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Causes of Acute Lymphoblastic Leukemia (All), Diagnosis and Treatment

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a malignancy of the blood and bone marrow affecting both adults and children. Despite significant advancements in the treatment of ALL, its etiology remains multifactorial and complex. This scientific article aims to comprehensively explore the current understanding of the causes of ALL, integrating genetic, environmental, and other potential risk factors with the intent to enhance future research, exploring methods of diagnosis and treatment, and ultimately improve preventative measures and therapeutic strategies.

Acute Lymphoblastic Leukemia (ALL) is characterized by the uncontrolled proliferation of immature lymphoid progenitor cells in the bone marrow. Although dramatic progress has been made in treating this disease, its etiology challenges scientists and clinicians alike. A better understanding of the underpinning causes of ALL is imperative to develop tailored interventions and preventive strategies. The etiology of Acute Lymphoblastic Leukemia remains a complex puzzle, tightly intertwined with a combination of genetic, environmental, and lifestyle factors. While significant progress has been made in identifying key genetic alterations and environmental exposures associated with ALL, further research is essential to understand the intricate interplay between genetic predispositions and environmental triggers. Improved understanding of the causes of ALL will aid in developing effective preventive strategies, targeted therapies, and personalized treatment approaches, ultimately reducing the burden of this devastating disease.

KEYWORDS: ALL, etiology of lymphoblastic leukemia, ALL diagnosis, ALL treatment, Prevalence of ALL. Herbal medicine to treat ALL leukemia.

CAUSES OF ALL

1. Genetic Factors:

In recent years, significant advancements have been made in unraveling the genetic determinants associated with ALL. Chromosomal abnormalities, such as translocations involving the MLL gene and deletions affecting genes such as IKZF1[1,2,3], have been strongly linked to the development of ALL. Additionally, germline genetic alterations in genes like ARID5B[4,5] and PAX5[6,7] have been identified, highlighting the growing role of inherited predispositions. Molecular profiling efforts have also identified various somatic mutations involved in the pathogenesis of ALL, shedding light on the interplay between genetic alterations and disease initiation and progression.

2. Environmental Factors:

Environmental factors have long been implicated in the development of ALL[8,9]. Prenatal exposures, such as maternal smoking, alcohol consumption, and certain chemicals, including polycyclic aromatic hydrocarbons (PAHs), have been associated with an increased risk of ALL. Early-life infections and immune modulation seem to play an important role in the etiology, suggesting that a dysregulated immune system may contribute to leukemogenesis. Notably, studies have also suggested a possible link between exposure to electromagnetic fields (EMFs) and the development of ALL, although further research is needed to elucidate this association

3. Lifestyle Factors:

Several lifestyle-related factors have emerged as potential influencers in ALL onset[10,11]. Maternal factors, including advanced maternal age and obesity, have been correlated with an increased ALL risk in offspring. Furthermore, the timing and patterns of breastfeeding, as well as exposure to certain dietary factors, such as high caloric intake and specific food additives, are being investigated as possible risk factors. However, more research is required to establish concrete associations between lifestyle choices and the development of ALL.

4. Inherited Predispositions:

Genetic predispositions to ALL have been identified in recent years. A growing list of genetic syndromes, such as Down syndrome, Bloom syndrome, and Li-Fraumeni syndrome, are known to confer an increased risk of developing ALL[12,13]. These insights provide valuable clues regarding the potential

molecular pathways implicated in disease initiation and progression.

5. Interplay of Genetic and Environmental Factors:
It is becoming increasingly evident that the etiology of ALL involves intricate interactions between various genetic and environmental factors. Studies have explored gene-environment interactions, including how specific genetic variants modify the impact of environmental exposures on disease susceptibility. Future research needs to delve deeper into these interactions to elucidate the mechanisms driving leukemogenesis.

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) DIAGNOSTICS:

Acute Lymphoblastic Leukemia (ALL) is a prevalent form of cancer characterized by the excessive proliferation of immature lymphoid cells in the bone marrow and peripheral blood. Due to its potentially fatal nature, early and accurate diagnosis is crucial for the effective management and treatment of ALL. The diagnostic methods used to diagnose Leukemia are :

1. Clinical Presentation and History:
The initial step in ALL diagnosis involves meticulously assessing the patient's medical history and clinical presentation. Key symptoms of ALL may include fatigue, pale skin, fever, bruising, swelling, and unexplained weight loss. A thorough examination of the lymph nodes, liver, and spleen, alongside additional tests such as blood counts, may provide initial clues regarding possible leukemia presence.

