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Review Article

Pediatric Acute Myeloid Leukemia and Target Therapies

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Abstract

Acute myeloid leukemia is a type of cancer that occurs when cells of myeloid origin in the bone marrow multiply uncontrollably, differentiate, and fail to perform their function. Acute myeloid leukemia is one of the rare cancers in children between the ages of 0 and 18. Pediatric acute myeloid leukemia is associated with various risk factors depending on genetic factors, environmental factors, geographical distribution, and the patient's medical history. The epidemiology and incidence of pediatric AML are shaped depending on genetic factors, age, gender, environmental factors, geographical distribution, and ethnicity. Pediatric AML is usually associated with a poor prognosis, and the symptoms appear in a short time. Well identifying the symptoms is crucial for diagnosis. There are various diagnostic methods available for pediatric acute myeloid leukemia. Pediatric AML is not examined in the standard staging system, but it consists of treatment steps that follow the duration of the treatment unit. Recently, targeted therapies have started to apply in treating pediatric AML instead of or in addition to classical treatment methods.

Keywords: Pediatric cancers; Acute myeloid leukemia; Target therapy; Inhibitor; Genetic factors

Introduction

Acute myeloid leukemia is a type of cancer that occurs when cells of myeloid origin in the bone marrow multiply uncontrollably, differentiate, and fail to perform their function. Acute myeloid leukemia is a disease with high incidence, mortality, and morbidity [1]. AML can occur in all age groups, but it is more common in childhood. Acute myeloid leukemia is one of the rare cancers in children between the ages of 0 and 18. The World Health Organization has identified more than pediatric acute myeloid leukemia in 25 subgroups [2]. Pediatric AML is associated with various risk factors, including genetic predispositions, environmental exposures, geographical distribution, and the patient's medical history [11]. Early diagnosis is crucial in pediatric AML, and a thorough understanding of risk factors is essential for diagnosis, treatment, and post-treatment monitoring.

The epidemiology and incidence of pediatric AML are related by genetic factors, age, sex, environmental factors, geographical distribution, and ethnic background. Pediatric AML is generally associated with a poor prognosis, and the symptoms typically manifest quickly. A clear understanding of these symptoms is vital for diagnosis. Many diagnostic methods are available for pediatric AML, including physical examination, genetic and molecular testing, flow cytometry, and HLA typing [18-23] Pediatric AML does not follow a standard staging system, and its treatment process involves sequential therapeutic steps. The treatment begins with induction therapy and consolidation therapy [25,26]. Supportive treatments may be applied to maintain the patient's overall health [28]. If necessary, a treatment plan is planned and implemented for potential relapse [29]. Post-treatment monitoring is crucial in pediatric AML, involving regular check-ups and a remission care process. Recently, in addition to or instead of conventional treatment methods, targeted therapies have been introduced in the treatment of pediatric AML [31].

Rısk Factors

Childhood acute myeloid leukemia is associated with various risk factors. These risk factors are mainly genetic risk factors, environmental risk factors, and other factors. The patient's general health status and the treatments he has previously received may affect the development of AML.

Genetic Risk Factors

Genetic mutations and inherited diseases are genetic risk factors for AML. Mutations occurring in the RUNX1- RUNX1T1 (AML-ETO) fusion genes are among the genetic risk factors for the development of AML [3]. Mutations in the RUNX1-RUNX1T1 (AML-ETO) fusion genes have been detected in

5-10% of childhood AML cases. Mutations in the FLT3 gene occur in 15-20% of childhood acute myeloid leukemia [4]. The RUNX1- RUNX1T1 (AML- ETO) genes are associated with a good prognosis, while the FLT3 genes are associated with a poor prognosis [5]. Mutations in the isocitrate dehydrogenase genes (IDH1 and IDH2) occur in about 20% of AML patients [6]. Another gene expression associated with AML is the Gata1 and Gata2 genes, the activity of these two genes activity should be taken into account when investigating risk factors [7]. Down Syndrome children are in a high-risk group in terms of the risk of developing acute myeloid leukemia [8]. Compared to normal children, this risk is 10-20 times higher. Inherited diseases such as Noonan Syndrome, Fanconi anemia, and Shwachman-Diamond Syndrome are among the other inherited diseases that affect childhood acute myeloid leukemia [9,10].

Environmental Factors

There is a risk of acute myeloid leukemia in children exposed to high doses of radiation from the environment or medical radiation. The use of drugs, stimulants, or alcohol during pregnancy increases the risk of AML in the fetus. Children who have previously received chemotherapy with drugs included in the group of alkylation agents, epipodophylotoxins, and Topoisomerase II inhibitors have a high risk of developing AML later [11]. Identifying risk factors increases the chances of early diagnosis for children in the high-risk group. Early diagnosis is crucial for monitoring the disease, the treatment process, and post-treatment follow-up.

