Journal of Current Medical Research and Opinion
Received 18-12-2024 | Revised 19-12-2024 | Accepted 18-01-2025 | Published Online 20-01-2025

DOI: https://doi.org/10.52845/CMRO/2025/8-1-6 ISSN (O) 2589-8779 | (P) 2589-8760
CMRO 08 (01) 3866-3878 (2025) www.cmro.in
Original Research

Pediatric Hematological Malignancies: Immunotherapy, Causes of Childhood Haematological Cancers, Clinical Manifestation, Treatment and Problems Occurring After Treatment

Ghoftan Jwaid Rafea [1] | Zahraa Adnan Auda Alamash [2] | Sajad Abbas Hadi [3]

[1]College of Science Nasiriyah, Department of Pathological Analyses, Iraq
[2]Thi-Qar university, College of Sinece Biology, Iraq
[3]University of Hilla, Medical Physics, Iraq

Abstract:

Cancers that start in the cells of tissues that produce blood, like bone marrow, are known as haematological malignancies. Despite their rarity, blood malignancies continue to top the list of killers among children ages 1–14. Reducing death rates is possible by early discovery, which improves the likelihood of effective treatment. Among youngsters, leukaemias and lymphomas make up over 50% of all new cancer cases. Despite significant progress—the overall survival rate has increased from 10% to about 90% today—the survival rate is significantly lower for many uncommon malignancies. If the mechanisms and genetic abnormalities involved in leukemogenesis can be better understood, tailored therapy has the potential to increase anti-leukemic efficacy while decreasing treatment-related morbidity or mortality. More than 80% of children survive childhood thanks to improvements in the last several decades. Clinical trials carried out by many research groups, including those specialising in paediatrics and oncology, have contributed to these advancements. These were complemented by the substantial contributions made by the discovery of efficient therapeutic agents when combined with different chemotherapeutic drugs. Cure rates for non-lymphoblastic leukaemia have barely reached 50%, despite the overall survival rate of malignancies improving to 90%. Additionally, stem cell transplantation and other intensified regimens have improved outcomes; yet, contemporary therapies are linked to several acute and late complications, and related consequences seem to be on the rise. Haematological cancers can be better treated and patients can have a better chance of survival if our knowledge of the genes and processes that cause them grows. Advances in molecular biology have greatly enhanced our capacity to detect and prevent illness recurrence, monitor how patients react to various treatment plans, make more accurate predictions about their prognoses, and personalise their treatments. In order to develop effective treatments for subsets of children with haematological malignancies, the paediatric oncology and allied research communities must first identify and confirm the most significant therapeutic targets.

Keywords: Acute myeloid leukemia, Cancer, Chemotherapy, Children, Cytogenetics, Etiology, Genetic abnormalities, Hematological malignancies,

Introduction:

Cancer is usually associated with aging. Different types of cancers are reported to occur in children and these differ from those that occur in adults and also manifest differently. Mostly, carcinomas occur in adults and prognosis is improved with early detection whereas hematological malignancies (leukemia and lymphoma), sarcomas and brain tumors (neuroblastoma, wilms tumor and tumor of muscle, bone and soft tissue) are observed in children while carcinomas are very rare. Despite the progress in treatment protocols, cancer remained as the leading cause of death in children and therefore, immediate attention is required to bring new therapies. UICC is the Union for International Cancer Control which primarily aims to enhance early diagnosis, quality treatment and care, and support the children in developing countries. Latest statistics (2016) given by IARC (International Agency for Research on Cancer) show that childhood cancer is found to be significantly more in number than previously observed. According to them, worldwide, ~215, 000 cancers are diagnosed per year in children < 15 years and about 85 000 cancers in those aged between 15–19 years. [1, 2] Leukemia in children can be classified either by the type of cell lineage (myelocytic/myelogenous/granulocytic - myeloid stem cell or lymphoblastic/ lymphocytic/ lymphatic - lymphoid stem cell) or by the way the disease progresses- acute or chronic. Acute and chronic does not refer to how serious the disease is but refer to how rapidly the disease progress. Acute leukemias develop and progress quickly and so should be treated as soon as they are diagnosed [3-5]. Acute leukemias in particular, affect immature blood cells, leading to their improper maturation. In chronic leukemias, accumulation of mature and abnormal white blood cells is observed and these are rarely seen in children. Four major types of leukemia include ALL, AML, CML and CLL. Lymphoma is the third most common childhood cancer that affects the lymphatic system. The incidence of lymphomas raises with an increase in age and all the lymphomas diagnosed are more common in children than in adults. Malignant lymphoma is found to be more frequent in adolescents. More than 40 different types of lymphomas have been observed so far. Malignant lymphocytes travel to many parts of the body, by means of the blood stream and the lymphatic system, and thus form tumors. The two major types of lymphomas that exist, namely HL [Hodgkin's lymphomas] and NHL [non-Hodgkin's lymphomas] have many sub types, each related to how the lymph node tissue appears, affecting cell types in diseased condition along with several other factors. Approximately 60% of pediatric lymphomas are related to non-Hodgkin's lymphomas (NHL), and the remaining are observed to be Hodgkin's lymphomas. As there is a greater frequency of death of children in developing countries due to the problems of malnutrition and infectious diseases, it is difficult to measure the exact incidence of childhood cancer accurately [6-9]. About 80,000 children died from cancer in 2012 where the mortality rates were less in developed countries due to the availability of good quality treatment and diagnosis. Childhood cancer is emerging as a major cause of death in Asia, Central and South America, Middle East and North Africa. Recent reports on childhood cancer by WHO also clearly state that more than 200,000 children are prone to cancer and 90% of deaths are reported, particularly from low income and middle income countries. Several lines of evidence indicate that there is a genetic predisposition to acute lymphoblastic leukemia (ALL), at least in a subset of cases. This evidence includes the existence of: (i) rare constitutional syndromes with increased risk for ALL; (ii) familial cancer syndromes; (iii) non-coding DNA polymorphisms that subtly influence the risk of ALL; and (iv) genes harboring germline non-silent variants presumed to confer a risk of sporadic ALL.

