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A brief look at genetic and environmental risk factors of leukemia and its preventions and treatment

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Abstract. Leukemia, the most diagnosed cancer in children and adolescents, is the malignancy of white blood cells that begins in hematopoietic stem cells in the bone marrow and brings severe impact to the lymphatic system in which ALL, AML, CML, and CLL are diagnosed most commonly. Risk factors of leukemia is highly evaluated in recent studies and treatments for leukemia have shown great advance too. However, the knowledge to public about leukemia, its risk factors, and its treatments is still limited. This article aims to introduce different types of leukemia including ALL, AML, CLL, CML, analyze genetic and environmental risk factors of leukemia, and describe some of its treatments such as chemotherapy, radiation therapy, and bone marrow transplantation in detail. To avoid and address mechanisms of resistance that arise during leukemia therapy, it is crucial to adopt a comprehensive strategy to the combination of medicine, to manage risk factors to the public, to make lifestyle interventions, to develop more advanced therapies, and to gain a deeper understanding of mechanism of resistance.

Keywords: Leukemia, inhibitor, treatments.

1. Introduction

Cancer, a disease caused by an uncontrolled division of abnormal cells in the body is widely known to be forming a malignant tumor in organs. However, there is a type of cancer that differentiates from all other cancers by not forming a tumor, and that is leukemia. Leukemia, the most diagnosed cancer in children and adolescents, is the malignancy of white blood cells that begins in hematopoietic stem cells in the bone marrow and brings severe impact to the lymphatic system.

In people with leukemia, their bone marrow produces immature white blood cells that do not go through apoptosis, carry out normal functions, and therefore crowd out healthy blood cells one's body needs. Genetic alterations and mutations in bone marrow cells' DNA sequence are the cause of leukemia. Although scientists have yet to determine what causes the genetic change, research has shown a variable trend of leukemia by age, sex, and country.

Leukemia can be divided into four basic categories, each with distinct characteristics: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). Only immature blood cells are generated in acute leukemia; these cells are unable to carry out their intended function, in contrast to the few mature blood cells that are created in chronic leukemia.

AML's full-term is acute myeloid leukemia. The term myeloid emphasizes that leukemia develops from the myeloid cells-myeloid cells mature into erythrocytes (red blood cells), granulocytes

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(neutrophils, eosinophils, and basophils), and platelets, which all play a crucial role in the human body. Therefore, as there is an uncontrolled growth of immature myeloid cells which all have their important mechanisms in the body, AML is the deadliest leukemia having only a survival rate of 28% with the greatest estimated death cases out of all leukemia death cases with 11,310 deaths out of 23,710 cases in the US in 2023 [1]; this may indicate that treatments are harder for AML than any other leukemias. Additionally, however, AML is also the most commonly diagnosed leukemia with 20,380 cases estimated to be diagnosed in the US in 2023 out of a total 59610 leukemia cases [1].

ALL can be broken down into several parts to explain. The word "acute" demonstrates the disease's ability to rapidly produce lymphocytes that are immature rather than mature. The word "lymphocytic" emphasizes that ALL causes a malignancy to white blood cells, specifically B or T lymphoblasts. This process of uncontrolled growth and creation of lymphocytes takes place in the bone marrow, where most of the human body's blood is made. ALL accounts for the most diagnosed cancer in children and adolescents. In 2023, an estimated 15190 youngsters under the age of 19 will be diagnosed with cancer, Among all types of cancer, the most common one among children and adults is leukemia occupying 22.7% of all cancer minorities [1]. Unlike AML, with current treatment regimens, about 80-90% of people diagnosed with ALL will reach a complete remission [2]; therefore, it is not as fatal and more curable compared to AML.

Various types of treatments have been used to counter these types of leukemia. This include chemotherapy, targeted therapy, immunotherapy, and so on. Although leukemia is a curable and preventable disease, in modern days, the knowledge of preventing and treating leukemias has not yet been popularized. This article will explore in the causes of leukemia, therapies of leukemia, and how should the world.