Epidemiology and Incidence

Every year, acute myeloid leukemia accounts for about 20% of cancer cases in children. Among the factors affecting the epidemiology and incidence of AML are genetic factors, age, gender, environmental factors, geographical distribution, and ethnic origin [12]. As AML can occur in any age group, it is usually seen in infants and adolescents between 0 and 14 years of age. According to recent studies, AML is more common in boys than girls. The relationship between geographical distribution and ethnicity with AML is as follows: the incidence of AML is higher in the yellow race of Asian origin compared to the white and black race [13]. Children exposed to chemical and physical mutagens, such as high radiation and chemotherapy, are highly likely to develop AML. Active nuclear events (attacks or explosions) are an example of high radiation exposure. After the Chornobyl explosion, the risk of developing cancer such as AML increased significantly in children in Ukraine, Russia, and the surrounding region. The risk of developing acute lymphoblastic leukemia after the Chornobyl explosion is four times higher than acute myeloid leukemia, while newborns are more likely to develop AML [14].

Symptoms and Diagnosis

AML progresses rapidly in children, and symptoms typically appear quickly. In children aged 0-18, symptoms of AML include the following:

The most common symptom of acute myeloid leukemia is anemia [15]. Insufficient erythrocyte production in the bone marrow causes insufficient oxygen transport in the blood. These lead to symptoms associated with anemia, such as chronic fatigue, weakness, and pallid skin. Notably, pallor and discoloration may occur on the face, lips, and nails. Anemia can also cause respiratory difficulties. Another common symptom of AML is frequent and recurrent infections [16]. Due to decreased white blood cell (leukocyte) levels, the immune system weakens, making the body more susceptible to infections. Noticeable swelling and enlargement of the lymph nodes may also occur. A decrease in platelet levels in the blood leads to reduced blood clotting, resulting in bruising in various parts of the body, prolonged bleeding from minor injuries, nosebleeds, and gum bleeding frequently seen in children. Bone and joint pain may seen due to the pressure exerted by the tumor developing in the bone marrow. Erythrocyte production also occurs in the liver and spleen except bone marrow. Due to insufficient erythrocyte production in the bone marrow, there is swelling in the liver and spleen. In children, symptoms such as loss of appetite, nausea, vomiting, and weight loss can occur due to both the cancer itself and the treatments received [17]. Additionally, night fevers and sweating are other symptoms of AML. Although rare, AML may involve the central nervous system, leading to neurological symptoms such as headaches, nausea, vomiting, vision disturbances, and other neurological deficits.

Pediatric acute myeloid leukemia has several diagnosis methods:

Physical Examination and Medical History

A general health assessment of the child is conducted, and the family's leukemia history is considered to identify any risk factors the child may have encountered. During the physical examination, checks are made for enlargement of the liver and spleen, swelling of the lymph nodes, and the presence of pallor or bruising on the skin [18].

Complete Blood Count (CBC)

Complete blood count is one of the most critical tests in diagnosing acute myeloid leukemia. This test examines the production, number, and function of blood cells. The number of erythrocytes and hemoglobin levels of abnormal leukocytes and total leukocyte count are evaluated. The test also checks for thrombocytopenia. A peripheral blood smear analyzes the structure of blast cells. Other blood tests are conducted alongside the CBC. These tests evaluate tumor markers and blood chemistry, including liver and kidney function, uric acid levels, and lactate dehydrogenase enzyme activity [19].

Bone Marrow Biopsy

Another diagnostic method is a bone marrow biopsy, where the structure of cancer cells in a bone marrow sample is examined, and further studies are conducted using molecular techniques. For a diagnosis of acute myeloid leukemia, the bone marrow sample must contain more than 20% blast cells. Bone marrow biopsies are generally straightforward procedures, and test results are typically available within 24 hours to a few days [20].

Genetic and Molecular Testing

Cytogenetic Analysis: This examines chromosomal anomalies. Common chromosomal abnormalities in AML include t(8;21), inv(16), and t(15;17) [21].

Fluorescence In Situ Hybridization (FISH): FISH can detect genetic alterations and translocations that may lead to AML [22].

Polymerase Chain Reaction (PCR): A molecular technique can be beneficial to detect gene mutations, such as FLT3 mutations.

Flow Cytometry

The structures of cells in bone marrow and blood samples are analyzed, and specific marker proteins are detected. Flow cytometry-based immunophenotyping to determine the subtypes of AML [24].

HLA Typing

HLA stands for human leukocyte antigen. If a stem cell transplant is considered for AML treatment, HLA typing is executed to determine compatibility between the donor and recipient. Compatible HLA types reduce the risk of rejection and increase the success of the stem cell transplant [25].

