**SURVIVAL TRENDS AND OUTCOMES IN ACUTE MYELOID LEUKEMIA- A COMPREHENSIVE REVIEW**

**ABSTRACT**

Acute myelomonocytic leukemia (AMML) is a subtype of acute myeloid leukemia (AML) characterized by the excessive proliferation of myeloblasts and monoblasts in the bone marrow and bloodstream. This proliferation disrupts normal blood cell production, leading to symptoms such as anemia, thrombocytopenia, and neutropenia. Patients often experience fatigue, frequent infections, easy bruising, and shortness of breath due to the lack of healthy red and white blood cells. The condition poses significant health risks, as the abnormal white blood cells are ineffective in fighting infections, resulting in increased susceptibility to illnesses. The classification of AML, including AMML, is primarily done through two systems: the French-American-British (FAB) classification and the World Health Organization (WHO) classification. The FAB system categorizes AML based on cell morphology and maturation, while the WHO system incorporates genetic abnormalities and other prognostic factors. Key classifications include AML with recurrent genetic abnormalities, therapy-related myeloid neoplasms, and AML not otherwise specified. Understanding these classifications is crucial for determining treatment approaches and expected outcomes, as certain genetic mutations are associated with different prognoses. Acute Myeloid Leukemia (AML) is still a major hematologic cancer with differing survival rates affected by elements like genetic mutations, treatment progress, and patient characteristics. This review intends to thoroughly examine survival patterns and results in AML, including up-to-date epidemiological information, treatment advancements, and prognostic factors.

Keywords: Acute myelomonocytic leukemia, myeloblasts, monoblasts, RBC, WBC, FAB, WHO, Aberrant hematopoiesis, cell transplant, India.

**1. INTRODUCTION**

Acute myelomonocytic leukemia (AMML), a variant of acute myeloid leukemia (AML), is marked by the excessive growth of myeloblasts and monoblasts within the bone marrow and bloodstream. This disorder results in various symptoms primarily stemming from the insufficient production of healthy blood cells, leading to conditions such as anemia, thrombocytopenia, and neutropenia. [1]

Acute myeloid leukemia (AML) is a rapidly progressing form of leukemia that originates from very immature white blood cells known as myeloblasts. It is also referred to as acute myelogenous leukemia. As these myeloblasts proliferate, they occupy space in the bone marrow, inhibiting the production of normal blood cells. A deficiency in red blood cells, termed anemia, can manifest as paleness, breathlessness, and fatigue. Thrombocytopenia, characterized by a low platelet count, may result in easy bruising or bleeding.[2]

**2. CLASSIFICATION OF AML**

Acute myeloid leukemia (AML) is classified into several categories based on genetic abnormalities, clinical features, and morphologic features. The two primary classification systems used are the French-American-British (FAB) classification and the World Health Organization (WHO) classification were described in Table 1 with version and key features of system.

Table 1 with version and key features of system.

|  |  |  |
| --- | --- | --- |
| **Classification System** | **Versions** | **Key features** |
| WHO | 2001 | Emphasis on morphology, cytogenetics  - Specific genetic translocations such as t(8;21)(q22;q22.1), inv(16)(p13.1q22), and t(15;17)(q24;q21) were recognized as distinct AML subtypes with specific clinical features and prognostic implications |
| 2008 | Inclusion of AML with NPM1 mutation  - Inclusion of AML with CEBPA mutation  - Refined the criteria for AML with multilineage dysplasia (AML-MDS)  - Details on therapy-related AML, specifying different subtypes  - Clarification and expansion of AML not otherwise specified (AML NOS) |
| 2016 | Expanded genetic and molecular abnormalities: mutated RUNX1, AML with BCR-ABL1 - Categorized therapy-related AML (t-AML) under the broader category of “therapy-related myeloid neoplasms” - Refined myelodysplastic/myeloproliferative neoplasms (MDS/MPN) and mixed-phenotype acute leukemia (MPAL) |
| 2022 | Refinement of genetic entities. Genes like NPM1, CEBPA, RUNX1, and others are based on updated research on their clinical significance - New recognized entities - Revised diagnostic criteria, updated blast count, and AML-defining abnormalities. - Terminology updates Focus on actionable mutations |
| ICC | 2022 Single version | Aims for broader clinical relevance and universal applicability Distinct AL subtypes based on molecular integrations. NPM1, CEBPA, TP53, FLT3 and others Alignment with other classification systems Flexible framework for future advances |
| ELN | 2010 | Primarily a risk stratification system rather than a detailed classification - Divides AML into favorable, intermediate 1 and 2, and adverse risk groups based on cytogenetic including t(8;21), inv(16), and t(15;17) for favorable risk, and complex karyotype or monosomal karyotype for adverse risk |
| 2017 | Continued the risk stratification framework, with favorable, intermediate, and adverse - Expanded genetic markers, RUNX1, ASXL1, and TP53 - FLT3-ITD refinements. A high allelic ratio of FLT3-ITD was classified as adverse, while a low ratio was considered intermediate when combined with other genetic factors |
| 2022 | The classification recognized the increasing importance of next-generation sequencing (NGS) in identifying genetic mutations that impact prognosis - New genetic markers such as DTA (DNMT3A, TET2, ASXL1) mutations were considered, particularly in relation to clonal hematopoiesis, and their role in risk stratification was further clarified - Personalized treatment emphasis. |

**2.1 FAB Classification**

The FAB classification system categorizes AML based on morphology and the maturation of leukemic cells. The subtypes include:

* **M0**: Undifferentiated acute myeloblastic leukemia
* **M1**: Acute myeloblastic leukemia with minimal maturation
* **M2**: Acute myeloblastic leukemia with maturation
* **M3**: Acute promyelocytic leukemia (APL)
* **M4**: Acute myelomonocytic leukemia
* **M4eo**: Acute myelomonocytic leukemia with eosinophilia
* **M5**: Acute monocytic leukemia
* **M6**: Acute erythroid leukemia
* **M7**: Acute megakaryoblastic leukemia [5,7]