Cancers of the Blood in Children:

More effective treatment stratification, improved experimental models for probing mechanisms and evaluating new treatments, and a deeper understanding of the genetic and biological basis of childhood acute lymphoblastic leukaemia (ALL) have all been developments of the past decade. The molecular taxonomy of ALL has been greatly improved by genomic investigations, which have prompted calls to include transcriptome and genome characterisation into clinical management of ALL for better risk-stratification and, in certain instances, tailored treatment. While only a small percentage of children with ALL have access to mutation-or pathway-directed targeted therapy (such as tyrosine kinase inhibitors for Ph-positive and Ph-like B-cell-ALL), numerous recently discovered molecular abnormalities have prompted the investigation of methods that target downregulated cell pathways [10-13]. When it comes to treating advanced disease, cellular or

humoral immunotherapy has proven to be effective with chimeric antigen receptor T-cell treatment and the bispecific engager blinatumomab. rate of cancer generally. Although leukemia-specific hereditary susceptibility is rare, it has led to the discovery of silent but predisposing variants that are also seen in sporadic ALL cases. These include PAX5 mutations and B-ALL with dicentric/isochromosome, ETV6 variants and hyperdiploid ALL, and TP53 germline mutations and low hypodiploid B-ALL. 9.10 to 13. In ALL, somatic mutations target these susceptibility genes: TP53 is altered in hypodiploid ALL, ETV6 and PAX5 are rearrangement, amplified/deleted, and mutated in B-ALL,14,15.10 IKZF1 gene variations are seen in immunodeficiency and familial B-ALL,16,17 and somatic IKZF1 mutations are more common in B-ALLs that are Ph-positive, Ph-like, or have DUX4 rearrangement.Germline mutations in RUNX1 can cause T-ALL and AML, while variations in ETV6 put carriers at risk for B-ALL and myelodysplasia (18–20). Acute lymphoblastic leukaemia involving B cells: a genetic study There are three main types of genetic alterations that can initiate B-cell acute lymphoblastic leukaemia (B-ALL): chromosomal aneuploidy, rearrangements that deregulate oncogenes or encode chimeric transcription factors, and point mutations. B-ALL comprises over twenty subtypes with varying prevalence according to age, each of which is associated with a unique gene expression profile. Subtypes differ in the genes involved and the frequency with which they occur, but all of them usually co-occur to disrupt lymphoid development, cell-cycle regulation, kinase signalling, and chromatin regulation.36 Up to 30% of childhood ALL cases have high hyperdiploidy (>50 chromosomes), which is linked to chromosomal modifiers such CREBBP and mutations in the Ras pathway, as well as favourable outcomes [14, 15]. While over 10% of individuals have low diploidy (31–39 chromosomes), it is found in about 1% of children with ALL. Approximately half of the cases are hereditary and are characterised by near-universal TP53 mutations and the deletion of IKZF2. Roughly 2% of paediatric ALL cases exhibit near haploidy (24-30 chromosomes), which is linked to Ras mutations (especially NF1) and IKZF3 deletions. Bad things happen when ALL is either low-hypodiploid or near-haploid. Hypodiploidy is more common than previously thought. However, there is a condition called "masked" hypodiploidy, where a hyper-diploid modal chromosome number results from duplicating the hypodiploid DNA.10,38 dollars The genetic (germline TP53 changes) and prognostic consequences make it necessary to distinguish masked-hypodiploid ALL from high-hyperdiploid ALL. Flow cytometric analysis of the DNA index typically shows peaks for both non-masked and masked clones, as well as methods that evaluate loss of heterozygosity, like SNP arrays, and patterns of chromosomal gain, which are more likely to be diploid and tetrasomic rather than trisomies in high-hyperdiploid ALL, can both raise suspicions of masked hypodiploidy [16, 17]. Also, both high-hyper-diploid and near-haploid ALL share similar transcriptomic profiles and co-occurring genetic alterations (such as Ras pathway and CREBBP alterations), which points to a shared origin for these entities. Among older children, those with ALL who have intrachromosomal amplification of chromosome 21 (iAMP21) tend to have a poor prognosis, but intensive treatment has improved their outcomes. The t(12;21)(p13;q22) subtype of B-ALL in children is the most prevalent translocation subtype; it is usually cryptic on cytogenetic analysis and is linked to a good prognosis; and it encodes ETV6-RUNX1. An increased risk of central nervous system (CNS) recurrence and worse results with earlier, non-modern treatment regimens are associated with the t(1;19)(q23;p13) translocation and variations that encode TCF3-PBX1, 40. This gene is more prevalent among African Americans. The formation of the Philadelphia chromosome, which encodes BCR-ABL1, is caused by the t(9;22)(q34;q11.2) translocation. This chromosome is present in a subset of childhood ALL patients who have had poor prognoses in the past, but this is no longer the case thanks to advances in combined chemotherapy and tyrosine kinase inhibition. Baby ALL is characterised by a poor prognosis and frequently involves a rearrangement of KMT2A (MLL) at 11q23 to more than 80 partners, the most prevalent of which is t(4;11)(q21;q23) encoding KMT2A-AFF1. In cytogenetic study, several novel subtypes were not apparent due to crypticand/or varied rearrangements or sequence mutations operating as driver lesions. However, genomic analyses, especially transcriptome sequencing, have revealed numerous new subtypes. Similar to ETV6-RUNX1 ALL, ETV6-RUNX1-like ALL is defined by an immunophenotype (CD27 +, CD44 low/negative) and gene expression profile. Transcription factors belonging to the ETS family (ECF1, ETV6, ERG, FLI1), IKZF1, or TCF3 are altered in these