2. Gene mutation

When mutations happen in the genes that are involved in cell division, cells will divide by mitosis uncontrollably. Proto-oncogenes will mutate into oncogenes, and tumor-suppressor genes will be "turned off". The result of the former two situations results in bone marrow cells growing and divide uncontrollably lead to leukemia. Over an investigation, 83.3% of the 126 patients examined had one or more mutations found in them, with the highest prevalence of FLT3-ITD and NRAS specific mutations [3]. This shows that leukemia is highly affected by genetics and genes.

2.1. FLT3 gene mutation

FMS-like tyrosine kinase 3 (FLT3) plays a crucial role in development of AML. FLT3 gene provides genetic information for making the FLT3 receptor polypeptide found on blood cells' surface. These FLT3 receptors assist in the growth and maturation of white blood cells as it signals important pathways that promote cell division, survival, and differentiation. However, if the FLT3 gene is mutated, aberrant and dysregulating signaling pathways will be induced, which will cause unregulated cell division, impaired differentiation, and a higher chance of leukemia cells surviving in the bone marrow.

Approximately one-third of patients with newly diagnosed AML have mutations in the FLT3 gene; internal tandem duplications (ITD) and point mutations in the tyrosine kinase domain (TKD) are the two most prevalent forms of FLT3 alterations with 20%-25% of ITD and 5-10% of TKD [4]. This mutated gene will induce an abnormal signaling which will promote the growth of leukemia cells and inhibit the process of normal maturation of blood cells. This will result in accumulation of immature and dysfunctional blood cells in the bone marrow, which in turn leads to leukemia.

2.2. RAS gene mutation

The RAS gene family, including HRAS, KRAS, NRAS, plays significant role in various types of leukemia. 10% to 25% of patients diagnosed with leukemia had mutations in either the NRAS or KRAS gene [5]. Similarly to FL3 gene mutation, these mutations are associated with older age, distinct cytogenetic abnormalities, and a poorer prognosis and lead to constitutive activation of the RAS signaling pathway that regulates cell growth, survival, and differentiation. For instance, one common

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method of resistance to FLT3 and IDH inhibitors is through RAS mutations [6], meaning that the genes mutate again causing the original inhibitor to malfunction as the active site of the protein changes shape. Therefore, this presence of RAS gene mutations in leukemia impact disease prognosis and treatment strategies as it may influence the choice of targeted therapies.

2.3. IDH mutation

Isocitrate dehydrogenase (IDH) is the enzyme involved in cellular metabolism. IDH1 or IDH2 mutations were present in 5% to 15% and 10% to 15% of patients with newly diagnosed AML, respectively. [5]. With these mutations, instead of converting chemical isocitrate to another chemical in the citric acid cycle, an oncometabolite called 2-hydroxyglutarate (2-HG) is produced. As it accumulates, normal cellular processes are disrupted and lead to leukemic transformations. Furthermore, as the concentration of 2-HG is elevated, epigenetic regulation of hematopoietic differentiation will be interfered [6], contributing to abnormal gene expression patterns and impair cellular differentiation and development. At last, leading to leukemia.

3. Mutation specific therapies

3.1. DH1 and IDH2 Inhibitor

IDH 2 inhibitors, such enasidenib, have the ability to restore aberrant epigenetic alterations and reduce the original serum total 2-HG level to less than 10% [7]. When 2-HG level is reduced, normal cellular processes and epigenetic regulation of hematopoietic differentiation will be less disrupted and affected, decreasing leukemic transformation frequency

In older patients who are 75 years old or older and are not eligible for intensive therapy, a single-agent IDH1 inhibitor ivosidenib, targeted for IDH1-mutated AML, was approved by the FDA in May 2019. According to trial results, 258 elderly patients with high rates of secondary AML who had been molecularly characterized as having a poor prognosis and receiving ivosidenib demonstrated excellent tolerance, caused lasting remissions, and achieved transfusion independence [8], indicating IDH1 inhibitors are friendly to and not as intensive as chemotherapy. This indicates that IDH1 inhibitors such as ivosidenib can be used to treat a wider range of people, especially the ones that cannot withstand the side effects of chemotherapy, radiated therapy, or transplantation of the bone marrow.