**2.2 WHO Classification**

The WHO classification system incorporates genetic abnormalities and other factors affecting prognosis. It categorizes AML into the following groups:

* **AML with Recurrent Genetic Abnormalities**
  + Examples include:
    - AML with t(8;21)(q22;q22.1): RUNX1-RUNX1T1 fusion
    - APL with PML-RARA fusion associated with t(15;17)
    - AML with inv(16)(p13.1;q22): CBFB-MYH11 fusion
* **AML with Myelodysplasia-Related Changes (AML-MRC)**
  + This includes AML that develops in patients with a history of myelodysplastic syndromes.
* **Therapy-Related Myeloid Neoplasms**
  + This category includes AML that arises as a result of previous chemotherapy or radiation therapy for other malignancies.
* **AML Not Otherwise Specified (NOS)**
  + This category encompasses cases that do not fit into the defined classifications above and may include various subtypes based on morphology.
* **Myeloid Sarcoma**
  + A tumor composed of myeloid cells occurring outside the bone marrow.
* **Myeloid Proliferations Related to Down Syndrome**
  + Includes conditions such as transient abnormal myelopoiesis and acute megakaryoblastic leukemia associated with Down syndrome. [6,7,8]

**2.3 Classification of Acute Myeloid Leukemia (AML) based on genetic factor**

1. AML with Recurrent Genetic Abnormalities

* + This category encompasses AMLs characterized by specific chromosomal abnormalities or mutations that impact prognosis and treatment. Examples include:
  + Acute Promyelocytic Leukemia (APL): Identified by the PML-RARA fusion gene associated with t(15;17).
  + AML with t(8;21): Involves the RUNX1-RUNX1T1 fusion.
  + AML with inv(16): Linked to the CBFB-MYH11 fusion.

2. AML with Defining Genetic Mutations

* + This classification highlights the presence of specific mutations that define the disease, such as:
  + NPM1 mutations: Often correlated with a favorable prognosis.
  + FLT3 mutations: Including FLT3-ITD and FLT3-TKD, associated with poorer outcomes.

3. Therapy-Related AML

* + This category refers to AML that occurs as a result of prior chemotherapy or radiation therapy for other cancers, typically associated with complex karyotypes and poor prognosis.

4. Myelodysplasia-Related Changes (MRC)

* + AML that develops in patients with a history of myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPNs), often exhibiting dysplastic features in the bone marrow.

5. Acute Myeloid Leukemia Not Otherwise Specified (AML-NOS)

* + This category includes AML cases that do not align with the above classifications and may require additional investigation to determine specific characteristics. [9,10]

**2.4 Classification of Acute Myeloid Leukemia (AML) Based on Severity**

Acute Myeloid Leukemia (AML) can be categorized by severity, reflecting its genetic traits, clinical features, and prognosis. Below are the primary classifications of AML based on severity, including examples and clinical implications:

1. Low-Risk AML

Description: This category comprises patients with favorable genetic mutations and a lower percentage of blasts.

Examples:

* Patients with NPM1 mutations without FLT3-ITD.
* AML associated with t(8;21) or inv(16).
* Clinical Implications: These patients typically experience better outcomes and may respond favorably to standard chemotherapy regimens.

2. Intermediate-Risk AML

Description: This group includes patients with mixed genetic features or those lacking specific high-risk mutations.

Examples:

* Patients with normal cytogenetics or mutations such as FLT3-TKD.
* AML with complex karyotypes but without high-risk characteristics.
* Clinical Implications: Patients in this category may necessitate more intensive treatment approaches and closer supervision.

3. High-Risk AML

Description: This category incorporates patients with adverse genetic mutations and elevated blast counts.

Examples:

* Patients with FLT3-ITD mutations, TP53 mutations, or complex karyotypes.
* Therapy-related AML (t-AML) that occurs following previous cancer treatments.
* Clinical Implications: These patients often face a poorer prognosis and may significantly benefit from stem cell transplantation and innovative targeted therapies.

4. Secondary AML

Description: This includes AML that arises as a progression from prior hematological disorders, such as myelodysplastic syndromes (MDS).

Examples:

* Patients transitioning from MDS to AML, especially those with 10-19% blasts in the bone marrow.
* Clinical Implications: Secondary AML is frequently linked to a worse prognosis due to previous disease and treatment background. [6,10,12]

**3. MECHANISM OF ACTION**

The general mechanism of action of Acute Myeloid leukemia provided as flow mechanism. The various mechanisms are responsible for the AML on body system were briefly accounted on table 2.

Genetic Mutations or Epigenetic Changes

↓

Aberrant Hematopoiesis

- Mutations in genes like FLT3, NPM1, or RUNX1

- Dysregulation of transcription factors and signaling pathways

↓

Clonal Expansion of Myeloid Precursors

- Accumulation of immature myeloid cells in bone marrow

- Proliferation of monocytes and neutrophil precursors

↓

Bone Marrow Failure

- Suppression of normal hematopoiesis

- Cytopenias (anemia, thrombocytopenia, neutropenia)

↓

Release of Leukemic Cells into Peripheral Blood

- Circulation of myeloblasts and monoblasts

- Leukocytosis and abnormal blood smears

↓

Infiltration of Tissues and Organs

- Liver, spleen, lymph nodes, and skin involvement

- Formation of myeloid sarcomas (tumor masses of myeloid cells)