2. Complete Blood Count (CBC):
A crucial component of ALL diagnostics, CBC entails a detailed analysis of the patient's blood sample. This examination allows healthcare professionals to evaluate the levels and characteristics of various blood cells, such as red blood cells, white blood cells, and platelets. In ALL, CBC typically reveals abnormal blood cell counts, specifically a decreased red blood cell count (anemia) and a higher or lower number of white blood cells (leukocytosis or leukopenia, respectively). Such observations serve as crucial indicators, suggesting the need for further investigation.

3. Peripheral Blood Smear:
A peripheral blood smear involves examining a slide of the patient's blood sample under a microscope. This technique enables the identification of morphological abnormalities in blood cells, which can be indicative of leukemia. In ALL, the smear may exhibit the presence of blasts, immature white blood cells characterized by a high nuclear-to-cytoplasmic ratio, scant cytoplasm, and a fine chromatin structure. Detecting blast cells in the peripheral blood smear strengthens the suspicion of ALL, guiding the subsequent diagnostic steps.

4. Bone Marrow Aspiration and Biopsy:
Bone marrow aspiration and biopsy are essential procedures performed to definitively diagnose ALL. In this diagnostic modality, a small sample of bone marrow is extracted from the patient's hipbone or sternum using a long, thin needle. The sample is subsequently analyzed in the laboratory for the identification and evaluation of abnormal cells. The presence of a high percentage of lymphoblasts in the bone marrow confirms the diagnosis of ALL. Additionally, specialized techniques like flow cytometry and immunohistochemistry may be employed to determine the immunophenotype and further classify the disease.

5. Cytogenetic and Molecular Testing:
Within the realm of ALL diagnostics, cytogenetic and molecular testing play a vital role in predicting prognosis and informing treatment options. These tests aim to identify specific genetic abnormalities and alterations in leukemic cells. Examples include fluorescent in situ hybridization (FISH), polymerase chain reaction (PCR), and multiplex ligation-dependent probe amplification (MLPA). By analyzing chromosomal rearrangements, mutations, and gene fusions, healthcare professionals can determine the presence of clinically significant markers, such as BCR-ABL1, ETV6-RUNX1, and MLL rearrangements. This information helps guide the selection of suitable therapies tailored to the patient's unique biological profile[14].

GENETIC CLASSIFICATION OF ALL

ALL exhibits remarkable genetic heterogeneity, with multiple subtypes identified through advanced molecular profiling techniques. The World Health Organization (WHO) Classification system has classified ALL into different subgroups based on their distinct genetic features. These classification systems aid in the better understanding of ALL subtypes and have important clinical implications for treatment stratification[15,16,17].

1. B-Cell ALL:
a. Hyperdiploid ALL: This subtype is characterized by a high number of chromosomes, typically more than 50. This condition is associated with favorable outcomes and is commonly observed in children.
b. ETV6-RUNX1 (TEL-AML1) fusion: This chromosomal translocation forms a fusion gene, resulting in the overexpression of TEL-AML1 protein. It is the most common fusion in ALL and is associated with good prognosis.
c. BCR-ABL1 fusion: This fusion gene occurs due to the Philadelphia chromosome (Ph) translocation and is associated with poor prognoses. It is commonly seen in adult ALL cases.

2. T-Cell ALL:
a. TLX1 and TLX3 rearrangements: These alterations involve the T-cell-specific homeobox genes resulting in aberrant expression. They are associated with an unfavorable prognosis.

b. NOTCH1 mutations: NOTCH1 signaling pathway mutations are frequently observed in T-ALL, altering cell differentiation, maturation, and proliferation, resulting in aggressive disease progression.

SPECIFIC GENETIC ABNORMALITY

There are several genetic abnormalities or mutations commonly associated with ALL. Some of the significant ones include:

1. Philadelphia Chromosome (Ph+): Around 25% of adults with ALL carry this abnormality. It results from a translocation between chromosomes 9 and 22, leading to the fusion of the BCR (breakpoint cluster region) gene and the ABL1 (abelson tyrosine kinase 1) gene. This fusion gene produces a novel protein called BCR-ABL1, which leads to uncontrolled cell growth[18].

