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Acute Myeloid Leukemia: A focus on Risk Factors, Clinical Presentation, Diagnosis and Possible Lines of Management

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Abstract The aim of this review was to shed light on the epidemiology, classification, possible risk factors, clinical presentation, diagnosis and possible lines of management of acute myeloid leukemia (AML). AML is one of the malignancies originating from the myeloid line of blood cells. It is characterized by rapid growth of abnormal white blood cells that build up in the bone marrow and interfere with production of normal blood cells. It is the most common acute leukemia affecting adults, and its incidence increases with age. Several risk factors and chromosomal abnormalities have been identified in AML. AML has several subtypes which determine the suitable lines of treatment and the overall prognosis. AML involves a high percentage of dedifferentiated and undifferentiated cells, including more myeloblasts, monoblasts and megakaryoblasts. Symptoms of AML are variable, including fatigue, shortness of breath, easy bruising and bleeding with increased risk of infections. AML is treated initially with chemotherapy to induce remission. Then, patients may receive additional chemotherapy or hematopoietic stem cell transplantation. In conclusion, AML is the most common type of acute leukemia in adults which is usually precipitated by mutations in the genes involved in hematopoietic proliferation and differentiation and its main lines of treatment remain combination of cytarabine- and anthracycline-based regimens with allogeneic stem cell transplantation for eligible patients.

Keywords: *myeloid, leukemia, risk factors, diagnosis, management*

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1. Introduction

Cancer is a group of diseases characterized by unregulated cell growth and differentiation [1]. Acute Myeloid Leukemia (AML), a rapidly progressive malignant disease, represents a group of clonal hematopoietic stem cell disorders characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency with or without leukocytosis [2]. AML involves higher percentages of dedifferentiated and undifferentiated cells, including more blast cells (Figure 1). It is the most common acute leukemia affecting adults, and its incidence increases with age [3]. Symptoms of AML are caused by replacement of normal bone marrow with leukemic cells, which causes a decrease in red blood cells, platelets, and normal white blood cells. They include fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infection. Several risk factors for the development of AML have been identified, but the specific cause is not yet fully understood [4]. AML usually progresses rapidly and may be fatal within weeks or months if left untreated. AML has several subtypes which determine the lines of treatment and prognosis. AML is treated initially with chemotherapy to induce remission. Then, patients may receive additional chemotherapy or a hematopoietic stem cell transplantation [5]. The aim of this review was to shed light on AML regarding its epidemiology, classification, possible risk factors, clinical picture, diagnosis, prognosis and possible lines of management.

2. Epidemiology of AML

Acute myeloid leukemia (AML) is infrequent, yet highly malignant neoplasms responsible for a large number of cancer-related deaths. The incidence has been near stable over the last years. It continuously shows 2 peaks in occurrence in early childhood and later adulthood. With an incidence of 3.7 per 100,000 persons and an age-dependent mortality of 2.7 to nearly 18 per 100,000 persons, there is a rising awareness in the Western world of AML's special attributes resulting from an ever-aging population [3]. To estimate outcome and discuss informed treatment decisions with AML patients of different age groups and different biologic risk categories, it is

mandatory to consider that the outcome results reported in clinical trials were until now heavily biased toward younger patients, whereas the overall dismal prognosis documented in population-based studies most likely reflects the exclusion of older patients from aggressive treatment [4].

3. Classification of AML

Determination of the subtype of AML can be very important, as it sometimes affects both a patient's outlook and the best treatment. For example, the Acute Promyelocytic Leukemia (APL) subtype is often treated using drugs that are different from those used for other subtypes of AML. Two of the main systems that have been used to classify AML into subtypes are: the French-American-British (FAB) classification and the newer World Health Organization (WHO) classification [5].

3.1. The French-American-British (FAB) Classification of AML

In the 1970s, a group of French, American, and British leukemia experts divided AML into subtypes, M0 through M7, based on the type of cell from which the leukemia develops and how mature the cells are. This was based largely on how the leukemia cells looked under the microscope after routine staining (Table 1). Subtypes M0 through M5 all start in immature forms of white blood cells. M6 AML starts in very immature forms of red blood cells, while M7 AML starts in immature forms of cells that make platelets [6].

