Recent Developments of Leukemia in Children

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Abstract

Childhood leukemia is one of the most common types of blood cancer in children. Despite advancements in treatment, challenges such as drug resistance and long-term side effects persist. Access to care remains a global issue. Objective: This systematic review aims to identify trends in childhood leukemia treatment, including novel therapies, challenges, and associated risk factors. Findings:Targeted therapy and immunotherapy have offered new hope in treating childhood leukemia. However, drug resistance remains a major challenge. Additionally, long-term side effects of intensive treatment, such as organ damage and increased risk of secondary cancers, need to be considered. Conclusion: Progress in treating childhood leukemia has yielded encouraging results. However, further research is still needed to overcome existing challenges. Future research should focus on developing more personalized therapies and gaining a deeper understanding of the genetic and environmental risk factors that contribute to the development of leukemia.

Keywords: Childhood Leukemia, Immunotherapy, Targeted Therapy, Drug Resistance, Side Effects, Health Disparities, Risk Factors.

Introduction

Childhood leukemia (CL) is a specific type of cancer that primarily affects children and adolescents. It is characterized by the abnormal growth and proliferation of immature white blood cells in the bone marrow. This uncontrolled growth inhibits the production of healthy blood cells, leading to a weakened immune system and various symptoms. As a cancer of the blood and bone marrow, CL has a significant impact on the lives of young patients and their

families. Globally, CL is a substantial problem, accounting for a large proportion of new cancer cases and cancer-related deaths among children aged 0–14 years. In 2014, this disease represented approximately 33% of all new cancer cases and 31% of cancer-related deaths in this age group.[1]

The incidence and mortality rates of CL exhibit significant variations worldwide, with higher rates observed in developed countries. Although CL incidence has been increasing in developed countries, mortality rates have been declining. However, in low- and middle-income countries, limited access to diagnostic facilities and treatment leads to lower survival rates for CL.[1]

Acute lymphoblastic leukemia (ALL) is the most common cancer among children, and through progressive advancements in chemotherapy, survival rates now exceed 90%.[2] Childhood acute lymphoblastic leukemia (ALL) is one of the most curable cancers in pediatric oncology, with 80-90% of children surviving into adulthood.[2] It has been known since early on that characteristics at the time of ALL presentation, namely, age and leukemia burden (white blood cell count or peripheral blast count), provide varying levels of treatment success, allowing patients to be categorized into distinct groups.[1]

Acute lymphoblastic leukemia (ALL) accounts for approximately 80% of all leukemia diagnoses among children aged 0-19 years, and acute myeloid leukemia (AML) represents ~15-20%. ALL and AML exhibit substantial differences in incidence patterns according to age, race/ethnicity, and gender.[3] Additionally, childhood ALL and AML differ from adult forms with respect to molecular features (e.g., cytogenetics), demographic characteristics (e.g., incidence by racial/ethnic group), risk factors, leukemogenic susceptibility related to specific exposures, and prognosis.[4]

The objective of this literature review is to gather, analyze, and synthesize the latest information on the causes, symptoms, diagnosis, treatment, and prognosis of childhood leukemia; to identify research areas that remain underexplored or controversial in the field of childhood leukemia; to determine factors that may predict treatment response and survival in pediatric leukemia patients; and to explore potential risk factors and prevention strategies for childhood leukemia.

Pathophysiology of Leukemia. Leukemia is characterized by the uncontrolled proliferation of immature white blood cells within the hematopoietic tissues. Although not a "tumor," leukemic cells exhibit neoplastic properties similar to those of solid cancer cells.[2]

Therefore, the pathological condition and clinical manifestations arise from the infiltration and replacement of various body tissues by non-functional leukemic cells.[2] Highly vascularized organs, such as the spleen and liver, are most severely affected.[4]

To comprehend the pathophysiology of leukemia, it is imperative to address two common misconceptions. Firstly, despite the overproduction of white blood cells, acute leukemias often present with low leukocyte counts. Secondly, these immature cells do not actively target and destroy normal blood cells or vascular structures. Cell destruction occurs secondary to infiltration and subsequent competition for metabolic resources. In all leukemic subtypes, the proliferating cells suppress the production of hematopoietic elements in the bone marrow by competing with normal cells and depriving them of essential nutrients for metabolism. [3]

The most common signs and symptoms of leukemia are a consequence of bone marrow infiltration. The three primary consequences are anemia due to decreased red blood cell production, infections due to neutropenia, and bleeding tendencies due to decreased platelet production. Leukemic cell invasion of the bone marrow can gradually weaken bones and predispose to fractures. As leukemic cells invade the periosteum, increased pressure causes severe pain. Leukemic cells may also infiltrate the testes, kidneys, prostate, ovaries, gastrointestinal tract, and lungs.[2] With increasing long-term survival rates.