2. Hyperdiploidy: Approximately 25-30% of ALL cases exhibit hyperdiploidy, which refers to an excess of chromosomes. The most common trisomies involved in hyperdiploid ALL are chromosomes 4, 10, 14, 17, and 21. The exact mechanism by which this abnormality contributes to ALL is not completely understood[19].

3. Hypodiploidy: In contrast to hyperdiploidy, hypodiploidy is the presence of fewer than the normal number of chromosomes. Hypodiploid ALL is associated with poor prognosis. The most common genetic abnormality in hypodiploid ALL is the loss of chromosomes, mainly chromosomes 7, 9, 17, and X[20].

4. TEL-AML1 Fusion (Translocation 12;21): This specific genetic abnormality is the result of a translocation between chromosomes 12 and 21, leading to the fusion of the TEL (ETV6) gene and the AML1 (RUNX1) gene. It is commonly found in pediatric ALL, especially with precursor B-cell immunophenotype, and is associated with a good prognosis[21,22].

5. MLL Gene Rearrangements: Rearrangements involving the MLL (Mixed Lineage Leukemia) gene are commonly found in infant ALL and are associated with a poor prognosis. Several partner genes can fuse with MLL, leading to the disruption of normal hematopoietic cell development and increased cell proliferation[23].

It's important to note that these genetic abnormalities are not always present in every case of ALL. The prevalence and significance of each mutation can vary depending on the age group, subtype of ALL, and other factors.

PREVALENCE FACTORS OF ALL

Its prevalence in humans is influenced by several factors, including age, gender, occupation, and lifestyle[24]. This essay will delve into the formal examination of these factors to gain a comprehensive understanding of the prevalence of ALL.

Age and Prevalence of ALL:

Age is a critical factor when it comes to the prevalence of ALL. This disease primarily affects children and adolescents, making it the most common pediatric malignancy worldwide. The incidence rate sharply increases in the first four years of a child's life, reaching its peak between the ages of two and five. However, ALL can also occur in adults, though the incidence is significantly lower compared to children. In adults, the risk of developing ALL increases with age, particularly in individuals over 50. This age dependency suggests that there may be underlying biological and genetic factors that make younger individuals more susceptible to this disease.

Gender Disparities in ALL Prevalence:

Gender also plays a role in the prevalence of ALL, albeit with slight variations. Studies consistently show that males have a slightly higher incidence rate compared to females, although the reasons for this difference remain unclear. Hormonal differences between males and females might contribute to the variation, as certain hormones have been linked to the development and progression of ALL. However, further research is required to better comprehend the intricate relationship between gender and the prevalence of ALL.

Occupational Influences on ALL Prevalence:

While there is limited direct evidence linking specific occupations to the prevalence of ALL, exposure to certain environmental factors may indirectly increase the risk. Workers involved in benzene-related industries, such as chemical manufacturing, petroleum refining, and rubber manufacturing, are potentially at a higher risk of developing ALL. Benzene, a known carcinogen, has been associated with the development of leukemia, including ALL. Additional research is crucial to pinpoint other occupational risks that could contribute to the prevalence of this disease.

Lifestyle Factors and ALL:

Lifestyle choices can also impact the prevalence of ALL. Maternal smoking during pregnancy is a significant risk factor, as it has been linked to childhood leukemia, including ALL. Exposure to ionizing radiation, whether through medical procedures or nuclear accidents, has also been associated with an increased risk of developing ALL. Additionally, a lack of physical activity, unhealthy diets, and high levels of pollution may contribute to the overall burden of this disease in certain populations.

As a life-threatening disease, the prevention of ALL assumes paramount importance in the field of medicine and public health. A multifaceted approach encompassing various domains such as education, genetic screening, immunization, and environmental awareness is vital to effectively combat this aggressive malignancy. We examines the importance of prevention programs and outlines strategies aimed at reducing the incidence and impact of ALL on society.