patients, either in terms of gene fusions or copy quantity. ETV6-RUNX1-like ALL is nearly always found in children (making up around 3% of paediatric ALL) and is linked to a generally good prognosis. In 5-10% of B-ALL, there is a cytogenetically cryptic translocation of DUX4, which encodes a double-homeobox transcription factor, to the immunoglobulin heavy-chain locus (IGH). Due to the translocation, the DUX4 protein without the C-terminal domain is overexpressed. Significant disruption of ERG transcriptional regulation occurs when this shortened protein attaches to an intragenic region of the ETS-related gene (ERG), a transcription factor belonging to the ETS family [18, 19]. This usually leads to the expression of an ERG deletion and/or a C-terminal ERG protein fragment. Although almost 40% of cases had the deletion of IKZF1, which is often a bad indicator of prognosis in ALL, the result is usually great in DUX4-rearranged B-ALL, which has a unique gene expression profile and immunophenotype (CD2±, CD371+).

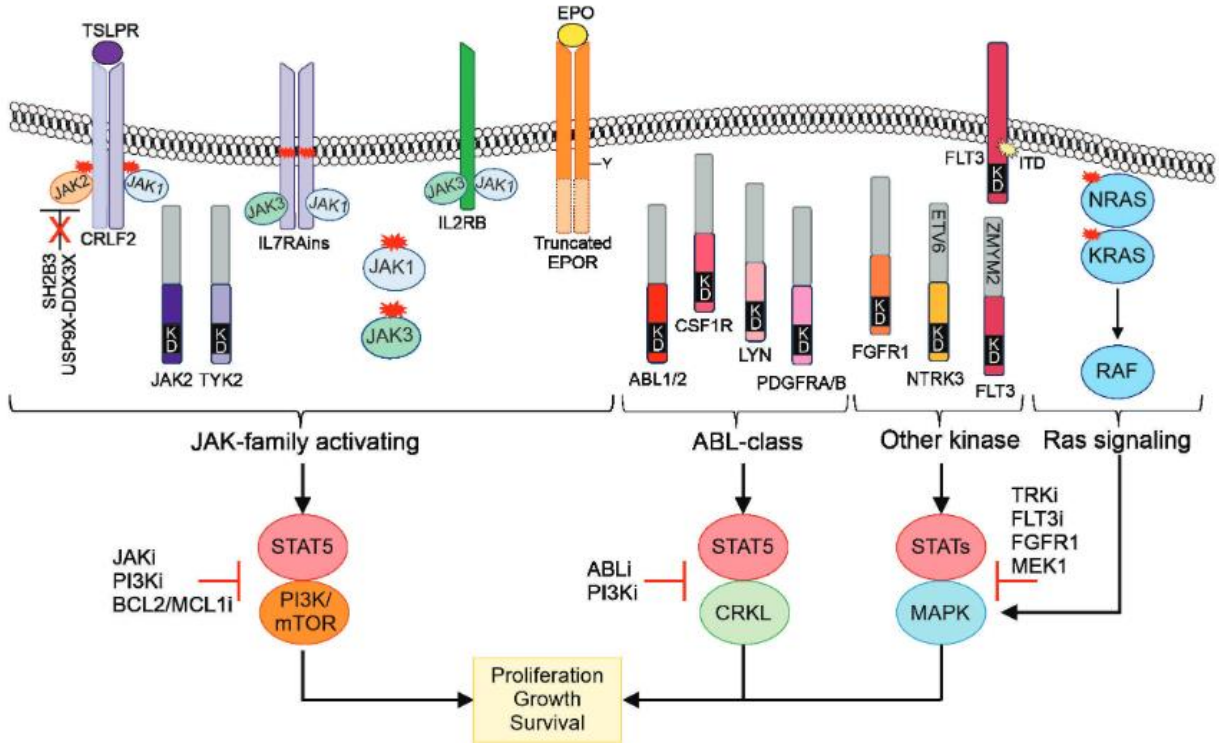

Figure 1. Deregulation of kinase pathways in acute lymphoblastic leukaemia (ALL) that shares the Philadelphia chromosome (Ph). The wide range of signalling abnormalities found in Ph-like ALL can be classified into several groups. These include lesions that activate JAK and STAT (such as CRLF2 rearrangement, IL7R mutation, truncating EPOR rearrangements, and SH2B3 deletion/mutation), alterations involving ABL-class tyrosine kinases, alterations of genes encoding other kinases (FGFR1, NTRK3, FLT3), and mutations in the Ras pathway. Other subtypes of leukaemia, such as hyperdiploid ALL and PAX5 P80R ALL, also exhibit Ras pathway alterations; this does not only affect Ph-like ALL.

Immunotherapy:

Treatment options for patients with relapsed or resistant B-ALL include immunotherapy based on T cells (e.g., tisagenlecleucel) or antibodies (e.g., blinatumomab or inotuzumab ozogamicin). Researchers are also looking into CAR T cells (targeting CD1a, CD5, and CD7) and antibodies (such as daratumumab, which targets CD38) that can combat T-ALL. On one side of blinatumomab is a single-chain Fv fragment that binds to the CD3 antigen and triggers T-cell cytotoxicity; on the other side is a fragment that binds to the B-cell antigen CD19, which is demonstrated on the vast majority of B-ALL cells. When compared to the gold standard treatment, blinatumomab improved survival and complete remission rates in a randomised study of persons with refractory/relapsed B-ALL. What's more, blinatumomab successfully eliminated MRD. Patients with intermediate- or high-risk recurrent B-ALL, ranging in age from 1 to 30 years, were randomly assigned to either two cycles of intense chemotherapy or two cycles of blinatumomab, administered four weeks apart following re-induction chemotherapy. When comparing the two groups, the blinatumomab group showed improved

disease-free survival, overall survival, and minimal residual disease (MRD) clearance at 2 years, as well as lower rates of febrile neutropenia, infection, and sepsis [20, 21]. Reducing the disease burden before therapy can lessen the incidence and severity of blinatumomab's side effects, such as cytokine release syndrome and neurotoxicity.

