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Review Journal of Acute Myeloid Leukemia

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ABSTRACT

Leukemia is a type of blood cancer, which caused 474,519 new cases recorded worldwide in 2020 with an age-standardized incidence rate of 5.4 in 100,000 and 311,594 linked deaths were reported in terms of mortality (Huang et al., 2022). Acute myeloid leukemia (AML) is one of the 4 subtypes in leukemia and it contributes to roughly 31% of all leukemia cases (Cancer.Net, 2019). The purpose of this paper is to conduct a general overview of the classification, pathogenesis, symptoms, diagnosis, treatments and the current research of AML.

Introduction

Leukemia is characterized by malignant cell growth in the bone marrow leading to the low white blood cell count in blood, which is related to gene mutation (Knottenbelt, 2015). The first Leukemia case can date back to 1811, when Peter Cullen, Scottish physician described a case of splenitis acutus with inexplicable milky blood. In 1844, Alfred Donné discovered that the white blood cells had maturation arrest (Kampen, 2011). Currently, based on its cause and pathogenesis, cellular phenotype and chemistry, and clinical manifestations, leukemia can be classified into 4 subtypes: chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML). AML is a malignant clonal illness, which is marked by recurrent mutations in particular somatic gene sequences or chromosomal aberrations (Abdullah et al., 2021 & Kassahun et al., 2020 & Cooper & Young,2017 & DiNardo et al., 2023).Myeloblast proliferation with expansion combined with differentiation disorder that is caused by AML can result in abnormal haematopoiesis, which can lead to life-threatening cytopenias, a low-blood-cell-count condition, and a need for blood transfusions and bone marrow transplant (Acute Myeloid Leukemia (AML) Subtypes and Prognostic Factors, n.d.). The difference between myeloid cells and lymphocytes can be summarized from figure 1 below.

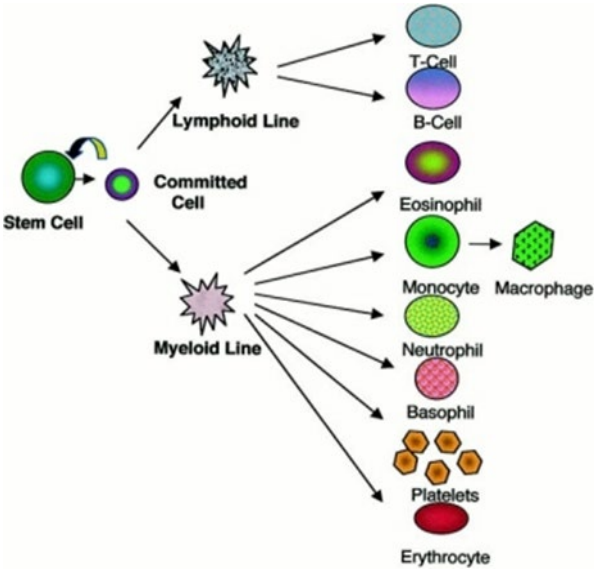

Figure 1. Difference between Myeloid Cells and Lymphoid Cells (Crans & Sakamoto, 2001).

Classification

As early as the 1970s, AML was initially classified into subtypes from M0 to M7 by a group of French, American and British (FAB) leukemia experts, and these subtypes were mainly determined by the type of cell from which the leukemia originates, alongside the maturity of the cells. M0 cells have the largest nucleus with minimal observed cytoplasm, marking stemness, while M7 have the most cytoplasm:nucleus ratio, marking high differentiation. In the following decades the World Health Organization (WHO) has set a new system that classifies AML into 6 groups which can be seen from the chart below (Hwang, 2020 & Ramaiah et al., 2013).

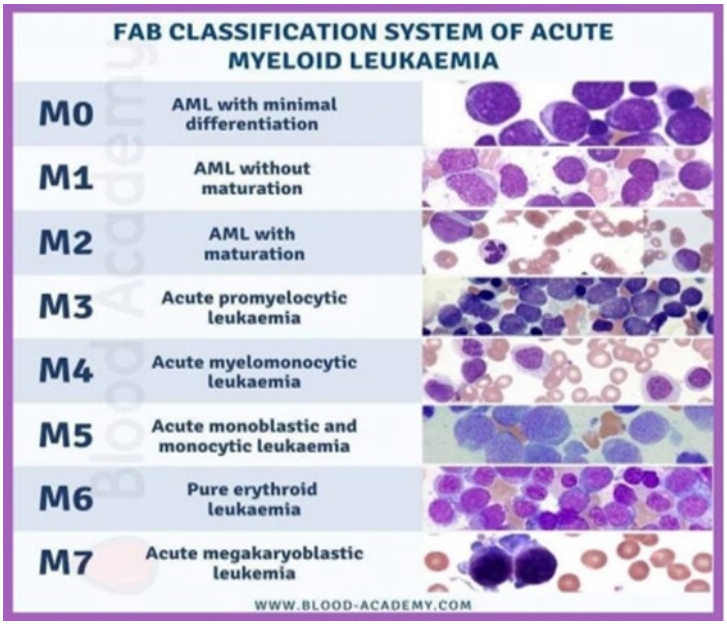

Figure 2. FAB classification of AML (*Acute Myeloid Leukemia - Ask Hematologist | Understand Hematology*, 2016).