1-Education as a Foundational Pillar

Education plays a pivotal role in preventing ALL by fostering awareness and empowering individuals to make informed decisions regarding their health. Educational initiatives should target both the general population and healthcare professionals. For the public, awareness campaigns should emphasize the early signs and symptoms of ALL, highlighting the importance of timely medical intervention. Additionally, disseminating information about the factors influencing the development of ALL, including genetic predisposition, radiation exposure, and potential risk factors, is paramount.

Healthcare professionals should receive comprehensive training on recognizing the clinical manifestations of ALL, facilitating early diagnosis. Furthermore, promoting the significance of routine health visits and regular screenings among healthcare providers can lead to earlier detection, thereby enhancing prognosis and treatment outcomes.

2-Genetic Screening and Counseling

Genetic screening for ALL susceptibility genes plays a crucial role in identifying individuals at risk. By conducting genetic testing, at-risk individuals can make informed decisions about lifestyle modifications, early intervention, or preventive measures in consultation with genetic counselors. Furthermore, such testing enables the identification of genetic mutations associated with familial ALL, helping to recognize individuals who may require further genetic evaluation.

3-Immunization Programs

Immunization programs geared towards preventing infections are fundamental in reducing the incidence of ALL[25,26]. Vaccination against key viral infections, such as human T-cell lymphotropic virus type 1 (HTLV-1), Epstein-Barr virus (EBV), and hepatitis B virus (HBV), has been linked to a decreased risk of developing ALL. Public health authorities should intensify efforts to disseminate information about the importance of immunization, ensuring optimal vaccination coverage across populations. By mitigating viral infection risks, immunization programs can significantly contribute to the prevention of ALL.

4-Environmental Awareness and Regulation

Environmental factors have been implicated in the development of ALL; therefore, raising awareness about potential carcinogens and implementing regulations aimed at reducing exposure is essential. To mitigate risks associated with ALL, governments should strengthen environmental regulations surrounding radiation, chemical pollutants, and occupational hazards. Efforts should include robust monitoring systems, public disclosure of environmental data, and appropriate enforcement mechanisms.

Moreover, promoting sustainable agricultural practices, safe disposal of hazardous waste, and encouraging a shift towards renewable energy sources can collectively contribute to a safer environment, reducing the risk of ALL development.

5-Collaborative Research and Funding

To achieve significant progress in the prevention of ALL, promoting interdisciplinary collaboration and allocating funds for research becomes crucial. Governments, pharmaceutical companies, and non-profit organizations should invest in research aimed at identifying novel risk factors, improving diagnostic tools, and developing preventive strategies. By supporting scientific studies, society can unlock breakthroughs in ALL prevention, fostering a future where preventing the disease becomes more attainable. As a result, preventing ALL necessitates a multi-pronged approach encompassing education, genetic screening, immunization, and environmental awareness. By imparting knowledge and empowering individuals, education lays the foundation for early diagnosis. Genetic screening aids in identifying those at risk, enabling personalized preventive measures. Immunization programs and environmental regulations contribute significantly to reducing infection and exposure risks. Collaborative research and funding drive progress towards improved prevention strategies.

With concerted efforts from healthcare professionals, policymakers, researchers, and society at large, preventing ALL can become a shared objective. Ultimately, a comprehensive prevention approach will alleviate the burden of ALL, providing a healthier and brighter future for generations to come.

TREATMENT

As mentioned, ALL is the most common form of leukemia in children, although it can also occur in adults. Over the years, significant advancements have been made in the diagnosis and treatment of ALL, resulting in improved survival rates. This part explores the common treatment approaches for Acute Lymphoblastic Leukemia, highlighting both traditional and contemporary treatments.

1. Chemotherapy:

Chemotherapy is the cornerstone of treating ALL[27]. It involves the administration of powerful drugs that target rapidly dividing cancer cells. Multiple drugs are usually combined in various treatment phases to improve efficacy and minimize the development of resistance. Chemotherapy protocols for ALL are further divided into induction, consolidation, and maintenance phases, each tailored to different goals and disease states. The objective is to achieve complete remission, eliminate any remaining cancer cells, and prevent relapse.

2. Radiation Therapy:

Radiation therapy involves the use of high-energy X-rays or other types of radiation to target and destroy cancer cells. It is usually employed as a localized treatment in specific areas affected by ALL, such as the brain or testicles. Radiation therapy may be used along with chemotherapy to ensure that leukemic cells are effectively eradicated in the affected regions[28].

