutations should also be considered.
AML is a highly heterogeneous disease with a variable prognosis. It can result from genetic mutations, chromosomal translocations, or changes in molecular levels. About 97% of the cases have been studied to have genetic mutations. Despite its heterogeneity, it can be categorized into favorable, intermediate, or adverse-risk groups based on cytogenetics. The prognosis within these categories varies widely. The chromosomal translocations t (8;21), t (15;17), or inv (16) have a favorable prognosis with 3-year overall

survival (OS) rate of about 66% and 33% in patients younger than 60 and older than 60 years of age respectively. People with t (9;11), monosomy 5 or 7, and normal cytogenetics (CN-AML) have an intermediate risk. A high risk of treatment failure and death was noted in people with t (6;9), inv (3). or 11q changes. The presence of c-KIT mutations in patients with t (8;21) increases the risk of relapse and decreases the OS.

About 25% to 30% of AML patients have Nucleophosmin 1 (*NPM1*) mutations. This is the most common mutation found in AML and has a female predominance. Clinically, the mutation has monocytic morphology and in the absence of FMS-like tyrosine kinase 3 or *FLT3-ITD*, predicts favorable OS. *NPM1* mutations are chemosensitive to intensive chemotherapy in both young and old patients. It is associated with other recurrent genetic abnormalities such as *FLT3-ITD* (40%), *FLT3-TKD* (10% to 15%), and *IDH* mutations (25%).

FLT3 is strongly expressed in hematopoietic stem cells with important roles in cell survival and proliferation. Mutations involving the Internal tandem duplications (ITD) and the tyrosine kinase domain (TKD) of the FLT3 gene have been found in 20% of AML cases and 30% to 45% of CN-AML patients. Both the mutations activate FLT3 signaling, promoting blast proliferation. Patients with FLT3 mutations can have severe leukocytosis. FLT3-ITD mutations have been associated with an increased risk of relapse. Tyrosine kinase inhibitors (TKI) are being tested in FLT3 mutated AML patients. Unfortunately, when used alone, TKIs showed only a transient reduction of blasts, and even if initially effective, the subsequent acquisition of secondary mutations induces resistance over time.

Runt-related transcription factor (*RUNX1*) is an essential component of hematopoiesis. It is also known as AML1 protein or core-binding factor subunit alpha-2 (*CBFA2*). *RUNX1* is located at chromosome 21 and is frequently translocated with the *ETO (Eight Two One)/RUNX1T1* gene located on chromosome 8q22, creating an *AML-ETO* or t(8;21)(q22;q22) AML which is seen in about 12% of AML cases. They are commonly associated with trisomy 13, trisomy 21 and show resistance to standard induction therapy.

Mutations in isocitrate dehydrogenase (*IDH)* are oncogenic. They are seen in 15% to 20% of all AML cases and 25% to 30% of patients with CN-AML. More commonly seen in older individuals.

TP53 mutations are associated with very poor prognosis and are resistant to chemotherapy.

**History and Physical**

Due to ineffective erythropoiesis and bone marrow failure, patients experience a variety of symptoms including recurrent infections, anemia, easy bruising, excessive bleeding, headaches, and bone pains. Depending on the degree of anemia, they can experience generalized weakness, fatigue, shortness of breath, and chest tightness. The physical examination can reveal bruises, pallor, hepatomegaly, and splenomegaly. Lymphadenopathy is rare. DIC is common in patients with AML. Signs of organ infiltration are not uncommon; they may include hepatosplenomegaly and lymphadenopathy. Sometimes a skin rash due to infiltration of leukemic cells will occur.

**Evaluation**

AML should be suspected in anyone with unexplained cytopenias (decreased cell count of white blood cells, hemoglobin, or platelets), the presence of circulating blast cells in the peripheral blood, easy bruising or bleeding or recurrent infections. In some cases, they can present with renal failure secondary to tumor lysis syndrome which is an oncologic emergency.[6][7][8][9]

Some patients may have elevated LDH and hyperuricemia, suggesting tumor lysis syndrome, which is a medical emergency.

The blood smear will reveal circulating blasts and schistocytes if DIC is present.

The presence of at least 20% blasts in the bone marrow or peripheral blood is diagnostic of AML. It can be diagnosed with bone marrow aspiration and biopsy. Additional diagnostics include flow cytometry, cytogenetics, and fluorescence in situ hybridization (FISH). The presence of Auer rods (clumps of azurophilic granules resembling elongated needles) is diagnostic of AML. Auer rods can be seen in many subtypes of AML, but abundantly seen in APL.

Oncologic emergencies associated with AML include neurologic or respiratory distress due to leukostasis, APL-induced DIC, tumor lysis syndrome, and central nervous system (CNS) involvement.[10]

Other tests include a chest x-ray, MUGA scan to assess the heart, and ECG.