3.2. World Health Organization (WHO) Classification of AML

The FAB classification system is useful and is still commonly used to group AML into subtypes. But it doesn't take into account many of the factors that are now known to affect prognosis. The World Health Organization (WHO) has developed a newer system that includes some of these factors to try to better classify AML [7]. The WHO system divides AML into several groups: (1) AML with certain genetic abnormalities: AML with a translocation between chromosomes 8 and 21; AML with a translocation or inversion in chromosome 16; AML with a translocation between chromosomes 9 and 11; APL (M3) with a translocation between chromosomes 15 and 17; AML with a translocation between chromosomes 6 and 9; AML with a translocation or inversion in chromosome 3; AML (megakaryoblastic) with a translocation between chromosomes 1 and 22. (2) AML with myelodysplasia-related changes. (3) AML related to previous chemotherapy or radiation. (4) AML not otherwise specified (This includes cases of AML that don't fall into one of the above groups, and is similar to the FAB classification.): AML with minimal differentiation (M0); AML without maturation (M1); AML with maturation (M2); Acute myelomonocytic leukemia (M4); Acute monocytic leukemia (M5); Acute erythroid leukemia (M6); Acute megakaryoblastic leukemia (M7); Acute basophilic leukemia; Acute panmyelosis with fibrosis. (5) Myeloid sarcoma (also known as granulocytic sarcoma or chloroma). (6) Myeloid proliferations related to Down syndrome. (7) Undifferentiated and biphenotypic acute leukemias (leukemias that have both lymphocytic and myeloid features). Sometimes called acute lymphoblastic leukemia (ALL) with myeloid markers, AML with lymphoid markers, or mixed phenotype acute leukemia [8].

Table 1. The French-American-British (FAB) classification of AML

FAB subtype	Name
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
M4	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

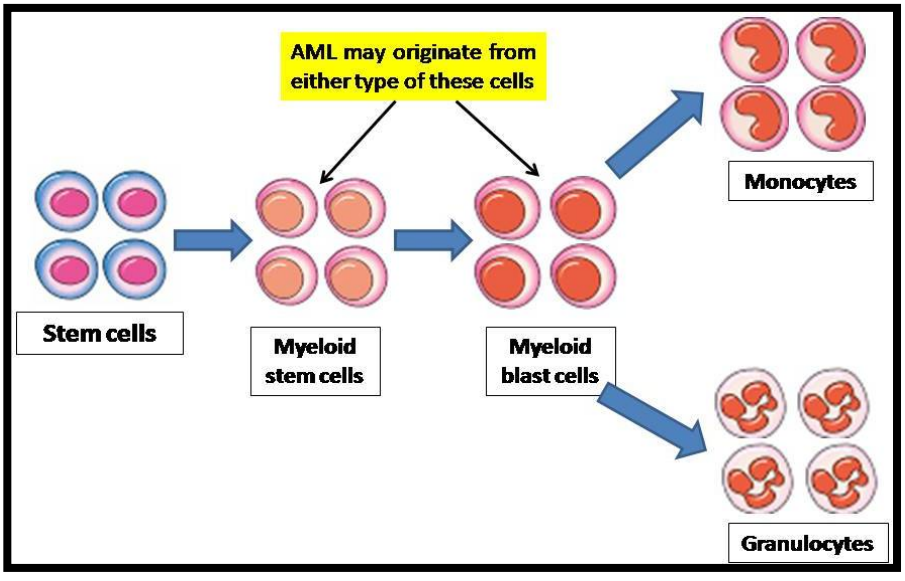

Figure 1. Origin of AML

4. Etiology of AML

The etiology for most cases of AML is unclear, but a growing knowledge concerning leukemogenenic agents within chemotherapy regimens for other malignancies is already available. This includes specific associations of the most frequent balanced translocations in AML, including the "good-risk" abnormalities comprised by the core binding factor leukemia (i.e., AML with the translocation (8;21) and inversion of chromosome 16, and acute promyelocytic leukemia with the translocation (15;17). In contrast to these genetic alterations, epigenetic lesions, e.g., promoter silencing by hypermethylation of the p15/INK4b and other genes, are increasingly recognized as important in the pathogenesis of AML [9].