3. Stem Cell Transplantation:

Stem cell transplantation, also known as a bone marrow transplant, is a potentially curative treatment option for ALL patients[29,30]. It involves replacing the diseased bone marrow with healthy stem cells from a matched donor. The new stem cells can generate healthy blood cells, thereby restoring the patient's immune system. Two types of stem cell transplantation are commonly used: autologous transplantation, utilizing the patient's own healthy cells, or allogeneic transplantation, using stem cells from a donor. Allogeneic transplantation, with its graft-versus-leukemia effect, is particularly advantageous in high-risk cases.

4. Targeted Therapy:

Targeted therapy involves drugs that specifically target the unique genetic mutations or proteins involved in leukemia growth. This approach minimizes damage to healthy cells and reduces side effects compared to traditional chemotherapy[31,32]. One such example is the use of tyrosine kinase inhibitors (TKIs), such as imatinib, to inhibit the uncontrolled growth of leukemia cells with specific genetic abnormalities, such as the Philadelphia chromosome.

5. Immunotherapy:

Immunotherapy harnesses the body's immune system to recognize and destroy cancer cells[33,34]. Monoclonal antibodies, such as rituximab[35], are employed to directly target specific markers on leukemic cells, marking them for destruction by the immune system. Other immunotherapies, such as CAR-T cell therapy, involve engineering a patient's immune cells to recognize and attack leukemia cells more effectively. These cutting-edge therapies have shown remarkable results in some cases, especially those with relapsed or refractory ALL.

It must be said that when treating, we must pay attention to important points such as genetic changes in order to take advantage of the most effective treatment methods.

Genetic Alterations and their Significance:

1. Chromosomal Translocations:

a. t(9;22)(q34;q11.2) - BCR-ABL1 fusion[36]: The presence of this fusion gene is pivotal in the diagnosis of Ph-positive ALL. It influences prognosis and determines eligibility for targeted therapies, such as tyrosine kinase inhibitors.

b. t(12;21)(p13;q22) - ETV6-RUNX1 fusion: This rearrangement is frequently seen in pediatric B-ALL and correlates with a favorable prognosis.

2. Copy Number Alterations:

a. Deletions in the CDKN2A/B gene on chromosome 9[37,38]: These deletions compromise cell cycle regulation, particularly in T-ALL, leading to cell proliferation and increased likelihood of relapse.

b. IKZF1 deletion: IKZF1 gene deletions are associated with poor outcomes in B-ALL, as they are implicated in B-cell development and play a role in treatment resistance.

3. Gene Mutations:

a. TP53 mutations: TP53 gene mutations are associated with a poor prognosis and tumor resistance to conventional chemotherapy.

b. IKZF1 mutations: Similar to deletions, mutations in the IKZF1 gene confer an unfavorable prognosis in B-ALL.

Genetic alterations in ALL have a profound impact on its diagnosis, prognosis, and therapeutic approaches. Over the past decades, substantial progress has been made in deciphering the genetic intricacies of this disease, leading to targeted therapies and improved outcomes. Comprehensive molecular profiling has allowed for the identification of genetic subgroups, providing novel insights into the biological mechanisms underlying ALL. Continued research on the genetic details of ALL is crucial to unravel its complex pathology and develop personalized treatment strategies for patients with this aggressive hematological malignancy.

CONCLUSIONS

Acute lymphoblastic leukemia (ALL) is a malignancy characterized by an overproduction of immature white blood cells, known as lymphoblasts, in the bone marrow. Numerous factors contribute to the development of this aggressive and complex disease. While specific causative factors are yet to be completely understood, research has identified some key causes that can lead to the onset of acute lymphoblastic leukemia.

Genetic alterations play a crucial role in the development of ALL. Certain genetic conditions and chromosomal abnormalities increase the likelihood of acquiring the disease. Down syndrome, for instance, has been closely linked to an increased risk of developing ALL. Individuals with Down syndrome possess an extra chromosome 21, which disrupts the normal functioning of genes involved in regulating cell growth and differentiation. This abnormality heightens the susceptibility to leukemia development.