Prognosis

Childhood Acute Myeloid Leukemia (AML), unlike adult acute myeloid leukemia, does not undergo a specific staging system. The course of the disease is related to the patient's general health condition and the treatments applied. The childhood AML treatment process consists of five steps:

Induction therapy

Induction therapy aims to reduce cancer cells in the bone marrow to less than 5% and ensure the reproduction of normal blood cells. For this purpose, a high dose of chemotherapy applies to the patient for 4-6 weeks. Cancerous cells in the bone marrow are cleared for transition to the remission period [26].

Consolidation Therapy

After remission, it tries to prevent the patient from relapsing to destroy the remaining leukemia cells in the bone marrow. In this process, 2-4 additional chemotherapy courses are applied, in which high doses or different chemotherapy drugs are used. Each cycle can last from one to two weeks. Chemotherapy can supplement with targeted drugs [27].

Supportive Treatment

The purpose of supportive therapy is to protect the patient's overall health condition by reducing chemotherapy-related complications and side effects [28].

Antibiotics usage, blood transfusions, growth factors, antifungal drugs, and cancer vaccines can be applied to prevent and treat possible infections.

Relapse

In high-risk cases of AML, high doses of chemotherapy and radiation therapy are used to ensure the re-formation of healthy bone marrow and blood cells and destroy leukemia. After chemotherapy and radiation therapy, appropriate stem cell transplantation is performed. Stem cell transplantation is performed with stem cells that will form a healthy marrow, either taken from a patient (autologous) or a donor (allogeneic) [29]. While the process of preparing for treatment may take several weeks, the transplant and recovery process may take several months. In addition to the classical treatment methods, the process is supported with targeted therapies aimed at achieving remission again [30].

Remission Care

Remission Care is the follow-up period after treatment. Regular checkups, blood tests, and bone marrow biopsies are to prevent recurrence. Follow-up after treatment is essential in maintaining the patient's overall health and quality of life [31].

Current Treatment Approaches

Targeted Treatments in pediatric acute myeloid leukemia, well-known treatment methods are multi-stage and complex. Possible side effects of chemotherapy are usually severe and can put a strain on both the physical health and mental health of the patient. Stem cell transplantation is another current treatment approach for patients at high risk. Recently, the focus has been on personalized and targeted treatment research, unlike chemotherapy or stem cell transplantation [32].

As molecular analyses have become more widespread and pervious, targeted therapies have started to come to the fore. Cancer-related gene sequences, proteins, receptors, or hormones are recognized, and new drugs with anti-cancer properties are improved in this way in targeted therapy. Targeted therapies offer the possibility of personalized treatment using inhibitors for gene mutations such as FLT3 and BCL2. Smart drugs developed with targeted therapies support immunotherapy. In this way, it is also a new treatment hope in the case of aggressive disease or relapse [33].

Target Therapıes

FLT3 Inhibitors

The FLT3 (FMS-like tyrosine kinase-3) signaling pathway plays a crucial role in hematopoiesis and is expressed in CD34+ hematopoietic stem/progenitor cells, but its expression diminishes during cellular differentiation. [34,35] Activation of the FLT3 receptor occurs through stimulation by the FLT3 ligand, leading to receptor dimerization, the tyrosine kinase domain, autophosphorylation, and subsequent binding of SH2 domain-containing proteins. [36,37,38] Upon activation, FLT3 signals via critical oncogenic pathways. Mutations in the FLT3 gene result in its activation and the transmission of growth signals and are associated with a poor prognosis in approximately 25% of children and adults with acute myeloid leukemia (AML) [39].

IDH1 and IDH2 Inhibitors

Mutations in the isocitrate dehydrogenase genes (IDH1 and IDH2) occur in about 20% of AML patients [40]. This mutation can lead to the production of R-2-hydroxyglutaric acid (R-2-HG). R-2-HG is a carcinogenic metabolite leading to DNA hypermethylation and hematopoietic stem cell differentiation inhibition [41]. IDH inhibitors may benefit AML patients with IDH mutations by inhibiting isocitrate dehydrogenase and show good clinical efficacy in AML patients with IDH mutations [42]. Ivosidenib and enasidenib, which are mutated IDH1 and IDH2 inhibitors, have recently been approved by the FDA for relapsed/refractory AML. Ivosidenib is approved for newly diagnosed AML patients who are not eligible for standard chemotherapy [43,44].