AML can arise in patients with an underlying hematological disorder, or as a consequence of prior therapy (for example, exposure to topoisomerases II, alkylating agents) [2]. However in majority of cases, it appears as a de novo malignancy in previously healthy individuals. Regardless of its etiology, the pathogenesis of AML involves the abnormal proliferation and differentiation of a clonal population of myeloid stem cells. large chromosomal rearrangements, molecular changes have also been implicated in the development of AML [10]. Actually the reason of the genetic mutation that Encourage the bone marrow into leukemia is unknown but the main causes of AML are exposure to high levels of radiation, benzene, or both [3].

5. Clinical Presentation of AML

The clinical signs and symptoms of AML are diverse and nonspecific, but they are usually directly attributable to the leukemic infiltration of the bone marrow, with resultant cytopenia. Typically, patients present with signs and symptoms of fatigue, hemorrhage, or infections and fever due to decreases in red cells, platelets, or white cells, respectively. Pallor, fatigue, and dyspnea on exertion are common [11]. Leukemic infiltration of various tissues, including hepatosplenomegaly or lymphadenopathy. Less commonly, tumours may present with gingival enlargement, skin chloromas, and soft tissue or meningeal leukemic infiltration. Coagulopathies are reasonably common with AML. An isolated mass of leukemic blasts is usually referred to as a granulocytic sarcoma. Hyperleukocytosis (more than 100,000 white cells per cubic millimeter) can lead to symptoms of leukostasis, such as ocular and cerebrovascular dysfunction or bleeding. There may also be metabolic abnormalities (e.g., hyperuricemia and hypocalcemia), although these are rarely found at presentation [3].

6. Complications of AML

Due to a weakened immune system and a highly decreased capacity of the body to fight infection, patient with acute myelocytic leukemia are vulnerable and in danger of developing a number of complications. These complications can be short-term or long-term [12]. As short term complications patients may develop tumour lysis syndrome which Occurs when chemotherapy is commenced in patients presenting with hyperleukocytosis due to breakdown of large number of leukemic cells. This results in electrolyte and metabolic disturbances in the form of hyperuricaemia, hyperphosphataemia, hypocalcaemia, hyperkalaemia, and renal impairment. Leukostasis which is consequence of the leukemic process. Presents as dyspnoea, chest pain, headaches, altered mentation, cranial nerve palsies, or priapism. Neutropenia and pancytopenia which are consequence of bone marrow in filtration by leukaemic cells and of adverse effects of treatment [3]. Infections are a major cause of morbidity and mortality in AML due to abnormally low concentration of granulocytes in the blood. Disseminated intravascular coagulation (DIC) is medium likelihood. Central nervous system (CNS) leukemia occurs in <5% of patients with AML. As long-term complications are chemotherapy related, such as myelodysplasia, secondary malignancies, endocrine dysfunction (mainly hypothyroidism), and cardiomyopathy [13].

7. Diagnosis of AML

Catching cancer early often allows for more treatment options. Some early cancers may have signs and symptoms that can be notice, but to say it's important to insure these signs by diagnostic tests [3].

7.1. Complete blood Count (CBC) with Differential Leucocytic Count

Despite the elevation in white blood cells (WBC), many patients have severe neutropenia (<500 granulocytes/microlitre), thus placing them at high risk for serious infections. Thrombocytopenia is very common, affecting most patients. The suspected Result: anaemia, macrocytosis, leukocytosis, neutropenia, and thrombocytopenia [14].

7.2. Peripheral Blood Smear

Blasts are immature cells and are not normally seen in the peripheral blood. The granulated and Auer rod content of blasts confirms AML. The classic appearance of acute promyelocytic leukaemia (APML) is a normal. white blood cells count, bi-lobed nuclei, hypergranulated blasts, and bundles of Auer rods. Finding of blasts on peripheral blood smear is not sufficient to establish and the diagnosis of AML and bone marrow biopsy is required. The suspected Result: blasts on blood film, presence of Auer rods [15].