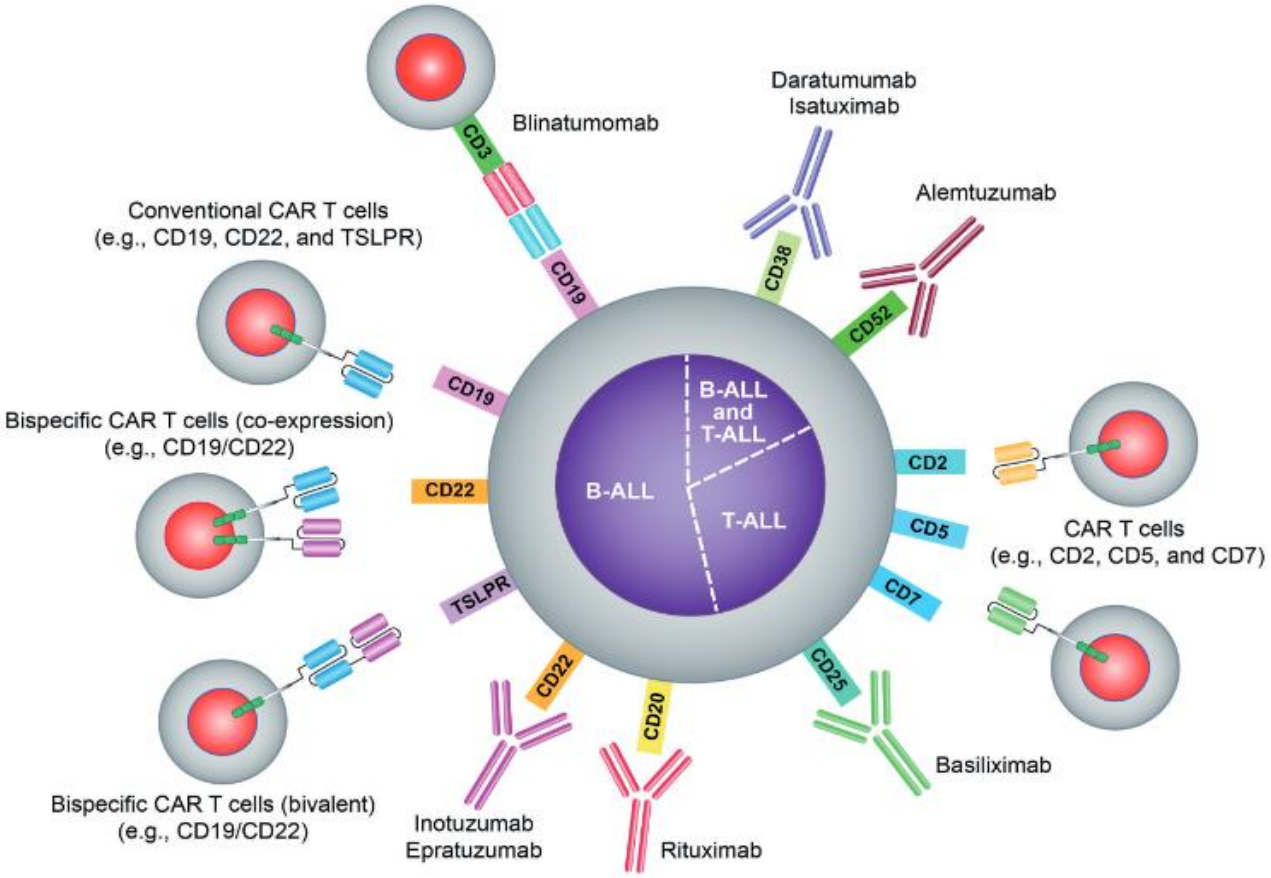

Figure 2. Immunotherapy in acute lymphoblastic leukaemia. Chimeric antigen receptor T cells, acute lymphoblastic leukaemia, and thymic stromal lymphopoietin receptor are all acronyms for "CAR T cells.

Causes of Childhood Haematological Cancers

The disease's aetiology changes depending on the person's age and where they live. There are a lot of things that contribute to the sickness in kids, either directly or indirectly. No one knows for sure what causes diseases, but researchers never stop trying to figure it out. Although the majority of cancers do not run in families, there are a few known genetic variables that increase the risk of leukaemia in children by a factor of 10 to 20. These include Down syndrome (DS), Bloom syndrome, Ataxia-telangiectasia, Nijmegen breakage syndrome, and Fanconi anaemia (FA). Two percent of all lymphomas in children and fifteen percent of all myeloid malignancies in children are caused by DS. Megakaryoblastic leukaemia is 400 times more likely in children with Down syndrome. Marrow failure, cancer, and other genetic disorders are all linked to FA. Equine gammavirus (EBV) Reasons for adults with mature B-cell ALL include human immunodeficiency virus (HIV), Helicobacter pylori (the bug that causes stomach ulcers), and human T-lymphocytotropic virus (HTLV). The proportion of HL cases confirmed by EBV testing is close to 30%.

Crucially, compared to young adults, the incidence of EBV DNA in R-S cells is higher in children younger than 14 years old. Ethnic and racial differences explain why 93% of Asian children, 86% of Hispanic children, 17% of African American children, and 46% of White children have evidence of an EBV genome. Exposure to high levels of ionising radiation either prior to birth or throughout early childhood may increase the chance of developing ALL and other types of leukaemia in children. Nearby sources of electro-magnetic radiation, such as high-voltage power lines, have been the subject of heated debate in recent years regarding their potential health implications.

Nevertheless, there is no evidence to suggest a connection between exposure to typical amounts of

electromagnetic radiation in our surroundings and childhood ALL, according to the findings of multiple large-scale worldwide research. Any type of cancer can develop after prolonged exposure to chemicals including pesticides, fertilisers, and organic solvents. Mutations in DNA can turn on or off oncogenes, which can lead to cancer [22-25]. Gene mutations can run in families (as in certain cases of childhood leukaemia) or develop at any point in a person's lifespan as a result of cellular blunders. A possible explanation for the detection of ALL in youngsters is aneuploidy. Another cause of some childhood malignancies