↓

Clinical Symptoms  
- Fatigue, fever, infections, bleeding, and weight loss

TABLE 2 VARIOUS MECHANISM OF ACTION OF AML

| **Mechanism** | **Description** | **Impact on Body Systems** |
| --- | --- | --- |
| Clonal Expansion of Hematopoietic  Cells [1,13] | Caused by mutations in hematopoietic stem cells (HSCs), resulting in the proliferation of abnormal myeloblasts and monoblasts that fail to mature into functional blood cells. | Results in decreased production of healthy blood cells, causing anemia, increased bleeding, and susceptibility to infections. |
| Leukemia Stem Cells (LSCs) [14,15] | LSCs possess self-renewal capabilities and are resistant to conventional therapies, contributing to disease persistence and relapse. | LSCs can evade immune detection, leading to sustained disease progression despite treatment efforts. |
| Bone Marrow Microenvironment (BMM)  Interaction [14,16] | The BMM provides a supportive niche for LSCs, promoting their survival through interactions with stromal cells and signaling pathways (e.g., CXCR4/CXCL12 axis). | Disruption of normal hematopoiesis, leading to further complications like organomegaly due to overcrowding by leukemic cells. |
| Hypoxia-Induced Adaptations [14, 16] | Hypoxic conditions in the bone marrow stimulate the expression of hypoxia-inducible factors (HIF-1α), which enhance cell survival and promote angiogenesis to supply nutrients to rapidly growing leukemic cells. | Increased angiogenesis can lead to vascular complications and further support tumor growth within the marrow. |
| Genetic Mutations and Pathways [1,13] | Mutations in genes such as FLT3, NPM1, and others lead to aberrant signaling pathways that promote cell proliferation and inhibit differentiation, contributing to the aggressive nature of AML. | Alters normal cellular functions and increases the risk of secondary malignancies due to genetic instability. |
| Hypoxia-Induced Adaptations [14,16] | Hypoxic conditions in the bone marrow stimulate the expression of hypoxia-inducible factors (HIF-1α), which enhance cell survival and promote angiogenesis to supply nutrients to rapidly growing leukemic cells. | Increased angiogenesis can lead to vascular complications and further support tumor growth within the marrow. |
| Genetic Mutations and Pathways [1,13] | Mutations in genes such as FLT3, NPM1, and others lead to aberrant signaling pathways that promote cell proliferation and inhibit differentiation, contributing to the aggressive nature of AML. | Alters normal cellular functions and increases the risk of secondary malignancies due to genetic instability. |

**4. GENERAL SYMPTOMS OF AML**

The symptoms of AMML can vary among individuals but typically include:

* Fatigue and weakness: Patients often experience significant fatigue and general weakness due to anemia, which is a lack of red blood cells.
* Fever: A persistent or recurring fever can be caused by an infection or the disease itself.
* Frequent infections: It is common to have a low white blood cell count (neutropenia), which increases your susceptibility to infections.
* Easy bruising and bleeding: Thrombocytopenia causes easy bruising and prolonged bleeding from small cuts, nosebleeds, and bleeding gums.
* Pale skin: A low red blood cell count can cause a person to appear pale or gaunt.
* Shortness of breath: Patients may experience shortness of breath, especially during physical activity, due to anemia.
* Bone or joint pain: Leukemia cells may invade these areas, causing discomfort.
* Bloating: An enlarged liver or spleen may cause a feeling of fullness in the   
  abdomen. [1,2,3,4]

**5. PHASES OF SYMPTOMS FOR AML ON DIFFERENT AGE GROUP OF POPULATION**

The phases of symptoms for acute myelomonocytic leukemia on different age groups of population were given in table 3.

TABLE 3 PHASES OF SYMPTOMS ON AML

| **Age Group** | **Phase** | **Symptoms** | **Description** |
| --- | --- | --- | --- |
| Children  (0-18 years) [24] | Early Phase | Fatigue, fever, easy bruising, joint pain | Common symptoms include fatigue, fever, and easy bruising. Children may also experience bone or joint pain, indicating potential leukemic infiltration. |
| Progressive Phase | Petechiae, swollen lymph nodes, abdominal fullness | As the disease advances, children may develop petechiae (small red spots), swollen lymph nodes, and a sensation of fullness in the abdomen from organ enlargement. |
| Advanced Phase | Painless lumps (leukemia cutis), loss of appetite | In advanced stages, skin manifestations such as leukemia cutis and significant weight loss due to decreased appetite may be evident. |
| Young Adults (19-39 years) [25] | Early Phase | Fatigue, night sweats, fever | Symptoms frequently include fatigue and night sweats, which may be misattributed to other conditions. |
| Progressive Phase | Easy bruising and bleeding, shortness of breath | Increased tendencies for bleeding and respiratory issues may emerge as the disease progresses. |
| Advanced Phase | Bone pain, frequent infections | Advanced disease can cause severe bone pain and recurrent infections due to low white blood cell counts. |
| Adults (40-64 years) [25] | Early Phase | Fatigue, weakness, pallor | Adults typically present with fatigue and pallor from anemia; they may also experience unexplained fevers. |
| Progressive Phase | Easy bruising or bleeding, increased infections | Symptoms related to thrombocytopenia become more pronounced, resulting in easy bruising and a heightened risk of infections. |
| Advanced Phase | Splenomegaly or hepatomegaly, significant weight loss | Organ enlargement can occur in later stages, along with substantial weight loss due to the systemic effects of leukemia. |
| Older Adults (65+ years) [26] | Early Phase | Fatigue, weakness, frequent infections | Older adults may display general weakness and a greater susceptibility to infections as initial signs. |
| Progressive Phase | Anemia symptoms (dyspnea on exertion), easy bruising | Symptoms of anemia become more pronounced; older patients are at an increased risk for complications due to comorbidities. |
| Advanced Phase | Severe bone pain, confusion | Advanced stages may cause severe discomfort from bone infiltration and possible neurological symptoms such as confusion due to leukemic infiltration in the central nervous system. |

**6. SIGNALING PATHWAYS INVOLVED IN AML**

Acute myelomonocytic leukemia (AMML) and other variants of acute myeloid leukemia (AML) are defined by multiple crucial signaling pathways that enhance cell survival, proliferation, and resistance to apoptosis were briefly presented in table 4.