Overall, when patients are given IDH1 and IDH2 inhibitors, almost all had lower 2-HG concentrations [6]. In addition, as a result of IDH gene mutations, such as transitioning from IDH1 to IDH2 mutations (or vice versa), secondary resistance to the inhibitor is also observed in these treatments [9]. This would decrease the efficiacy of these inhibitors, resulting in ineffective treatment of leukemia. Development of resistance to inhibitors due to mutations will be a severe obstacle in managing leukemia.

3.2. RAS Pathway Inhibitor

Considering that FL3 and IDH inhibitor resistance is frequently caused by RAS mutations, patients with baseline RAS mutations may receive FLT3 or IDH inhibitors in addition to RAS pathway-targeting agents to prevent primary resistance, or they may receive FLT3, IDH, or BCL2 inhibitors in order to treat individuals who, while receiving treatment, acquire a newly discovered RAS mutation [6]. This is to maximize the effectiveness of treatment for leukemia by preventing and cooperating with the resistance to inhibitors induced by RAS mutations.

3.3. FLT3 Inhibitors

Numerous FLT3 inhibitors have entered clinical studies throughout the previous 15 years [4]. The mechanism of action of the FLT3 inhibitors is by competitively inhibiting the FLT3 receptor's ATP-binding sites. FLT3 inhibitors specifically target and inhibit the mutated FLT3 receptors in leukemia cells by blocking signaling pathways activated by FLT3 mutations. Therefore, it will reduce the amount of leukemia cells presented.

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For instance, randomized phase III studies of FLT3 inhibitors such as midostaurin have demonstrated a significant improvement in overall survival with FLT3 inhibitors as compared to conventional therapy. Midostaurin displayed significant improvement with a 4-year overall survival rate of 51.4% in treating all types of FLT3 mutation [6], which suggests that all FLT3 mutated leukemia patients can be treated with it along with a decent efficiacy.

Nonetheless, FLT3 inhibitor treatment failure is still frequently encountered. There are several known resistance pathways to FLT3 inhibitors. The efficacy of the FLT3 inhibitor is often reduced by resistance caused by secondary mutations [6]. For instance, it gains resistance to FLT3 inhibitors by RAS gene mutation, causing the inhibitors to function less effectively.

By combining standard chemotherapy regimens for treatment of FLT3-mutated leukemia, improving the response rates and increasing the rates of complete remission with a greater understanding of resistance mechanisms, numerous clinical trials assessing logically constructed combination treatments involving FLT3 inhibitors have been started [6] to improve the effectiveness of the inhibitor.

4. Environmental factors and Preventions for leukemia

Research has shown a variable trend of leukemisa by age, sex, and country, in which the highest incidence and mortality rates of leukemia came from more developed countries with these aspects of higher HDI, GDP per capita, prevalence of smoking, inactivity, overweight, obesity, and hypercholesterolemia populations especially in men and younger children [10], indicating that leukemia is closely connected with the nations' HDI and GDP per capita.

Several common, avoidable lifestyle and metabolic risk factors such as smoking, physical inactivity, overweight, obesity, and hypercholesterolemia have been identified to be connected with leukemia incidence and mortality nationally [10]. For instance, according to a meta-analysis of 23 studies, smokers had a 40% and 25% higher chance of having AML compared to non-smokers [11].

An additional study comparing high and low levels of leisure-time physical activity investigated in 1.44 million adult participants [12]. Leisure-time physical activity was found to be associated with lower risks of getting all types of leukemia [12]. A link between hypercholesterolemia and CLL is also achieved by another study [13]. These examples, therefore, support the claim that lifestyles affect incidence rate of leukemia.

Therefore, making changes to intensive lifestyles—such as quitting smoking, getting more exercise, managing weight, and properly regulating hypercholesterolemia — may aid in reducing the risk of leukemia, especially in younger and male individuals.