7.3. Morphology

A bone marrow aspirate is part of the routine diagnostic work-up of a patient with suspected AML. The panel considers a marrow trephine biopsy optional, but it should be performed in patients with a dry tap [14].

7.4. Immunophenotyping

Immunophenotyping using multiparameter (commonly at least 3- to 4-color) flow cytometry is used to determine lineage involvement of a newly diagnosed acute leukemia.

There is no general consensus on the cutoff point for considering an acute leukemia to be positive for a marker. For most markers, a commonly used criterion is 20% or more of leukemic cells expressing the marker [3].

Whereas for selected markers eg, cytoplasmic CD3, MPO, TdT, CD34, CD117) a lower cutoff has been applied (10%). Quantification of expression patterns of several surface and cytoplasmic antigens is necessary for lineage assignment, to diagnose mixed phenotype acute leukemia (MPAL), and to detect aberrant immunophenotypes allowing for measurement of minimal residual disease (MRD). Flow cytometry determination of blast count should not be used as a substitute for morphologic evaluation [16].

7.5. Bone Marrow Biopsy or Aspiration

Definitive diagnosis requires bone marrow biopsy. Presence of blast cells in >20% of the bone marrow cells confirms the diagnosis. Additional immunophenotyping and immunochemistry is required to confirm the diagnosis. The suspected results include bone marrow hypercellularity and infiltration by blasts [17].

7.6. Chest X-ray

Pulmonary infiltrates at higher WBC counts due to leukostasis may occur. The suspected result: may show evidence of consolidation, pulmonary infiltrates, cardiomegaly. Differential diagnosis FOR Acute lymphocytic leukaemia; Clinically indistinguishable from AML. Bone marrow biopsy, peripheral blood smear, immunophenotyping, and immunochemistry may be helpful in establishing the diagnosis. Blast cells are positive for deoxynucleotidyl transferase and lack staining for myeloperoxidase; also demonstrate the presence of lymphoid markers [3].

8. Management of AML

Several types of treatment may be used for people with AML. The main treatment for AML is chemotherapy, sometimes followed by a stem cell transplant. Other drugs (besides standard chemotherapy drugs) may also be used to treat people with acute promyelocytic leukemia (APL). Surgery and radiation therapy may be used in special circumstances [11]. A number of chemotherapy medications are effective against AML. The goal of treatment is to kill the malignant cells without damaging the residual normal bone marrow cells. Studies are underway to find the best medicines, doses, and treatment schedules for AML [3].

Researchers have discovered that the genetic makeup of the abnormal myeloid cells can vary, which affects how you respond to treatment. The treatment can be tailored based upon a careful analysis of genetic material. These genetic changes are due to mutations that are acquired within bone marrow stem cells and thereby affect all of the malignant daughter cells that are produced. It is not known how these mutations develop. They are generally not thought to be inherited but rather develop by chance. Treatment of AML depends upon the patient specific subtype of AML. For example, people with a certain type of AML, called "acute promyelocytic leukemia," may be treated with other (non-chemotherapy) medications [18].

The backbone of treatment is chemotherapy, specifically, cytarabine plus an anthracycline (e.g., daunorubicin or idarubicin). In general, for patients able to tolerate intensive chemotherapy regimens (usually but not exclusively patients <60 years of age) intensive chemotherapy, given with curative intent, begins with an induction regimen. The aim of induction is to reduce the tumour burden and restore normal haematopoiesis. Usually one course is sufficient (although 2 courses may be given in Europe) [19]. For all newly diagnosed patients, evaluation and referral for a clinical trial is recommended. If a patient is unsuitable for a clinical trial, a similar induction regimen (i.e., cytarabine plus an anthracycline) may be used, or mitoxantrone may be used in combination with cytarabine. In patients under 60 years of age, such regimens induce complete remission in 70% to 80% of patients [3].