TABLE 4 KEY SIGNALING PATHWAYS INVOLVED IN AML CELL SURVIVAL AND PROLIFERATION

| **Signaling Pathway** | **Description** | **Role in AML** |
| --- | --- | --- |
| PI3K/AKT/mTOR Pathway [17] | This pathway is essential for cellular growth and survival. Activation of AKT enhances cell proliferation and inhibits apoptosis by regulating proteins such as Mcl-1. | Promotes AML cell survival and resistance to therapy; PI3K inhibitors enhance anti-leukemic activity. |
| MAPK/ERK Pathway [18] | The RAS/RAF/MEK/ERK signaling cascade governs cell proliferation, differentiation, and survival. Mutations in RAS genes result in the constitutive activation of this pathway. | Enhances proliferation and inhibits apoptosis; targeted therapies against this pathway show promise in AML. |
| JNK Signaling Pathway [19] | The c-Jun N-terminal kinase (JNK) pathway is integral to stress responses and apoptosis. Its dysregulation can lead to a reduction in pro-apoptotic signals in AML cells. | Suppression of JNK activity is linked to drug resistance; targeting this pathway may restore apoptosis. |
| CREB Signaling [17] | Cyclic AMP Response Element Binding Protein (CREB) facilitates cell survival and proliferation through gene regulation. Its expression is frequently elevated in AML cells, which contributes to a poor prognosis. | CREB overexpression is associated with increased proliferation; potential therapeutic target in AML. |
| Bcl-2 Family Proteins [20] | These proteins regulate apoptosis, with anti-apoptotic members (e. g. , Bcl-2, Mcl-1) inhibiting cell death. Overexpression of these proteins is prevalent in AML, leading to resistance against chemotherapy. | High levels of anti-apoptotic proteins support leukemic cell survival; BH3-mimetics are being explored as treatments. |
| Hedgehog Signaling Pathway [20] | This pathway is involved in stem cell maintenance and has been linked to the survival of leukemia stem cells (LSCs). Aberrant activation can aid in the persistence of LSCs in AML. | Targeting this pathway may help eliminate LSCs and reduce relapse rates in AML patients. |

**7. DIAGNOSIS**

The diagnosis of acute myeloid leukemia (AML) requires a variety of tests and assessments to verify the existence of myeloid blast cells and to identify the precise subtype of the condition. Criteria for Diagnosis

* Full Blood Count (FBC): A CBC is conducted to evaluate the counts of red blood cells, white blood cells, and platelets. In AML, patients frequently exhibit pancytopenia (decreased levels of red blood cells, white blood cells, and platelets) along with an increased count of immature white blood cells (blasts) in the bloodstream.[12]
* Peripheral Blood Smear: A peripheral blood smear enables the microscopic analysis of blood cells. The occurrence of a significant proportion of blast cells in the smear (frequently reaching 90% of the white blood cell count) suggests acute leukemia.[1,12]
* Bone Marrow Analysis: A bone marrow biopsy is essential for diagnosing AML. A diagnosis is established when myeloid blast cells make up ≥20% of nucleated cells in the marrow or if there are persistent cytogenetic abnormalities, irrespective of the blast percentage. [1,12]
* Histochemical Research and Cytogenetics: Further tests like histochemical staining and cytogenetic analysis assist in pinpointing specific genetic abnormalities linked to various AML subtypes, potentially affecting treatment choices.[9]
* Immunophenotyping: Flow cytometry helps identify the surface markers on blast cells, assisting in differentiating various leukemia types and validating the diagnosis.[13]
* Research in Molecular Biology: Genetic testing can be conducted to detect mutations that may offer insights into prognosis and treatment choices. For instance, alterations in genes like FLT3 or IDH1/2 can influence treatment options.[9]

**8. MEDICATION THERAPY USED IN AML**

The management of acute myelomonocytic leukemia (AMML) entails the use of multiple chemotherapy agents, targeted therapies, and supportive medications. The various Medication Therapy Used in Acute Myelomonocytic Leukemia (AMML) with Mechanisms and Dosage are provided in table 5.

TABLE 5 MEDICATION THERAPY USED IN AML

| **Medication** | **Type** | **Mechanism of Action** | **Dosage** | **Administration Route** |
| --- | --- | --- | --- | --- |
| Cytarabine (Ara-C) [21] | Chemotherapy | A pyrimidine analog that disrupts DNA synthesis by integrating into DNA and causing chain termination, resulting in the apoptosis of rapidly dividing leukemic cells. | 100-200 mg/m²/day for 7 days (continuous IV infusion) | Intravenous (IV) or subcutaneous |
| Daunorubicin [21] | Chemotherapy | An anthracycline that intercalates into DNA, inhibiting topoisomerase II, which obstructs DNA replication and transcription, ultimately leading to cell death. | 60-90 mg/m² on days 1-3 | IV |
| Idarubicin [21] | Chemotherapy | Similar to daunorubicin, it intercalates into DNA and inhibits topoisomerase II, promoting apoptosis in leukemic cells. | 12 mg/m² on days 1-3 | IV |
| Midostaurin (Rydapt) [22] | Targeted Therapy | A FLT3 inhibitor that obstructs the FLT3 receptor tyrosine kinase signaling pathway, frequently mutated in AML, which results in decreased proliferation and increased apoptosis. | 50 mg orally twice daily (for 14 days) | Oral |
| Gemtuzumab ozogamicin (Mylotarg) [22] | Targeted Therapy | A monoclonal antibody conjugated to a cytotoxic agent targeting CD33 on AML cells; it delivers the drug directly into the cells, inducing cell death. | 6 mg/m² on day 1; repeat every 28 days | IV |
| Ivosidenib (Tibsovo) [22] | Targeted Therapy | An IDH1 inhibitor that targets the mutated IDH1 enzyme, reversing the production of the oncometabolite 2-hydroxyglutarate (2-HG), thereby promoting differentiation of leukemic cells. | 500 mg orally once daily | Oral |
| Enasidenib (Idhifa) [22] | Targeted Therapy | An IDH2 inhibitor that similarly targets mutant IDH2 enzymes to lower 2-HG levels and encourage differentiation of AML cells. | 100 mg orally once daily | Oral |
| Venetoclax (Venclexta) [21,23] | Targeted Therapy | A BCL-2 inhibitor that induces apoptosis in leukemic cells by counteracting the anti-apoptotic effects of BCL-2 proteins, enhancing chemotherapy efficacy. | Start at 100 mg orally daily; increase to 400 mg | Oral |
| Azacitidine (Vidaza)  [21, 23] | Hypomethylating Agent | Incorporates into RNA and DNA, inhibiting DNA methyltransferase activity; this leads to reactivation of silenced genes and encourages differentiation of leukemic stem cells. | 75 mg/m² subcutaneously or IV for 7 days every 28 days | Subcutaneous or IV |
| Decitabine (Dacogen) [21,23] | Hypomethylating Agent | Similar to azacitidine, it inhibits DNA methylation and promotes gene expression alterations that can result in differentiation and apoptosis in AML cells. | 15 mg/m² IV over 1 hour for 5 days every 28 days | IV |