is chromosomal translocations between the numbers 12 and 21. In rare instances, CML can result from a translocation involving 2–14 chromosomes. Another cause of cancer is a malfunction in one of the signalling pathways. Some children are predisposed to cancer because they inherit cancer-causing mutations from one or both parents. One example is Li-Fraumeni syndrome, which increases a person's risk of getting leukaemia and other malignancies due to a hereditary mutation of the TP53 tumour suppressor gene. Chromosome rearrangement, most commonly between chromosomes #8 and #14, is the most common cause of Burkitt's lymphoma. This rearrangement alters gene locations and functions, leading to unchecked cell development. In most cases, leukemia-related DNA mutations do not run in families but instead appear during pregnancy. It is possible that some of the acquired mutations happen much earlier, perhaps even before birth. Rarely, radiation or chemical exposure can cause acquired mutations, but in the vast majority of cases, there is no clear cause.

Signs and Symptoms

In order to improve patient survival rates, it is crucial to be aware of the most prevalent symptoms of the disease. This will allow for faster diagnosis, more suitable therapy, and better disease control. Symptoms manifest in the early stages of a disease because it progresses quickly. A deficiency of healthy red blood cells in the bloodstream is the most common cause of symptoms. Children should not be ignored when they have a fever of unknown origin (FUO), since fever is the most prevalent symptom. Many forms of juvenile cancer, including those that cause weight loss or other worrisome symptoms, are linked to anorexia. Fatigue, malaise, and a lack of energy are often noted as symptoms. In children diagnosed with Hodgkin lymphoma, symptoms such as night sweats, fever, and weight loss accompanied by lymphadenitis are more common. Weakness, vomiting, convulsions, headaches, issues concentrating, impaired vision, and problems with balance are symptoms that some children experience when their leukaemia spreads to the spinal cord and brain. Gum swelling, bleeding, and excruciating pain are symptoms of AML in youngsters. Leukaemia that has metastasised to the skin can cause a granulocytic sarcoma or chloroma, two types of tiny rashes characterised by black patches. Slurring of speech, fatigue, and weakness are extremely dangerous side effects of AML that are uncommon in youngsters. When there is a low platelet count, even a small cut or injury might cause excessive or protracted bleeding for no apparent reason [26, 27]. Signs of bleeding gums and noses may be observed in certain children. When bleeding occurs under the skin's surface, some of them display "petechiae," which are flat, pinhead-sized patches.