8.1. Post-induction/consolidation Regimen

Selection of therapy depends on risk factors for relapse such as cytogenetics and WBC count at presentation. 3 to 4 courses of regimens consisting of higher doses of cytarabine (HiDAC) alone or in combination with other drugs such as mitoxantrone, etoposide, or amsacrine [20]. For patients over the age of 65 years, the benefit of consolidation with intensive chemotherapy courses is not clear. For high-risk patients <60 years of age, one course of consolidation chemotherapy may be followed by or combined with an allogeneic, or less commonly an autologous, stem cell transplant (SCT). For patients 60 years or older who achieve complete remission with induction regimens, further consolidation with the induction regimen is used. In the context of a clinical trial, an allogeneic SCT with reduced-intensity conditioning may also be considered [21].

8.2. Patients unable to Tolerate Intensive Chemotherapy

A small-dose subcutaneous cytarabine is the standard of care for patients unable to tolerate intensive chemotherapy. Clinical trials that compare low-dose subcutaneous cytarabine with a novel agent, or with a novel agent plus low-dose subcutaneous cytarabine, should be offered if available. Patients unable to tolerate chemotherapy**.** Best supportive care (e.g., hydration, blood products, treatment of infections, leukoreduction measures, treatment of tumour lysis syndrome, symptom relief) may be more suitable in patients unable to tolerate chemotherapy [22].

8.3. Management of Refractory or Relapsed Disease

Relapse occurs in 50% of patients, but 50% to 60% of these can achieve a second remission with salvage chemotherapy. Important predictors of response to such re-induction chemotherapy are age, karyotype, duration of first remission, and history of previous SCT [23]. Where possible, patients should be offered enrolment in a clinical trial. In the younger and fit patients who achieve remission with salvage chemotherapy (usually a combination of higher doses of cytarabine with other drugs), allogeneic SCT should be offered to reduce the risk of relapse. Older

patients with high-risk disease or beyond first remission may be offered a reduced-intensity conditioned transplant or novel therapies in the context of a clinical trial. A further option for this group is best supportive care. If relapse occurs after 6 months, treatment with the original induction therapy may be considered for all patients [24].

8.4. Induction of Remission

For more than 30 years, daunorubicin and cytarabine have been the backbone of treatments to induce remission. Conventionally, daunorubicin is administered three times at a dose of 40 to 60 mg per square meter of body-surface area during each course of chemotherapy. In recent years, prospective, randomized trials of alternative agents have suggested that idarubicin or mitoxantrone 64 is more effective than daunorubicin in younger patients, although both resulted in more prolonged cytopenia [25]. Therefore, the question was raised as to whether the doses used in these comparisons were equivalent in terms of levels of toxicity Studies directly comparing mitoxantrone and idarubicin are ongoing. In most induction regimens, cytarabine is given intravenously in bolus doses of 100 to 200 mg per square meter per day or by continuous infusion over a period of 7 to 10 days. Several groups have suggested that escalation of the dose during this period would be more effective than conventional dosing strategies [26].

With the use of daunorubicin and cytarabine or their analogues, complete remission can be routinely induced in 70 to 80 percent of patients who are 60 years of age or younger and in approximately 50 percent of older patients. There is some evidence that the addition of etoposide to combinations of daunorubicin and cytarabine can further increase remission rates. The use of high-dose cytarabine (3 g per square meter twice a day) did not increase the rate of remission, but in one randomized study it favorably influenced relapse and survival [27].

8.5. Management of Acute Promyelocytic (M_3) Leukemia

Early diagnosis and treatment of acute promyelocytic leukemia (APL), the M3 subtype of AML, are important because patients with APL can develop serious blood-clotting or bleeding problems. This is less often a problem now that treatment includes differentiating drugs like all-trans-retinoic acid (ATRA). Other treatments might include chemotherapy and transfusions of platelets or other blood products [28].