**9. PREVENTION**

Acute Myelomonocytic Leukemia (AML) is a form of acute myeloid leukemia distinguished by the proliferation of myeloblasts and monoblasts. While the precise causes of AML remain incompletely understood, certain factorsincluding exposure to ionizing radiation, occupational and environmental carcinogens, and toxinsmay elevate the risk.

* Routine Blood Testing: Early identification through routine blood tests can aid in detecting asymptomatic individuals, as 20%-30% of patients may initially present without symptoms. [27]
* Avoidance of Risk Factors: Reducing exposure to ionizing radiation, occupational and environmental carcinogens, and toxins may help lower the risk of developing AML. [27]
* Prophylactic Measures: The administration of fluoroquinolones (FQs) and antifungal prophylaxis can diminish the risk of infections in patients with severe neutropenia. [28]

**10. TREATMENT**

The percentage of treatment process used in AML are graphically represented on figure 1.

|  |  |
| --- | --- |
| * Early diagnosis and timely treatment are crucial for improving the prognosis of AML.[29] * AML is typically treated with chemotherapy and bone marrow/stem cell transplant. * Chemotherapy: The primary treatment for AML involves chemotherapy to kill cancer cells.27 In the case presented, the patient received standard induction therapy with cytarabine and idarubicin.30 The study mentions the use of cytosine arabinoside (ara-C) and daunorubicin (DNR) in various regimens. [31] * Stem Cell Transplant: Hematopoietic stem cell transplantation (HSCT) is often used as a curative treatment for AML, especially in cases where chemotherapy alone is insufficient. * Supportive Care: Advances in supportive care during transplantation have improved outcomes by reducing treatment-related mortality (TRM).30Zolendronic acid was administered for hypercalcemia, and bisphosphonates were used to manage bone-related complications.[30] * Targeted Therapy: New therapeutic agents targeting specific genetic mutations and pathways involved in AML are being developed and show promise in improving treatment outcomes.[27] * Radiation Therapy: Local radiation was used to relieve symptoms of granulocytic sarcoma in the joint space. * Salvage Therapy: When the leukemia was found to be refractory to initial chemotherapy, salvage therapy with mitoxantrone and etoposide was initiated. | * Pain Management: Pain from granulocytic sarcoma was managed with chemotherapy and local radiation.[30] * Induction Therapy: Four regimens were tested, with the 7-day ara-C infusion combined with DNR showing the highest complete remission (CR) rates. Patients under 60 years had a 59% CR rate with this regimen. [31,32] * Maintenance Therapy: After achieving remission, maintenance therapy with ara-C and other drugs (thioguanine, cyclophosphamide, CCNU, and DNR) was used to prevent relapse. Subcutaneous (s.c.) administration of ara-C was found to be more effective than intravenous (i.v.) bolus, with a median remission duration of 18 months for s.c. ara-C compared to 8 months for i.v. ara-C. [31] * Surgical Intervention: The patient underwent spinal surgery for the removal of epidural lesions and stabilization of the spine.[33] * Leukocytapheresis: This procedure is used to quickly decrease a patient’s circulating blast count, which can prevent the development of leukostasis and provide symptomatic relief. It is primarily used in AML but also in other leukemias with hyperleukocytosis.[34] * Allogeneic Hematopoietic Cell Transplantation (allo HCT): This is the only curative therapy for MDS and MPN. The study explored the use of TLI-ATG conditioning to establish donor hematopoiesis necessary for the graft-versus-malignancy effect while minimizing direct cytotoxicity against myeloid diseases. [33,35] * Graft-Versus-Host Disease (GVHD) Prophylaxis: GVHD prophylaxis consisted of cyclosporine A (CsA) and mycophenolate mofetil (MMF). The study reported a low incidence of acute GVHD (14%) and chronic GVHD (33%). [35] |

FIGURE 1 Treatments carried out for AML

**11. EPIGENETIC EFFECT OF AML**

Epigenetic changes are crucial in the development of Acute Myeloid Leukemia (AML). These alterations do not alter the DNA sequence but instead influence gene expression and cellular activity, playing a role in the development and advancement of the disease. Here is a summary of the main epigenetic impacts identified in AML, according to the given search results.