Acute lymphoblastic leukemia arises from a complex interplay of genetic and environmental factors. Genetic abnormalities, exposure to ionizing radiation, infections, and exposure to specific chemicals and toxins have all been identified as potential causes of ALL. However, further research is still required to fully comprehend the intricate mechanisms underlying the development of this devastating disease. Understanding these causes will not only facilitate early detection and accurate diagnosis but also aid in the development of novel therapeutic interventions for combating acute lymphoblastic leukemia.

The diagnosis of Acute Lymphoblastic Leukemia (ALL) requires employing a series of comprehensive diagnostic techniques to assess the patient's clinical presentation, bone marrow aspirate, blood counts, and cytogenetic and molecular markers. The integration of these diverse diagnostic modalities enables accurate identification, subclassification, and risk stratification of ALL. These formal diagnostic tools aid healthcare professionals in tailoring treatment options to maximize therapeutic effectiveness and

improve patient outcomes in their battle against this life-threatening disease.

Understanding the factors influencing the prevalence of Acute Lymphoblastic Leukemia (ALL) is essential for developing effective prevention strategies and improving patient outcomes. Age has a prominent association with ALL prevalence, with children and adolescents being the most susceptible group. Gender differences also exist, although the underlying causes remain inconclusive. While the direct impact of occupation is not well-established, workers exposed to certain environmental hazards might face an increased risk. Furthermore, lifestyle factors, including maternal smoking, radiation exposure, and lifestyle choices, can contribute to the overall burden of ALL. Research efforts should continue to shed light on these factors and facilitate the implementation of targeted interventions to prevent this devastating disease.

Effective treatment of Acute Lymphoblastic Leukemia involves a combination of different approaches tailored to each patient's unique characteristics. While chemotherapy remains the primary treatment, radiation therapy, stem cell transplantation, targeted therapy, and immunotherapy are increasingly integrated into treatment protocols, yielding higher survival rates and improved long-term outcomes. A multidisciplinary approach, with collaboration between hematologists, oncologists, and other specialists, facilitates the optimal management of ALL, ensuring that patients receive the best possible care. Overall, the continuous advancement in treatment strategies for Acute Lymphoblastic Leukemia offers hope for improved quality of life and increased survival rates for those affected by this challenging condition.

We conducted laboratory-level research that shows the treatment of ALL Leukemia with herbal medications is to some extent possible.

REFRENCES

I. Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, Ma J, Liu W, Cheng C, Schulman BA, Harvey RC. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. New England Journal of Medicine. 2009 Jan 29;360(5):470-80.

II. Vairy S, Tran TH. IKZF1 alterations in acute lymphoblastic leukemia: The good, the bad and the ugly. Blood Reviews. 2020 Nov 1;44:100677.

III. Marke R, van Leeuwen FN, Scheijen B. The many faces of IKZF1 in B-cell precursor acute lymphoblastic leukemia. haematologica. 2018 Apr;103(4):565.

IV. Wang P, Deng Y, Yan X, Zhu J, Yin Y, Shu Y, Bai D, Zhang S, Xu H, Lu X. The role of ARID5B in acute lymphoblastic leukemia and beyond. Frontiers in Genetics. 2020 Jun 12;11:598.

V. Xu H, Cheng C, Devidas M, Pei D, Fan Y, Yang W, Neale G, Scheet P, Burchard EG, Torgerson DG, Eng C. ARID5B genetic polymorphisms contribute to racial disparities in the incidence and treatment outcome of childhood acute lymphoblastic leukemia. Journal of clinical oncology. 2012 Mar 3;30(7):751.

VI. Gu Z, Churchman ML, Roberts KG, Moore I, Zhou X, Nakitandwe J, Hagiwara K, Pelletier S, Gingras S, Berns H, Payne-Turner D. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nature genetics. 2019 Feb;51(2):296-307.

VII. Shah S, Schrader KA, Waanders E, Timms AE, Vijai J, Miething C, Wechsler J, Yang J, Hayes J, Klein RJ, Zhang J. A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia. Nature genetics. 2013 Oct;45(10):1226-31.

VIII. Fujita TC, Sousa-Pereira N, Amarante MK, Watanabe MA. Acute lymphoid leukemia etiopathogenesis. Molecular Biology Reports. 2021 Jan;48:817-22.

IX. Perentesis JP. Why is age such an important independent prognostic factor in acute lymphoblastic leukemia?. Leukemia (08876924). 1997 May 2;11.