Methods

A systematic literature review was conducted using electronic databases, including PubMed, ScienceDirect, and Google Scholar. Five international journals published between 2019 and 2024 were included in this review. The inclusion criteria were as follows: articles with titles and content relevant to childhood leukemia, full-text availability, and publication within the last five years. All selected articles met the inclusion criteria.

Discussion

Table 1 Summary of Article Results

Author Name	Title	Research Method	Results
Truong, T. H., Jinca, C., Mann, G., Arghirescu, S., Buechner, J., Merli, P., & Whitlock, J. A. (2021).	Allogeneic Hematopoietic Stem Cell Transplantation for Children With Acute Lymphoblastic Leukemia: Shifting	This research using a qualitative approach, participative methods	This journal provides a comprehensive overview of the changing indications for hematopoietic stem cell transplantation (HSCT) in children with leukemia acute lymphoblastic (ALL)

	Indications in the Era of Immunotherapy.		
Marcotte, E. L., Spector, L. G., Mendes- de-Almeida, D. P., & Nelson, H. H. (2021).	The prenatal origin of childhood leukemia: potential applications for epidemiology and newborn screening.	This research using a quantitative approach with an explanatory design	This journal discusses the prenatal origins of childhood leukemia, the use of newborn screening to detect leukemia translocations in healthy children. The presence of this translocation may indicate an increased risk of developing leukemia later in life. However, more research is needed to determine how best to use this information for prevention and treatment.
rabant, C., Geerinck A., Beaudart C., Tirelli, E., Geuzaine, C., &Bruyere, O. (2023).	Exposure to magnetic fields and childhood leukemia : a systematic review and meta-analysis of case control.	This research using a qualitative approach, participative methods	This journal concludes that although further research evidence is still needed, current evidence shows that high exposure to very low frequency magnetic fields can increase the risk of developing leukemia in children, especially acute lymphobatic leukemia.

Mohammadia Hafshejani, Farber, I. M & Kheiri S. (2024)	Global incidence and mortality of childhood leukemia and its relationship with the human development index	This research using a qualitative approach, quantitative methods	This journal discusses childhood leukemia rates and mortality of this disease explored the relationship between childhood leukemia and the human development index (HDI) and found a positive correlation between childhood leukemia and HDI
Moles, E., Howard, C. B., Huda, P., Karsa, M., McCalmont, H., Kimpton, K., ... & Kavallaris, M. (2023)	Delivery of PEGylated liposomal doxorubicin by bispecific antibodies improves treatment in models of high-risk childhood leukemia.	This research using a quantitative approach to the correlation method	This journal discusses the various subtypes of leukemia and the challenges in treating them. Researchers are developed a new treatment using drug-carrying nanoparticles that target leukemia cells. These nanoparticles are coated with antibodies that bind to specific proteins on the surface of leukemia cells. This approach has the potential to deliver drugs to leukemia cells more effectively and reduce side effects.

Journal 1:

The first journal employed a qualitative, participatory approach to provide a comprehensive overview of the evolving indications for hematopoietic stem cell transplantation (HSCT) in pediatric acute lymphoblastic leukemia (ALL).

Journal 2:

Using a quantitative, explanatory design, the second journal investigated the prenatal origins of childhood leukemia and the feasibility of newborn screening for this disease. The authors reviewed studies on the detection of leukemic translocations in dried blood spots (DBS) collected at birth. While current methods lack sufficient sensitivity for widespread screening, they suggested that next-generation sequencing (NGS) could enable it. The primary objective was to identify children at risk for leukemia to facilitate early intervention.