Crucial Epigenetic Changes in AML are as follow:

Alterations in DNA Methylation

* Description: DNA methylation consists of adding methyl groups to cytosine residues, generally resulting in gene suppression. In AML, unusual methylation patterns may inhibit tumor suppressor genes and trigger oncogenes.
* Consequences: In AML, global hypomethylation frequently occurs, resulting in the activation of typically silenced genes and aiding in leukemogenesis. [45,46]

Modifications of Histones

* Description: Histone proteins experience numerous post-translational modifications, including acetylation and methylation, which change the chromatin structure and the accessibility of genes.
* Consequences: Dysregulation of histone-modifying enzymes (such as histone deacetylases (HDACs) and histone methyltransferases) has been associated with AML, resulting in abnormal gene expression patterns. [47,48]

Non-Coding RNAs

* Description: Non-coding RNAs, such as microRNAs (miRNAs), are vital in controlling gene expression after transcription.
* Impacts: Changes in the expression of particular miRNAs have been associated with AML advancement and can influence cell growth and differentiation. [45]

Modified Expression of Epigenetic Modulators

* Description: Alterations in genes that code for epigenetic regulators (e.g., DNMT3A, TET2, IDH1/2) are commonly observed in AML patients.
* Consequences: These alterations impair standard epigenetic control and aid in the clonal progression of leukemic cells. [49,50]

Clinical Significance of epigenetic effect in AML

* Targeted Epigenetic Treatment: Since epigenetic alterations can be reversed, there is considerable enthusiasm for creating therapies aimed at these modifications. Agent types like hypomethylating agents (HMAs), including azacitidine and decitabine, are being studied for their potential to reverse atypical methylation patterns and return gene expression to normal levels. [46,51]
* Combination Treatments: The integration of epigenetic therapies with alternative treatments (such as chemotherapy or immunotherapy) could improve treatment effectiveness by counteracting resistance mechanisms linked to epigenetic dysregulation. [48]
* Prognostic Markers: Recognizing particular epigenetic modifications could assist in classifying patients by their prognosis and customizing treatment approaches as needed. [46,47]

**12. RISK FACTORS FOR ACUTE MYELOID LEUKEMIA (AML)**

The management of risk factors related to Acute Myeloid Leukemia (AML) centers on addressing underlying conditions, reducing exposure to identified risks, and employing preventive measures. Below is a summary of the principal risk factors and their associated treatment or management strategies given in figure 2. [36,37,38]

FIGURE 2 Risk factors for Acute Myeloid Leukemia (AML)

**13. LATEST ADVANCEMENT IN AML TREATMENT**

The latest advancement in Acute Myeloid leukemia treatment is represented on the figure 3.

FIGURE 3 Latest Advancement in AML Treatment

**14. CONCLUSION**

In conclusion, while the exact causes of AMML remain unclear, factors such as exposure to radiation and certain chemicals may increase risk. Routine blood tests can aid in early detection, and avoiding known risk factors is advisable. Current treatment strategies involve chemotherapy, targeted therapies, and supportive care to manage symptoms and improve prognosis. Continuous advancements in AML research are essential for enhancing treatment options and patient outcomes.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

I am hereby declare that NO generative AI technologies have been used during the writing or editing of this manuscript

Option 2:

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

1.

2.

3.