X. Rafieemehr H, Calhor F, Esfahani H, Gholiabad SG. Risk of acute lymphoblastic leukemia: Results of a case-control study. Asian Pacific journal of cancer prevention: APJCP. 2019;20(8):2477.

XI. Fujita TC, Sousa-Pereira N, Amarante MK, Watanabe MA. Acute lymphoid leukemia etiopathogenesis. Molecular Biology Reports. 2021 Jan;48:817-22.

XII. Churchman ML, Qian M, Te Kronnie G, Zhang R, Yang W, Zhang H, Lana T, Tedrick P, Baskin R, Verbist K, Peters JL. Germline genetic IKZF1 variation and predisposition to childhood acute lymphoblastic leukemia. Cancer cell. 2018 May 14;33(5):937-48.

XIII. Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, Ma J, Coustan-Smith E, Harvey RC, Willman CL, Mikhail FM. Rearrangement of CRLF2 in B-progenitor–and Down syndrome–associated acute lymphoblastic leukemia. Nature genetics. 2009 Nov;41(11):1243-6.

XIV. Mrozek K, Harper DP, Aplan PD. Cytogenetics and molecular genetics of acute lymphoblastic leukemia. Hematology/Oncology Clinics. 2009 Oct 1;23(5):991-1010.

XV. Mancini M, Scappaticci D, Cimino G, Nanni M, Derme V, Elia L, Tafuri A, Vignetti M, Vitale A, Cuneo A, Castoldi G. A comprehensive genetic classification of adult acute lymphoblastic leukemia (ALL): analysis of the GIMEMA 0496 protocol. Blood. 2005 May 1;105(9):3434-41.

XVI. Ross ME, Zhou X, Song G, Shurtleff SA, Girtman K, Williams WK, Liu HC, Mahfouz R, Raimondi SC, Lenny N, Patel A. Classification of pediatric acute lymphoblastic leukemia by gene expression profiling. Blood. 2003 Oct 15;102(8):2951-9.

XVII. Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. Journal of Clinical Oncology. 2017 Mar 3;35(9):975.

XVIII. Hofmann WK, de Vos S, Elashoff D, Gschaidmeier H, Hoelzer D, Koeffler HP, Ottmann OG. Relation between resistance of Philadelphia-chromosome-positive acute lymphoblastic leukaemia to the tyrosine kinase inhibitor STI571 and gene-expression profiles: a gene-expression study. The Lancet. 2002 Feb 9;359(9305):481-6.

XIX. Paulsson K, Johansson B. High hyperdiploid childhood acute lymphoblastic leukemia. Genes, Chromosomes and Cancer. 2009 Aug;48(8):637-60.

XX. Safavi S, Olsson L, Biloglav A, Veerla S, Blendberg M, Tayebwa J, Behrendtz M, Castor A, Hansson M, Johansson B, Paulsson K. Genetic and epigenetic characterization of hypodiploid acute lymphoblastic leukemia. Oncotarget. 2015 Dec 12;6(40):42793.

XXI. Stams WA, den Boer ML, Beverloo HB, Meijerink JP, van Wering ER, Janka-Schaub GE, Pieters R. Expression levels of TEL, AML1, and the fusion products TEL-AML1 and AML1-TEL versus drug sensitivity and clinical outcome in t (12; 21)-positive pediatric acute lymphoblastic leukemia. Clinical cancer research. 2005 Apr 15;11(8):2974-80.

XXII. Woerden NL, Pieters R, Loonen AH, Hubeek I, van Drunen E, Beverloo HB, Slater RM, Harbott J, Seyfarth J, van Wering ER, Hählen K. TEL/AML1 gene fusion is related to in vitro drug sensitivity forl-asparaginase in childhood acute lymphoblastic leukemia. Blood, The Journal of the American Society of Hematology. 2000 Aug 1;96(3):1094-9.

XXIII. Jansen MW, Corral L, Van der Velden VH, Panzer-Grümayer R, Schrappe M, Schrauder A, Marschalek R, Meyer C, Den Boer ML, Hop WJ, Valsecchi MG. Immunobiological diversity in infant acute lymphoblastic leukemia is related to the occurrence and type of MLL gene rearrangement. Leukemia. 2007 Apr;21(4):633-41.