Children often experience lymphadenopathy, which can be either localised or generalised. In addition to lymphadenopathy, symptoms may include coughing up blood or shortness of breath, fever, lack of appetite, night sweats, and excessive weariness. The thymus and lymph nodes are passed by the large vein superior vena cava (SVC) as it delivers blood from various regions of the body to the heart. When lymphoma develops in this area, it presses on the superior vena cava (SVC), which causes blood to return to the veins and causes swelling in the upper chest, arms, face, and neck. It has an effect on the brain that leads to lightheadedness and unconsciousness. Medical professionals refer to this potentially fatal illness as SVC syndrome. Headaches, altered eyesight, facial numbness, and difficulty speaking are some of the symptoms that might result when the spinal cord is also damaged. A number of Lymphoma symptoms include reddening of the skin and the development of irritating nodules or lumps under the skin that may be purple or even red. The risk of cancer is highest in regions where the lymph nodes are enlarged, such as the supraclavicular and epitrochlear lymph nodes. Signs and symptoms related to the digestive system: A suspicious abdomen should prompt immediate medical attention. Most benign genitourinary tumours in babies are located in the abdomen region. Major causes in children younger than five years old include neuroblastoma and nephroblastoma. Cysts and benign tumours on internal organs such the

kidneys, ovaries, or soft tissues are also included in the differential diagnosis. Ultrasound was used to further investigate abdominal masses and any degree of hepatosplenomegaly, especially when these conditions were linked to symptoms such as vomiting with headache or neurological issues, anorexia, discomfort, fever, and anorexia without headache. Discomfort with bowel regularity can be caused by a spinal cord lesion in the sphincters of intestine or a bowel obstruction [28, 29]. Leukaemia and lymphoma are two diseases that can cause diarrhoea. Musculoskeletal symptoms: One of the most common indications of cancer is persistent or intermittent pain in the bones. Localised pain and oedema are symptoms of a bone tumour. It is possible to assess the patient's condition with the use of two-view site-specific radiography, C-reactive protein assay, and full blood analysis. Patients with neuroblastoma and leukaemia often experience arthritic-like symptoms and widespread bone discomfort. Some patients may get abnormal giat due to different types of cancer. In rare cases, cancer patients may experience unusual symptoms such as back pain, kyphoscoliosis, lordosis, and torticollis. Osteosarcoma, Ewing sarcoma, and histiocytosis are additional causes of fractures seen in youngsters.

Characteristics of the cardiovascular system and the respiratory system There is a relatively small correlation between cardiorespiratory symptoms and cancer. Lymphoma or leukaemia could be the cause of your dyspnoea and cough if they last longer than two to three weeks and are unresponsive to medicines. Rarely seen in children, hypertension symptoms are often linked to neuroblastoma, Wilms tumour, and pheochromocytoma. A buildup of leukaemia cells in the tiny blood veins of the lungs is another symptom of a very high white blood cell count that can make it difficult to breathe. If you have leukaemia or hystiocytosis, you may notice swelling or bleeding in your gums as a result of gum infiltration. Middle ear histiocytosis, rhabdomyosarcoma, and nasopharyngeal cancer are among the causes of chronic otorrhea in children. Nasal blockage, difficulty swallowing, and epistaxis can be symptoms of carcinoma of the nasopharynx or another type of tumour. Symptoms related to the skin: There are visible symptoms such as paleness, blisters, and bruises. Leukaemia, neuroblastoma, and histiocytosis are among conditions that can cause subcutaneous nodules to appear bluish. Another unusual symptom of Hodgkin's lymphoma is pruritus. A scaly eczematoid rash that doesn't go away with corticosteroids can also be seen; it spreads to the inside of the ear, the belly, the scalp, and parts of the face and neck. Diabetic insipidus (polyuria, polydipsia), growth arrest, precocious puberty (Adrenal tumours, central nervous system tumours, human chorionic gonadotropin-secreting germ cell tumours, rhabdomyosarcoma), and pubertal delay (pituitary tumours) are the most common endocrine symptoms associated with childhood malignancies. The symptoms mentioned above can be caused by tumours in the brain, which can lead to hypopituitarism, or by tumours in the germ cells that secrete hormones. Neoplasms of the hypothalamic-optic chiasmatic region are related with diencephalic syndrome, an extremely rare cause of stunted growth in infants and toddlers.

Occular Symptoms

You should pay close attention to a number of eye problems right away. Diplopia and squinting are noted. Retinoblastoma patients may experience leukokoria, often known as the cat's eye response, while patients with orbital space-occupying tumours (such as rhabdomyosarcoma, optic glioma, histiocytosis, or leukaemia) may face proptosis. Rarely, neuroblastoma can manifest with opsoclonusmyoclonus syndrome, Horner syndrome, acquired heterochromia of the iris, or periorbital ecchymoses ("raccoon eyes"). The presence of Aniridia could be linked to Wilms tumour.