**15. REFERENCE**

1. PDQ® Adult Treatment Editorial Board. PDQ Acute Myeloid Leukemia Treatment. Bethesda, MD: National Cancer Institute. Updated 10/15/2024. Available at: <https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq>. Accessed <02/21/2025>. [PMID: 26389377]
2. American Cancer Society (2024, February 27). Signs and Symptoms of Acute Myeloid Leukemia (AML). <https://www.cancer.org/cancer/types/acute-myeloid-leukemia/detection-diagnosis-staging/signs-symptoms.html>
3. The Leukemia & Lymphoma Society. AML Signs and Symptoms.   
   <https://www.lls.org/leukemia/acute-myeloid-leukemia/signs-and-symptoms>
4. U.S. National Library of Medicine MedlinePlus (2020, January 1). Acute promyelocytic leukemia. <https://medlineplus.gov/genetics/condition/acute-promyelocytic-leukemia/>
5. Bennett, J. M., Catovsky, D., Daniel, M. T., Flandrin, G., Galton, D. A., Gralnick, H. R., & Sultan, C. (1976). Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *British journal of haematology*, *33*(4), 451–458. https://doi.org/10.1111/j.1365-2141.1976.tb03563.x
6. Hwang S. M. (2020). Classification of acute myeloid leukemia. *Blood research*, *55*(S1), S1–S4. <https://doi.org/10.5045/br.2020.S001>
7. Park H. S. (2024). What is new in acute myeloid leukemia classification?. *Blood research*, *59*(1), 15. https://doi.org/10.1007/s44313-024-00016-8
8. Shimony S, Stahl M, Stone RM. Acute myeloid leukemia: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2023; 98(3): 502-526. doi:[10.1002/ajh.26822](https://doi.org/10.1002/ajh.26822)
9. Hartmut Döhner, Andrew H. Wei, Frederick R. Appelbaum, et al., Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022; 140 (12): 1345–1377. doi: <https://doi.org/10.1182/blood.2022016867>
10. James W. Vardiman, Nancy Lee Harris, Richard D. Brunning; The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood* 2002; 100 (7): 2292–2302. doi: <https://doi.org/10.1182/blood-2002-04-1199>
11. Salman, H. (2024). Comparative Analysis of AML Classification Systems: Evaluating the WHO, ICC, and ELN Frameworks and Their Distinctions. *Cancers*, *16*(16), 2915. <https://doi.org/10.3390/cancers16162915>
12. Ashkan Emadi and Jennie York Law, 2023. Acute Myeloid Leukemia (AML), MSD Manual, Vol. 2023. <https://www.msdmanuals.com/professional/hematology-and-oncology/leukemias/acute-myeloid-leukemia-aml>
13. Vakiti A, Reynolds SB, Mewawalla P. Acute Myeloid Leukemia. [Updated 2024 Apr 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507875/
14. Chen, Y., Li, J., Xu, L. *et al.* The genesis and evolution of acute myeloid leukemia stem cells in the microenvironment: From biology to therapeutic targeting. *Cell Death Discov.* **8**, 397 (2022). <https://doi.org/10.1038/s41420-022-01193-0>
15. Franziska Wachter, Yana Pikman; Pathophysiology of Acute Myeloid Leukemia. *Acta Haematol* 25 March 2024; 147 (2): 229–246. <https://doi.org/10.1159/000536152>
16. Bouligny, I. M., Maher, K. R., & Grant, S. (2023). Mechanisms of myeloid leukemogenesis: Current perspectives and therapeutic objectives. *Blood reviews*, *57*, 100996. <https://doi.org/10.1016/j.blre.2022.100996>
17. Sakamoto, K. M., Grant, S., Saleiro, D., Crispino, J. D., Hijiya, N., Giles, F., Platanias, L., & Eklund, E. A. (2015). Targeting novel signaling pathways for resistant acute myeloid leukemia. *Molecular genetics and metabolism*, *114*(3), 397–402. <https://doi.org/10.1016/j.ymgme.2014.11.017>
18. Ugo Testa, Roberta Riccioni. Deregulation of apoptosis in acute myeloid leukemia. Haematologica 2007;92(1):81-94; https://doi.org/10.3324/haematol.10279.
19. Modarres, P., Mohamadi Farsani, F., Nekouie, A. *et al.* Meta-analysis of gene signatures and key pathways indicates suppression of JNK pathway as a regulator of chemo-resistance in AML. *Sci Rep* **11**, 12485 (2021). <https://doi.org/10.1038/s41598-021-91864-2>
20. Carter, J.L., Hege, K., Yang, J. *et al.* Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy. *Sig Transduct Target Ther* **5**, 288 (2020). <https://doi.org/10.1038/s41392-020-00361-x>
21. Nwosu, G.O., Ross, D.M., Powell, J.A. *et al.* Venetoclax therapy and emerging resistance mechanisms in acute myeloid leukaemia. *Cell Death Dis* **15**, 413 (2024). <https://doi.org/10.1038/s41419-024-06810-7>
22. Brown, E., & Guinn, B. A. (2022). Molecular Mechanisms and Therapies of Myeloid Leukaemia. *International journal of molecular sciences*, *23*(11), 6251. <https://doi.org/10.3390/ijms23116251>
23. Zhang J, Gu Y, Chen B. Mechanisms of drug resistance in acute myeloid leukemia. *Onco Targets Ther*. 2019;12:1937-1945  
    <https://doi.org/10.2147/OTT.S191621>
24. PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment. Bethesda, MD: National Cancer Institute. Updated 06/05/2024. Available at: <https://www.cancer.gov/types/leukemia/patient/child-aml-treatment-pdq>. Accessed <MM/DD/YYYY>. [PMID: 26389303]
25. Appelbaum, F. R., Kopecky, K. J., Tallman, M. S., Slovak, M. L., Gundacker, H. M., Kim, H. T., Dewald, G. W., Kantarjian, H. M., Pierce, S. R., & Estey, E. H. (2006). The clinical spectrum of adult acute myeloid leukaemia associated with core binding factor translocations. *British journal of haematology*, *135*(2), 165–173. <https://doi.org/10.1111/j.1365-2141.2006.06276.x>
26. Grimwade, D., Walker, H., Harrison, G., Oliver, F., Chatters, S., Harrison, C. J., Wheatley, K., Burnett, A. K., Goldstone, A. H., & Medical Research Council Adult Leukemia Working Party (2001). The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood*, *98*(5), 1312–1320. <https://doi.org/10.1182/blood.v98.5.1312>
27. Meyran D, Arfeuille C, Chevret S, Neven Q, Caye-Eude A, Lainey E, Petit A, Rialland F, Michel G, Plantaz D, Jubert C, Theron A, Gandemer V, Ouachée-Chardin M, Paillard C, Bruno B, Buchbinder N, Pochon C, Calvo C, Fahd M, Baruchel A, Cavé H, Dalle J-H, Strullu M. A predictive classifier of poor prognosis in transplanted patients with juvenile myelomonocytic leukemia: a study on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire. Haematologica 2024;109(9):2908-2919; <https://doi.org/10.3324/haematol.2023.284103>.