5. Bone Marrow Transplantation Treatment

Bone marrow transplantation removes sick cells as leukemia is characterized by the uncontrolled proliferation and buildup of aberrant, immature blood cells in the bone marrow and circulation. Blood cell production can return to normal, and the equilibrium between blood cell production and function can be reestablished. By replacing the diseased bone marrow with healthy stem cells, leukemia cells can be eradicated and achieve full remission particularly in ALL and AML. Graft-versus-leukemia effect may be reached, indicating the transplanted immune cells from the donor can recognize and attack remaining leukemia cells in the recipient's body, which reduces the risk of disease relapse.

However, acute or chronic complications may happen after the transplantation. Acute complications include mucositis, sinusoidal obstruction syndrome, bacterial infections with gram-positive and gram-negative organisms, Herpesviridae infections, fungal infections with Candida and Aspergillus, and myelosuppression with neutropenia, anemia, or thrombocytopenia that manifest in the first ninety days [14]. Reactivation of the varicella-zoster virus, infection with encapsulated microorganisms, and persistent graft-versus-host-disease are examples of chronic consequences after transplantation.

6. Radiation Therapy

Radiation therapy is a not major treatment for people with leukemia, but it is used to kill leukemia cells that have spread outside of the bone marrow and blood. Moreoever, it is a crucial part of treatment before

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stem cell or bone marrow transplantation and can be used to relief pain in bones caused by invasion of leukemia if chemotherapy hasn't helped [15], thereby having a close connection to bone marrow transplant and chemotherapy which are treatments to leukemia.

However, it is not a main treatment method for leukemia as leukemia does not form well-defined tumors that can be easily targeted with high-energy radiation beams. Other healthy organs are unavoidably exposed to ionizing radiation during radiation therapy, which raises the possibility of acquiring additional genetic abnormalities that cause different kinds of cancer. As healthy cells are also damaged during radiation therapy, side effects such as fatigue, hair loss, memory or concentration problems, nausea and vomiting, skin changes, headache, organ failure are commonly recognized.

7. Conclusion

In conclusion, there are multiple environmental and genetic factors that contribute to leukemia of different types. Leukemia is a disease that arises when genes that are essential for regulating blood cell division, proliferation, and programmed cell death (apoptosis) mutate. Meanwhile, the risk of leukemia is also affected by ones' lifestyle, gender, age, health status, and country they are in.

Corresponding treatments and solutions can therefore be provided and given to enhance patients' status of health by countering leukemia aiming to reach a full remission or to improve patients' quality of life. However, early detection, care, surveillance for elderly and young patients also need to be emphasized. When treatments are given, patients should be closely monitored to check if resistance has developed to the treatment. If any mechanisms of resistance are detected, a different combination of treatment plans should be introduced; this can also lower the economic burden for the cost of treatment as they are not paying for a drug that is not working at its best.

Patients should be informed of the advantages and disadvantages of different treatment combinations before treatment begins. Therefore, in the process of treating leukemia, not only the efficacy is an important factor to be considered, but the financial status of the patient cannot be ignored. With that in mind, public's awareness of risks factors, such as smoking, being physically inactive, of developing leukemia should also be raised to prevent leukemia. Not only this would decrease the probability of getting leukemia, but also individuals' health can improve greatly and other acute or chronic diseases can be avoided.

This paper investigated different treatments for leukemia and risk factors that lead to leukemia. As this paper only focused on a few main gene mutations, a more comprehensive gene mutation analysis could be done. However, mechanisms of resistance will still be an obstacle to surpass and an area for all scientists to study. Further investigation is to investigate the best combination of treatments to treat leukemia in patients of different age groups. Also to develop drugs that is friendly to ones that cannot withstand intensive chemotherapy, bone marrow transplantation, or radiation therapy due to various health factors. More clinical trials should be done to evaluate and improve the response rates increase rate of complete remission and build on deeper understanding of mechanisms of resistance.

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