Genitourinary Symptoms

Patients with cancer often experience blood in urine. The condition known as enuresis or urine retention can be a sign of a tumour in the spine or pelvis. Prepubescent girls who experience vaginal bleeding may be suffering from a hormone-secreting germ cell tumour or vaginal rhabdomyosarcoma. Isolated varicocelen on the right side can indicate priapism, leukaemia, or a tumour in the right kidney. Genomic analysis: Molecular diagnostics rely heavily on genomes, DNA and RNA testing, and plays an important part in the diagnosis of haematological malignancies. Our understanding of the biology of haematological neoplasms has been considerably enhanced over the last 20 years, thanks to a knowledge boom that has translated into highly sophisticated laboratory assays. Almost all of the symptoms that are found in cancer patients are also

seen in people with regular infections. Because of this, the only way to treat the illness is with a definitive diagnosis. To get to the bottom of the symptoms, doctors run a battery of tests and exams. In order to diagnose childhood cancer, doctors take a blood and bone marrow sample. If the diagnosis is confirmed, additional tests will be required to establish the type of cancer, the severity of the disease, and the best course of treatment. In most cases, morphological examination aided by molecular markers is used to diagnose haematological malignancies. Gene expression profiling and other modern approaches have been useful in understanding biology and clinical variety. Here, microarrays are utilised to simultaneously evaluate the expression of several genes inside the tumour sample. Cancers are classified using a variety of analytical methods based on gene expression profiling study results. A number of chromosomal abnormalities have been identified as potential causes of childhood cancer, including leukaemia. In particular, the majority of the case studies demonstrated the importance of chromosomal translocations. Leukemic cell shape and chromosome count can be better understood with the use of cytogenetic assays. Because leukemic blast cells contain chromosomal defects, they do not pass them on to children. Favourable cytogenetics refers to a set of cytogenetic abnormalities that improve outcomes, whereas unfavourable cytogenetics describes a set of abnormalities that increase the likelihood of recurrence [30]. Childhood ALL cases with high risk cytogenitical characteristics are uncommon.

It is also possible to examine chromosomes using in situ hybridisation (ISH) by affixing fluorescent dyes to DNA and then seeing the resulting micrographs. Researching translocations in samples of blood and bone marrow is a speciality of fluorescent in situ hybridisation, or FISH.

Immunophenotyping confirms a diagnosis of myeloid neoplasms like AML, whereas cytogenetics and molecular testing determine the underlying causes. AML can develop as a result of genetic predisposition or as a secondary cancer after chemotherapy or other chemical exposures. Patients are grouped into three risk categories—poor, moderate, and favorable—based on cytogenetic analysis. Molecular testing is the gold standard for those with an intermediate risk. The NCCN and WHO both favour the analysis of genes such as FLT3, NPM1, and CEBPA. Different forms of myeloid leukaemia have different diagnostic tools; for example, APL is the gold standard for pro myelocytic leukaemia (www.nccn.org). Chromosomal translocations 9, 22, and the Philadelphia chromosome are the known causes of chronic myeloid leukaemia (CML). Tests like cytogenetics, FISH, or PCR can identify this. Cancer of the blood (CML) patients often have the BCR/ABL fusion gene targeted. RT-PCR is used to track CML levels and tyrosine kinase inhibitor medications are used for treatment. The use of highly sensitive assays allows doctors to detect illness recurrence or treatment failure at an early stage.

Childhood lymphoid neoplasms: ALL and other lymphoid neoplasms are more common in youngsters. When doctors have doubts about a child's leukaemia diagnosis, they typically conduct regular testing including blood smears and blood counts. Leukaemia is suspected when there are too many white blood cells, not enough red blood cells, low haemoglobin, too few platelets, and too few neutrophils. Additionally, children with cancer often have abnormal blast cells in their blood. After that, cells from the bone marrow are examined. Bone marrow aspiration is necessary for the development of a treatment plan in children with abnormal blood cell counts and symptoms associated with leukaemia. Bone marrow aspiration and biopsy are the two most common ways to collect samples of bone marrow. To do an aspiration, a sample is taken from the back of the hip bone and then examined. Following aspiration, which involves the removal of a tiny sample of bone and bone marrow, a biopsy is typically conducted. An overabundance of blast cells in bone marrow is a sure sign of cancer. In healthy bone marrow, the percentage of blast cells is typically around 5%, but it can rise to 20-100% in cases of abnormalities. Another reason for these tests is to see how well patients are responding to treatment. If complicated genetic abnormalities or translocations are present, a bone marrow test will detect them. Immunophenotyping is crucial in lymphomas because it directs the selection of molecular tests including IGVH, targeted FISH, and T-cell clonality analysis. The best way to treat leukaemia is to do this test, which uses special markers called antigens on blast cell surfaces to determine the specific subtype of the disease. Flow cytometry is the method used to conduct the test. Cells extracted from bone marrow, blood, and other bodily fluids as well as lymph nodes can undergo this procedure. Flow cytometry may also

be used to measure the DNA content of cancer cells; this is useful since leukaemias with cells that contain a higher DNA content tend to respond better to chemotherapy. In addition to detecting little residual disease, flow cytometry can track a patient's reaction to treatment.