Cause and Pathogenesis

Under normal homeostatic conditions, cellular differentiation and division are highly regulated. The development of mature white blood cells and myeloid cells is tightly controlled. A small proportion of the cellular population include hematopoietic stem cells and progenitor cells (HSPCs) that are capable of self-renewal and participate in cellular turnover. Recurrent Mutations in genes contribute to DNA methylation and myeloid transcription factors controlling hematopoietic differentiation are mainly observed in AML. The former mutation would cause an abnormal DNA methylation environment in cells that would misregulate gene expression. The lattermutation would result in a change of some transcription factors that are essential for healthy myeloid differentiation in terms of their expression and activity. These two major genetic events are usually sequential, with a driver mutation occuring first followed by supporting mutations accelerating the disease later on, leading to abnormal hematopoietic differentiation and blood cell proliferation and causing leukemia eventually (Steffen et al., 2005 & The Cancer Genome Atlas Research Network, 2013).

In terms of the genes involved, the genes that are responsible for FMS-like tyrosine kinase 3 (FLT3) have been observed to participate in the signal transduction change

In 60 to 92% of the AML instances, FLT3 gene is strongly expressed and its mutation is the most common genetic abnormality in individuals with this disease (Kiyoi et al. & Gilliland & Griffin). The gene that is responsible for coding receptor tyrosine kinase called FLT3 is located on 13q12 and is involved in hematopoietic cell proliferation and differentiation (Kiyoi et al., 2019). FLT3 mutation can be further divided into 2 subtypes: internal tandem duplication, a kind of structural variation in human genome, at the juxtamembrane domain (FLT3- ITD) and mutations in the tyrosine kinase domain (FLT3-TKD) (Hasserjian & Shumilov et al.). The expression of FLT3 is limited to early progenitors in normal people's bone marrow (Kiyoi et al., 2019). Combined with the ligand of FLT3 (FL), a growth factor secreted by some cells in bone marrow, some of the tyrosine residues on FLT3 are trans-phosphorylated. After this, multiple intracellular signaling pathways are induced by activated FLT3, which promotes the survival, proliferation, and differentiation of hematopoietic cells (Gilliland and Griffin, 2002).

However, in an AML patient's body, FL can be dangerous.The proliferation and survival of leukemia blasts are improved by FLT3 activated by FL. In addition to stimulating the proliferation of myeloid and monocytic leukemia cell lines and primary AML cells that express FLT3, FL also works with other growth factors to promote the proliferation of primary AML cells. Moreover, in serum-free circumstances, FL significantly reduces apoptosis, the death of cells, and increases survival in both primary AML cells and myeloid cell lines. Furthermore, stem cells deficient in FLT3 have a decreased capacity to reconstitute T cells and myeloid cells (Fedorov et al., 2023).

In addition to FLT3 mutated AML, nucleophosmin (NPM1) mutation is also a dominant factor, which is thought to be present in 25% to 35% of adult AML cases. Among these cases, 75% to 80% of them have an insertion in exon 12 (classic type A mutation), and it's the most common NPM1 mutation documented. This mutation causes an additional nuclear export signal (NES) in the C-terminus, which results in abnormal cytoplasmic localization (Yao et al., 2023 & Brunangelo Falini, 2023).The NPM1 gene in normal human beings is located on chromosome 5q35 and is responsible for a multifunctional chaperon encoding and relates to genome stability, chromatin remodeling, mRNA transport, and apoptosis. Several studies have shown that down-regulating NPM1 makes cells more sensitive to apoptosis, whereas higher amounts of the protein shield cells against apoptosis in a range of cell-based models (Box et al., 2016).

Symptoms

The clinical symptoms of the majority of AML cases include a build up of immature poorly differentiated, or abnormal myeloid cells in the patients' bone marrow or peripheral blood, but not often in other organs. Leukocytosis, an increasing or high count of leukocytes or white blood cells in the body, the indications of bone marrow failure such as anemia, an insufficient red blood cell count to carry oxygen, and thrombocytopenia, a decrease of platelets cell count, together are present in most of the AML patients. As a result, they would commonly report fatigue, weight loss, and anorexia. Infections and bleeding frequently caused by thrombocytopenia can result in mortality if treatment is not received within months of diagnosis (*Leukemia - Acute Myeloid - AML - Latest Research*, 2022).