28. Vilorio-Marqués L, Castañón Fernández C, Mora E, et al. Relevance of infections on the outcomes of patients with myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia treated with hypomethylating agents: a cohort study from the GESMD. *Therapeutic Advances in Hematology*. 2022;13.
29. A Case of Granulocytic Sarcoma or Extramedullary Acute Myelomonocytic Leukemia of the Gallbladder, Rare disease. *Erik A. Holzwanger*1AEF, *Zainab Alam*1EF, *Emily Hsu*1F, *Andrew Hsu*1A, *Mark Mangano*2DE, *Deirdre L. Kathman*3AEF\*. Am J Case Rep 2018; 19:1262-1266. DOI: 10.12659/AJCR.911390
30. Mueller, M., & Calvo, A. R. (2010). Acute Shoulder Monoarthritis in a Patient With Acute Myelomonocytic Leukemia With Novel Translocation t(5;13). *World journal of oncology*, *1*(1), 50–51. <https://doi.org/10.4021/wjon2010.02.194w>
31. Rai, K. R., Holland, J. F., Glidewell, O. J., Weinberg, V., Brunner, K., Obrecht, J. P., Preisler, H. D., Nawabi, I. W., Prager, D., Carey, R. W., Cooper, M. R., Haurani, F., Hutchison, J. L., Silver, R. T., Falkson, G., Wiernik, P., Hoagland, H. C., Bloomfield, C. D., James, G. W., Gottlieb, A., … Kaan, S. K. (1981). Treatment of acute myelocytic leukemia: a study by cancer and leukemia group B. *Blood*, *58*(6), 1203–1212.
32. Koerber, RM., Held, S.A.E., Vonnahme, M. *et al.* Blastic plasmacytoid dendritic-cell neoplasia: a challenging case report. *J Cancer Res Clin Oncol* **148**, 743–748 (2022). <https://doi.org/10.1007/s00432-021-03777-2>
33. Li, Y., Xie, Y. D., He, S. J., Hu, J. M., Li, Z. S., & Qu, S. H. (2022). Breast and dorsal spine relapse of granulocytic sarcoma after allogeneic stem cell transplantation for acute myelomonocytic leukemia: A case report. *World journal of clinical cases*, *10*(7), 2315–2321. <https://doi.org/10.12998/wjcc.v10.i7.2315>
34. Aqui, N., & O'Doherty, U. (2014). Leukocytapheresis for the treatment of hyperleukocytosis secondary to acute leukemia. *Hematology. American Society of Hematology. Education Program*, *2014*(1), 457–460. <https://doi.org/10.1182/asheducation-2014.1.457>
35. Benjamin, J., Chhabra, S., Kohrt, H. E., Lavori, P., Laport, G. G., Arai, S., Johnston, L., Miklos, D. B., Shizuru, J. A., Weng, W. K., Negrin, R. S., & Lowsky, R. (2014). Total lymphoid irradiation-antithymocyte globulin conditioning and allogeneic transplantation for patients with myelodysplastic syndromes and myeloproliferative neoplasms. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*, *20*(6), 837–843. <https://doi.org/10.1016/j.bbmt.2014.02.023>
36. Onyee Chan, Najla Al Ali, Hammad Tashkandi, Austin Ellis, Somedeb Ball, Justin Grenet, Caroline Hana, Yehuda Deutsch, Ling Zhang, Mohammad Hussaini, Jinming Song, Seongseok Yun, Chetasi Talati, Andrew Kuykendall, Eric Padron, Alison Walker, Gail Roboz, Pinkal Desai, David Sallman, Kendra Sweet, Rami Komrokji, Jeffrey Lancet; Mutations highly specific for secondary AML are associated with poor outcomes in ELN favorable risk *NPM1*-mutated AML. *Blood Adv* 2024; 8 (5): 1075–1083. doi: <https://doi.org/10.1182/bloodadvances.2023011173>
37. Raffel GD, Cerny J. Chapter 106: Molecular Biology of Acute Leukemias. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg’s Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2015.
38. Stock W, Thirman MJ. Pathogenesis of acute myeloid leukemia. UpToDate. 2018. Accessed at www.uptodate.com/contents/pathogenesis-of-acute-myeloid-leukemia on June 14, 2018.
39. Cortes, J., Jonas, B. A., Schiller, G., Mims, A., Roboz, G. J., Wei, A. H., Montesinos, P., Ferrell, P. B., Yee, K. W., Fenaux, P., Schwarer, A., & Watts, J. M. (2024). Olutasidenib in post-venetoclax patients with mutant isocitrate dehydrogenase 1 (m*IDH1*) acute myeloid leukemia (AML). *Leukemia & lymphoma*, *65*(8), 1145–1152. <https://doi.org/10.1080/10428194.2024.2333451>
40. Daniel A. Pollyea, Maria Amaya, Paolo Strati, Marina Y. Konopleva; Venetoclax for AML: changing the treatment paradigm. *Blood Adv* 2019; 3 (24): 4326–4335. doi: <https://doi.org/10.1182/bloodadvances.2019000937>
41. Candoni, A., & Coppola, G. (2024). A 2024 Update on Menin Inhibitors. A New Class of Target Agents against KMT2A-Rearranged and NPM1-Mutated Acute Myeloid Leukemia. *Hematology reports*, *16*(2), 244–254. <https://doi.org/10.3390/hematolrep16020024>
42. Kantarjian, H., Borthakur, G., Daver, N. *et al.* Current status and research directions in acute myeloid leukemia. *Blood Cancer J.* **14**, 163 (2024). https://doi.org/10.1038/s41408-024-01143-2
43. Chen, Y. J., Abila, B., & Mostafa Kamel, Y. (2023). CAR-T: What Is Next?. *Cancers*, *15*(3), 663. <https://doi.org/10.3390/cancers15030663>
44. Gosline, S.J.C., Tognon, C., Nestor, M. *et al.* Proteomic and phosphoproteomic measurements enhance ability to predict ex vivo drug response in AML. *Clin Proteom* **19**, 30 (2022). <https://doi.org/10.1186/s12014-022-09367-9>
45. Plass, C., Oakes, C., Blum, W., & Marcucci, G. (2008). Epigenetics in acute myeloid leukemia. *Seminars in oncology*, *35*(4), 378–387. <https://doi.org/10.1053/j.seminoncol.2008.04.008>
46. Gambacorta, V., Gnani, D., Vago, L., & Di Micco, R. (2019). Epigenetic Therapies for Acute Myeloid Leukemia and Their Immune-Related Effects. *Frontiers in cell and developmental biology*, *7*, 207. <https://doi.org/10.3389/fcell.2019.00207>
47. San José-Enériz, E., Gimenez-Camino, N., Rabal, O. *et al.* Epigenetic-based differentiation therapy for Acute Myeloid Leukemia. *Nat Commun* **15**, 5570 (2024). <https://doi.org/10.1038/s41467-024-49784-y>
48. Rausch, J., Ullrich, E., & Kühn, M. W. M. (2023). Epigenetic targeting to enhance acute myeloid leukemia-directed immunotherapy. *Frontiers in immunology*, *14*, 1269012. <https://doi.org/10.3389/fimmu.2023.1269012>
49. Friederike Pastore, Ross L. Levine. Epigenetic regulators and their impact on therapy in acute myeloid leukemia. Haematologica 2016;101(3):269-278; <https://doi.org/10.3324/haematol.2015.140822>
50. Conway O’Brien, Emma, Prideaux, Steven, Chevassut, Timothy, The Epigenetic Landscape of Acute Myeloid Leukemia, *Advances in Hematology*, 2014, 103175, 15 pages, 2014. <https://doi.org/10.1155/2014/103175>
51. Bas J. Wouters, Ruud Delwel; Epigenetics and approaches to targeted epigenetic therapy in acute myeloid leukemia. *Blood* 2016; 127 (1): 42–52. doi: <https://doi.org/10.1182/blood-2015-07-604512>