XXIV. Reddick WE, Glass JO, Helton KJ, Langston JW, Xiong X, Wu S, Pui CH. Prevalence of leukoencephalopathy in children treated for acute lymphoblastic leukemia with high-dose methotrexate. American Journal of Neuroradiology. 2005 May 1;26(5):1263-9.

XXV. François G, Duclos P, Margolis H, Lavanchy D, Siegrist CA, Meheus A, Lambert PH, Emiroglu N, Badur S, Van Damme P. Vaccine safety controversies and the future of vaccination programs. The Pediatric infectious disease journal. 2005 Nov 1;24(11):953-61.

XXVI. van Tilburg CM, Sanders EA, Rovers MM, Wolfs TF, Bierings MB. Loss of antibodies and response to (re-) vaccination in children after treatment for acute lymphocytic leukemia: a systematic review. Leukemia. 2006 Oct;20(10):1717-22.

XXVII. Brown RT, Madan-Swain A, Pais R, Lambert RG, Sexson S, Ragab A. Chemotherapy for acute lymphocytic leukemia: cognitive and academic sequelae. The Journal of pediatrics. 1992 Dec 1;121(6):885-9.

XXVIII. Sugita M, Yamazaki T, Alhomoud M, Martinet J, Latouche JB, Golden E, Boyer O, Van Besien K, Formenti SC, Galluzzi L, Guzman ML. Radiation therapy improves CAR T cell activity in acute lymphoblastic leukemia. Cell Death & Disease. 2023 May 4;14(5):305.

XXIX. Merli P, Algeri M, Del Bufalo F, Locatelli F. Hematopoietic stem cell transplantation in pediatric acute lymphoblastic leukemia. Current hematologic malignancy reports. 2019 Apr 15;14:94-105.

XXX. Dhédin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, Thomas X, Chevallier P, Nguyen S, Coiteux V, Bourhis JH. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood, The Journal of the American Society of Hematology. 2015 Apr 16;125(16):2486-96.

XXXI. Portell CA, Advani AS. Novel targeted therapies in acute lymphoblastic leukemia. Leukemia & lymphoma. 2014 Apr 1;55(4):737-48.

XXXII. Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, Fietkau R, Freund M, Ganser A, Ludwig WD, Maschmeyer G. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood, The Journal of the American Society of Hematology. 2012 Aug 30;120(9):1868-76.

XXXIII. Mathé G, Amiel JL, Schwarzenberg L, Schneider M, Cattan A, Schlumberger JR, Hayat M, De Vassal F. Active immunotherapy for acute lymphoblastic leukaemia. The Lancet. 1969 Apr 5;293(7597):697-9.

XXXIV. Inaba H, Pui CH. Immunotherapy in pediatric acute lymphoblastic leukemia. Cancer and Metastasis Reviews. 2019 Dec;38(4):595-610.

XXXV. Jabbour E, O'Brien S, Ravandi F, Kantarjian H. Monoclonal antibodies in acute lymphoblastic leukemia. Blood, The Journal of the American Society of Hematology. 2015 Jun 25;125(26):4010-6.

XXXVI. Cazzaniga G, van Delft FW, Lo Nigro L, Ford AM, Score J, Iacobucci I, Mirabile E, Taj M, Colman SM, Biondi A, Greaves M. Developmental origins and impact of BCR-ABL1 fusion and IKZF1 deletions in monozygotic twins with Ph+ acute lymphoblastic leukemia. Blood, The Journal of the American Society of Hematology. 2011 Nov 17;118(20):5559-64.

XXXVII. Mullighan CG, Williams RT, Downing JR, Sherr CJ. Failure of CDKN2A/B (INK4A/B–ARF)-mediated tumor suppression and resistance to targeted therapy in acute lymphoblastic leukemia induced by BCR-ABL. Genes & development. 2008 Jun 1;22(11):1411-5.

XXXVIII. Ou Z, Sherer M, Casey J, Bakos HA, Vitullo K, Hu J, Friehling E, Gollin SM, Surti U, Yatsenko SA. The genomic landscape of PAX5, IKZF1, and CDKN2A/B alterations in B-cell precursor acute lymphoblastic leukemia. Cytogenetic and Genome Research. 2017 Mar 28;150(3-4):242-52.