Diagnosis

Several methods can be used in order to confirm AML, primarily blood and bone marrow test or lumbar puncture. Cells in their peripheral blood and spinal fluid, will be taken out and sent to the for the test (*Acute Myelogenous Leukemia - Diagnosis and Treatment - Mayo Clinic*, 2022). The medical laboratory scientists would perform complete blood cell count, blood smear (a blood sample spread out on a glass slide and stained with a unique dye), and some routine cell exams by microscope, which includes looking at the size, shape and other characteristics of cells from patients' samples which can be seen from figure 3 below (*Blood Smear*, n.d.). Usually, a composition of about 20% blasts, an immature white blood cell (WBC), in the blood or bone marrow would indicate AML compared to a 5% rate in a healthy body. Even in cases when the blast percentage falls below 20%, AML can still be identified if a chromosomal alteration unique to a particular form of the disease is discovered in the blasts. In order to determine the subtype, cytochemistry, flow cytometry, and chromosome tests would be used (*Tests for Acute Myeloid Leukemia (AML)*, n.d.).

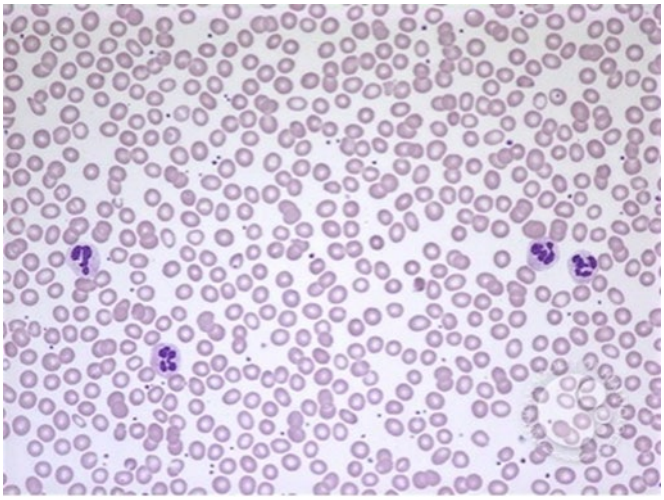

Figure 3. Image of normal blood smear (*Normal Peripheral Blood Smear*, 2008).

Treatments

In general, physicians can use various treatments on patients for AML in two phases: remission induction therapy and consolidation therapy. Killing most of the leukemia cells in patients' blood and bone marrow is the

main aim in the initial stage of remission induction therapy. By contrast,at the consolidation therapy phase, which is also known as maintenance therapy or post-remission therapy, any remaining leukemia cells will be eradicated.

Chemotherapy, radiation therapy and targeted therapy, which uses targeted drugs, are most commonly used clinically. In chemotherapy, "7+3" regimens are always used, which includes continuously infusing cytarabine for 7 days (100mg/m2 per day) and daunorubicin for 3 days (45mg/m2 per day) (Tefferi & Letendre, 2012). As AML happened initially in the bone marrow, bone marrow transplant also works as a treatment (*Acute Myeloid Leukemia Treatment,* 2023).

In terms of the FLT3 mutation AML, since it is a high incidence cause of AML, many inhibitors of it have been proved to work as a treatment to AML. Depending on the mechanism of action of these inhibitors, they can be categorized into Type I and II; depending on their specificity, the limited range of chemicals that the inhibitor can function or be effective with, the inhibitors can be categorized into first- and second- generation. While both FLT3-ITD and FLT3-TKD are both susceptible to Type I inhibitors such as lestaurtinib, midostaurin, crenolanib and gilteritinib, which bind to both active and inactive receptor conformations, only ITD mutations can be successfully treated with Type II inhibitors, sorafenib and quizartinib for instance, who interact with the hydrophobic area that is exclusively accessible in the inactive state next to the ATP-binding site. Compared to first-generation inhibitors like midostaurin and sorafenib, the second-generation inhibitors represented by gilteritinib, quizartinib, and crenolanib have a greater effectiveness, longer half-lives, and improved specificity. Only midostaurin and gilteritinib have got the approval from the Food and Drug Association (FDA) to treat patients with FLT3 mutation AML (Dong et al., 2020).

Conclusion

Although AML has been discovered for more than 50 years, the pathogenesis of it has not been fully understood, so researchers keep working on AML biology in order to give better treatment. Various drugs have been used on cell lines and patient samples to test for their effectiveness (*Leukemia - Acute Myeloid - AML - Latest Research* & Skopek et al., 2022).

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