The treatment of most cases of APL differs from usual AML treatment. Initial treatment includes the non-chemotherapy drug all-trans-retinoic acid (ATRA), which is most often combined with an anthracycline chemotherapy (chemo) drug (daunorubicin or idarubicin), sometimes also with the drug cytarabine (ara-c). Another option is to give ATRA plus another differentiating drug called arsenic trioxide (Trisenox). This is often used in patients who can't tolerate an anthracycline drug, but it's an option for other patients as well [29].

8.6. Maintenance Therapy

For some patients, consolidation may be followed by maintenance therapy with ATRA for at least a year. Sometimes low doses of the chemo drugs 6-mercaptopurine (6-MP) and methotrexate are given as well [26].

8.7. Supportive/Palliative Care

Intensive chemotherapy provides only marginal, if any, survival benefit to older AML patients, so non-intensive (or non-chemotherapy-based) approaches are reasonable. We use the phrase aggressive supportive care to emphasize that symptoms will be treated vigorously and to distinguish this modality from hospice. Blood and platelet transfusions should be administered to alleviate symptoms stemming from anemia and thrombocytopenia, and antibiotics started when appropriate. Low-dose chemotherapy should only be used in the setting of leukocytosis and/or associated symptoms [30].

Any recommendations for the institution of neutropenic precautions (i.e., avoiding crowds, refraining from ingestions of raw foods) must be balanced with the lack of evidence supporting the benefit of these maneuvers and the impact such restrictions will have on a patient's quality of life. Hospice services should be instituted within 6 months of anticipated demise. While some hospice organizations prohibit blood product transfusions, we consider these to be palliative in this population as they may result in improved quality of life interminal cancer patient populations [26].

9. Prognosis of AML

The 5-year survival of patients with AML is approximately 25%. Younger (<60 years of age) and fit patients, Overall only about one third of patients between 18 and 60 years of age with AML will be cured with treatment. However, patients are stratified into risk groups using 2 parameters that are highly significant prognostic markers for relapse: cytogenetics at diagnosis and percentage of blasts in the bone marrow after the first course of chemotherapy [31,32]. For good-risk patients with favourable cytogenetics (i.e., t(8;21) or inv16), and irrespective of marrow results after the first course, the 5-year survival and risk of relapse are 76% and 23%, respectively. For standard-risk patients (neither good nor poor cytogenetics, not >15% blasts in the bone marrow after the first course), the 5-year survival and risk of relapse are 48% and 52%, respectively. Poor-risk patients with adverse cytogenetics (i.e., -5, -7, del(5q), abnormal 3q, t(9,22)), and/or >15% blasts in the bone marrow after the first course of chemotherapy, the 5-year survival and risk of relapse are 21% and 73%, respectively [33].

The overall outlook for older patients is poorer than that of the younger patients. This is based on the higher prevalence of unfavourable cytogenetics, antecedent myelodysplasia in the older patients, a higher incidence of multi-drug resistance, and an increased frequency of coexistent medical conditions that affect the ability to tolerate intensive treatment. Although complete remission rates of almost 60 % can be achieved with standard induction chemotherapy for patients ≥60 years of age treated with intensive chemotherapy, almost 90 % relapse within 3 years. Only about 5% to 15% of these patients have long-term disease-free survival [34]. Only marginal survival benefit has been demonstrated with intensive

chemotherapy in trials comparing it with a less aggressive or palliative approach. Outcomes with investigational agents and reduced-intensity allogeneic stem cell transplants in the fitter patients in this group are being studied in various clinical trials [3]. The cure rates for acute promyelocytic leukaemia (APML) with current treatment protocols exceed 80%. The aim of current trials is to determine schedules that offer maximum cure rates with minimal toxicities [35].

10. Conclusion

AML is the most common acute leukemia in adults. Large chromosomal translocations and mutations in the genes involved in hematopoietic proliferation and differentiation result in accumulation of poorly differentiated myeloid cells. Despite advances in supportive care, the main lines of treatment remain combination of cytarabine- and anthracycline-based regimens with allogeneic stem cell transplantation for eligible patients. Elderly patients often can't tolerate such regimens and unfortunately have poor prognosis.

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