BCL-2 Inhibitors

The B-cell lymphoma-2 (BCL-2) protein family, which plays a critical role in the intrinsic apoptosis pathway, is dysregulated in numerous malignancies, including acute myeloid leukemia (AML) [45]. This dysregulation allows cells to evade apoptosis. High levels of BCL-2 expression in AML have been associated with drug resistance in cancer cells. Venetoclax is a potent and selective BCL-2 inhibitor. It binds directly to the BH3-binding groove of BCL-2, inducing mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death by displacing pro-apoptotic proteins containing the BH3 motif, such as BIM [46]. Studies have shown the efficacy of venetoclax in combination with chemotherapy in pediatric AML cases that are heavily relapsed or refractory. Such findings suggest that combination could also be effective in newly diagnosed high-risk pediatric AML patients [47].

E-selectin Inhibitors

Endothelial (E)-selection is an adhesion protein that regulates

neutrophil and monocyte trafficking by promoting leukocyte binding and stimulating the proliferation of hematopoietic stem and progenitor cells in the bone marrow. [48]. E-selectin also affects pro-survival signaling in hematologic cancers and potentially promotes chemotherapy resistance. One of the inhibitors identified in recent years is E-selectin inhibitors, which prevent the development of chemotherapy resistance in AML [49,50]. Uproleselan is an E-selectin antagonist [50,51]. It prevents E-selectin from binding to E-selectin by mimicking its carbohydrate ligand. This disrupts the adhesion of leukemic cells to the bone marrow and eliminates the microenvironment-mediated protection of AML cells. Uproleselan has shown promising safety and efficacy in early-phase trials in adults, and a phase III trial is currently underway in adults [52]. In pediatric patients, a phase I trial is intensively ongoing to investigate the safety and pharmacokinetics of uproleselan in combination with fludarabine/cytarabine chemotherapy [54].

CD33 and CD123

CD33 and CD123 molecules are usually found in subgroups of hematopoietic cells [55]. Both are over-expressed in AML blasts [56]. The therapeutic targeting of CD33 is promising in AML because about 80% of AML cases express CD33 [57]. High levels of CD33 expression in pediatric AML are associated with poor prognosis [58]. Gemtuzumab ozogamicin is a humanized anti-CD33 monoclonal antibody conjugated with kalikeamicin, a cytotoxic drug [59]. After gemtuzumab ozogamicin binds to CD33, kalikeamicin is released into the cell. This, in turn, causes DNA double-chain breaks that trigger cell death [60]. FDA approved Gemtuzumab ozogamy in June 2020 to treat pediatric patients with newly diagnosed CD33-positive AML [61]. CD123 expression in adult AML patients has been associated with higher rates of chemotherapy resistance and high-risk genetic changes [62,63]. CD123 expression has also been shown to be at high levels in leukemic stem cells [64,65]. The incidence and prognostic significance of CD123 expression in pediatric AML have not yet been elucidated [66]. Tagraxofusp is a recombinant anti-CD123 (IL-3 receptor alpha chain) antibody fused to diphtheria toxin. When bound to CD123, tagraxofusp is internalized and inhibits protein synthesis through eEF2 inhibition. Tagraxofusp is effective in blastic plasmacytoid dendritic cell neoplasm. This neoplasm, a specific type of myeloid malignancy, overexpresses CD123 [67].

Targeting of Leukemic Stem Cells

Although they give rise to blast cells with different phenotypes, the cell surface characteristics of LSCs in AML subtypes are similar. Researchers have shown that LSCs are typically CD34+, CD38−, CD71−, HLA-DR−, CD90−, CD1 1 7−, and CD123+ cells through in vitro culture experiments and transplantation into NOD/SCID mice [68,69,70,71,72,73,74]. Most of these markers are similar to normal HSCs, but there are also leukemia-specific antigens. CD34, CD38, CD71, and HLA-DR antigens are similar in LSC and HSC, while CD90, CD117, and CD123 are leukemia-specific antigens. No studies have reported an antigenic difference between LSCs derived from different AML subtypes. Targeting LSCs has become an attractive strategy because it will lead to the regression of the disease, but the heterogeneity of LSCs makes it rough to find the best potential target [75]. The best potential target should reflect a conserved characteristic of the LSC population. Signaling pathways that ensure the continuation of the self-renewal properties of LSCs are among such targets [76,77]. Inhibition of NFkB signaling and induction of oxidative stress may help eliminate LSCs [78,79]. Since they are expressed more in LSCs than HSCs, inhibition of antigens such as CD123, CLL-1, CD44, CD96, and CD47 and kinases such as c-Kit or SRC family kinases may be promising therapeutic approaches [80-88] Overexpression of BCL-2 in LSCs also makes them attractive targets.

Conclusıon

Pediatric Acute myeloid leukemia is among the rare diseases. Although it is treated with conventional methods, these methods have various limitations. In particular, the failure to destroy leukemic stem cells increases the chance of relapse. Overcoming this undesirable situation has led to the development of new treatment methods. Finding new targets and continuing their research is a promising strategy to increase the chance of disease treatment.

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