**Treatment / Management**

Individuals who achieve complete remission (CR) with a blast count of less than 5% in the bone marrow after induction therapy tend to have increased survival. Despite induction therapy, there is still minimal residual disease for which consolidation therapy is initiated to prevent any risk of relapse by eliminating the residual disease. Despite many advances, the mainstay of therapy remains a combination of cytarabine-based and anthracycline-based regimens. For eligible candidates, allogeneic stem cell transplantation should be considered.[11][12][13][14]

**Induction Therapy**

This is a standard of care for younger patients, elderly with a low risk of treatment-related mortality (TRM), and ones with favorable and intermediate-risk factors. The induction therapy is highly toxic to bone marrow, causing pancytopenias and bleeding complications, gastrointestinal system issues, kidney failure due to tumor lysis syndrome, and electrolyte disturbances. It may take up to 1 month for the cell counts to recover, and these patients need aggressive monitoring to manage any complications. Baseline cardiac function should be estimated before initiating the treatment, and the ejection fraction (EF) needs to be monitored carefully, as anthracyclines can cause significant cardiotoxicity. Studies have shown greater benefit with higher doses, but toxicities may limit its use. It consists of the "7+3" regimen that includes continuous infusion of cytarabine for seven days along with anthracycline on days 1 to 3. Patients with refractory disease have shown higher CR and similar overall survival (OS) by using higher doses of cytarabine or by using a combination of fludarabine, cytarabine, and idarubicin. Despite TRM in older patients, chemotherapy has shown to improve the survival rate among the elderly (older than 65 years). Decitabine, a methylating agent used in the treatment of MDS, has shown improvement in OS in the elderly population. The response should be evaluated by repeating the bone marrow aspirate and biopsy after 2 weeks of initiating the induction therapy. Reinduction can be done with high dose cytarabine or by combining with etoposide if there is persistent evidence of disease. About 60% to 80% de novo AML will achieve CR with induction therapy.

Even before the diagnosis, if APL is suspected, then the treatment should be initiated with all-trans retinoic acid (ATRA), as early use of ATRA decreases the risk of disseminated intravascular coagulation (DIC) and mortality associated with it.

**Consolidation Therapy**

After achieving CR with induction therapy, consolidation therapy is initiated with high dose cytarabine, called HiDAC, and hematopoietic cell transplantation (HCT). HCT is preferred in individuals less than 60 years of age with intermediate or unfavorable prognoses. If a donor is available, then allogeneic HCT is preferred over autologous HCT. They should be monitored for signs or symptoms of acute or chronic graft versus host disease (GVHD).

**Novel Targets**

Ongoing studies with Fms-like tyrosine kinase 3 (FLT3) inhibitors, IDH inhibitors, and immune therapies.

All blood products must be irradiated to prevent transfusion-related graft versus host disease, which is usually fatal.

IV antibiotics are given to febrile patients, and prophylactic antifungal therapy is recommended.

**Prognosis**

By assessing the prognostic factors, clinicians can decide whether a standard therapy or more intense therapy would be helpful in maintaining CR and OS rates. The prognostic factors are chromosomal abnormalities (favorable abnormalities include t(8;21), t(15;17), inversion of chromosome 16), genetic mutations (*NPM1* gene has a favorable prognosis, and *FLT3* gene has unfavorable prognosis). Worse outcomes have been noted with older age, white blood cell count greater than 100,000 at the time of diagnosis, s-AML, t-AML, the presence of leukemic cells in the central nervous system (CNS).

Recent techniques such as PCR and flow cytometry can detect the presence of minimal residual disease among CR patients. Persistently elevated levels of RUNX1-RUNX1T1 despite induction therapy in patients with t(8;21) AML are associated with an increased incidence of relapse.

**Enhancing Healthcare Team Outcomes**

AML is a common hematological malignancy in adults. Despite many advances, the malignancy still carries a poor prognosis. Hence, it is best managed by an interprofessional team that includes a hematologist, oncologist. internist, pathologist, and an intensivist. The key is to prevent more harm to the patient, and hence a universal treatment plan must be developed and carried out.

The pharmacist should educate the patient on the chemotherapeutic drugs, their benefits, and their adverse effects. The oncology nurse is vital for treatment administration and monitoring for potential complications. The nurse should educate the patient on infection prevention by washing hands, rinsing all fruits and vegetables, avoiding crowds, and seeking help at the first sign of fever.

The radiologist is essential for the placement of long-term venous catheters and other imaging studies. The primary care physician should educate the patient on personal hygiene, hand washing, and immunization. The dietitian should help manage nutrition, and the social worker should ensure that the patient has all the support to complete the treatment.

The only person who should make changes in medications is the oncologist. A conference should be held on a weekly basis, and all concerns attended to at that time. Patients should be provided with a realistic message about survival.

An interprofessional approach to evaluation and management will lead to the best outcomes. [Level 5] Overall, life expectancy has increased slightly, but most patients have a markedly shortened lifespan.[15][16]

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