Journal 3:

This quantitative systematic review and meta-analysis examined the association between exposure to extremely low-frequency magnetic fields (ELF-MF) and childhood leukemia risk. The study aimed to clarify whether there is a causal relationship between exposure to ELF-MF from various sources, such as power lines and household electrical appliances, and the development of childhood leukemia.

Journal 4:

Employing a quantitative correlational approach, the fourth journal examined global incidence and mortality rates of childhood leukemia. The article explored the association between childhood leukemia and the Human Development Index (HDI), finding a positive correlation between the age-standardized incidence rate (ASIR) of childhood leukemia and HDI. This suggests that socioeconomic factors may play a role in the incidence of childhood leukemia. Childhood leukemia is a major global health problem, with children in low- and middle-income countries (LMICs) facing a significantly higher risk of death compared to children in high-income countries due to limited access to diagnosis and treatment in LMICs.

Journal 5:

Using a quantitative correlational approach, the fifth journal explored various subtypes of childhood leukemia and the challenges associated with treating them. Researchers are developing novel treatments using drug-delivery nanoparticles that target leukemic cells. These nanoparticles are coated with antibodies that bind to specific proteins on the surface of leukemic cells. This approach has the potential to deliver drugs more effectively to leukemic cells and reduce side effects.

Conclusions

The five journals provide a comprehensive overview of various aspects of childhood leukemia, ranging from diagnosis and treatment to risk factors. These studies employed a variety of methodological approaches, both qualitative and quantitative, to delve deeper into this complex disease. Journal 1: Identifies changes in indications for hematopoietic stem cell transplantation (HSCT) in children with acute lymphoblastic leukemia (ALL). The qualitative

approach used provides a deep understanding of evolving clinical practices. Journal 2: Investigates the possibility of newborn screening for leukemia. This study demonstrates the potential of using NGS technology to detect leukemic translocations earlier. Journal 3: Analyzes the association between exposure to extremely low-frequency magnetic fields (ELF-MF) and childhood leukemia risk. The findings of this study may provide clues about environmental factors that could contribute to the development of the disease. Journal 4: Explores global incidence and mortality rates of childhood leukemia, as well as its relationship with the Human Development Index (HDI). These findings highlight disparities in access to care between developed and developing countries. Journal 5: Discusses various subtypes of leukemia and the development of new treatments using nanoparticles. This approach offers hope for improving treatment efficacy and reducing side effects.

Childhood leukemia is a complex global health problem with varying incidence and mortality rates worldwide [5]. Ongoing research is needed to better understand the causes, mechanisms, and treatment of childhood leukemia. Disparities in access to quality care in developing countries remain a significant challenge that needs to be addressed

References

1. Mohammadian-Hafshejani A, Farber IM, Kheiri S. Global incidence and mortality of childhood leukemia and its relationship with the Human Development Index. PLoS One. 2024;19(7):e030435.
2. Moles E, Howard CB, Huda P, Karsa M, McCalmont H, Kimpton K, et al. Delivery of PEGylated liposomal doxorubicin by bispecific antibodies improves treatment in models of high-risk childhood leukemia. Sci Transl Med. 2023;15(696):eabm1262.
3. Brabant C, Geerinck A, Beaudart C, Tirelli E, Geuzaine C, Bruyere O. Exposure to magnetic fields and childhood leukemia: a systematic review and meta-analysis of case-control and cohort studies. Rev Environ Health. 2023;38(2):229-53.
4. Marcotte EL, Spector LG, Mendes-de-Almeida DP, Nelson HH. The prenatal origin of childhood leukemia: potential applications for epidemiology and newborn screening. Front Pediatr. 2021;9:639479.
5. Truong TH, Jinca C, Mann G, Arghirescu S, Buechner J, Merli P, et al. Allogeneic hematopoietic stem cell transplantation for children with acute lymphoblastic leukemia: shifting indications in the era of immunotherapy. Front Pediatr. 2021;9:782785.
6. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378:439-48.

7. Maude SL, Frey NV, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-17.
8. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemia: Integrating Morphological, Clinical, and Genomic Data. Blood. 2022.
9. Dinardo CD, Jonas BA, Pullarkat VA, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-29.
10. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med. 1997;3:730-7.