Cancers of the Blood and Lymph:
Leukaemia Staging:

Improving treatment efficacy and prognosis depends on accurately diagnosing the type of leukaemia. Importantly, the size and spread of the tumour determine the stage of the cancer, which in turn determines the type of leukaemia (acute, chronic-lymphoid, myeloid). The leukaemia cell line quickly multiplies after originating in the bone marrow and entering the bloodstream. Consequently, it is crucial to determine whether leukemic cells have begun to accumulate in significant organs such as lymph nodes, the liver, the spleen, the reproductive organs, and portions of the central nervous system. If one is familiar with staging, they can undergo extensive treatment after an early diagnosis. ALL: The French-American-British (FAB) group divided ALL into three subtypes, L1, L2, and L3, according to their morphology. The nucleus to cytoplasm ratio is high in L1 lymphoblasts, which are tiny cells. The nucleus is not visible, and the nuclear membranes are either spherical or cleft shaped; the cytoplasm is tiny and pale blue in colour. Large L2 lymphoblasts with a lower nucleus cytoplasmic ratio, conspicuous nuclei, and uneven nuclear membranes are distinguishable from smaller, earlier lymphoblasts. L3 cells have deep basophilic cytoplasm and significant vacuolization, like Burkitt leukaemia cells. The prevalence of L1 morphology was around 85% in ALL children, 14% in L2 patients, and 1% in L3 patients. Leukaemia classification relies more on immunophenotypic and cytoplasmic marker research. Depending on the level of differentiation, monoclonal antibodies and the fluorescence-activated cell sorter (FACS) technology divide ALL patients into two groups: T cells and B cells. Only 2% of cases are B-cell ALL, which is characterised by the presence of IgM on its surface. Early, intermediate, and late stages of differentiation are used to classify T-cell ALL.

AML is a rapidly developing malignancy that falls under two classification systems: FAB and WHO. A wide variety of cells, such as myeloblasts, monoblasts, erythroblasts, and megakaryoblasts, can proliferate in malignancy. The FAB method classifies it into seven distinct phases, M0 through M7, according on the shape of the cells.

Methods for Treatment :

Following a cancer diagnosis, a thorough evaluation of the disease's kind, severity, and potential treatments is conducted. Chemotherapy is the mainstay in the treatment of haematological malignancies in children. Based on the current state of patients, a wide variety of additional treatments are utilised.

1. Chemotherapy: This treatment modality involves the administration of anticancer medicines. Chemotherapy is effective against cancer and leukaemia because most of the medications used in the treatment are cytotoxic, meaning they kill cells. The exact illness, the child's age, overall health, and treatment procedure dictate the dosing, timing, and kinds of medications utilised. Combination chemotherapy refers to the administration of multiple medicines at once during chemotherapy. These medications kill leukemic cells in various methods, some of which work simultaneously. It is common practice to administer chemotherapy in multiple cycles, with intervals in between. Spaces provide a kid's body, and the bone marrow especially, a chance to heal from the negative consequences. There are a variety of methods for administering chemotherapy, including the use of pills or liquids for oral administration, as well as intravenous, intramuscular, or subcutaneous injections. To stop tumour cells from spreading to the CNS, it is also administered intrathecally (IT) or into the spinal fluid (SSF) via a lumbar puncture. Central venous catheters, often known as central lines or portacaths, or infusaports, are the most common entry points for intravenous medication administration. Surgically placed into a big vein in the patient's arm, neck, or chest, these are introduced through the skin. A variety of cathetars are utilised, including those designed for short-term and long-term use.

Treatment of childhood leukaemia by surgery is extremely limited. Leukaemia cells metastasise (spread) through the blood to other organs, including the bone marrow, making surgical treatment ineffective. Since leukaemia is typically diagnosed with a bone marrow aspirate and biopsy, surgery can occasionally play a useful role in the diagnostic process. Surgery is often necessary prior to the initiation of chemotherapy. It is occasionally

necessary to remove a child's testicles during surgery if their leukaemia relapses in that area.

Thirdly, radiation therapy can eradicate cancer cells by use of high-energy ionising radiation. Damage to the cell's DNA and its capacity to divide are the results. Normal cells can repair themselves and keep their normal activities in shorter time with ease, therefore killing abnormal cells with least effect on them is still the goal, even though the process damages healthy cells along with tumour cells. Among the several radiation procedures available are: 1. Fractionation

2. 3D conformal radiation therapy (3DCRT)

Three, IMRT, or intensity-modulated radiation treatment

Fourth, IGRT, or image-guided radiation therapy

5. SBRT, or stereotactic body radiotherapy

Problems Occurring After Treatment

In recent decades, there has been an improvement in the survival rates of children diagnosed with leukaemia or lymphoma. Due to therapy, which may take months or even years, some of these survivors may have few complications. Malignancy treatments like leukaemia and lymphomas aim to destroy tumour cells, but they can occasionally harm healthy cells as well. This effect can cause secondary malignancies to emerge in later life, disrupt normal development, and affect the appropriate functioning of a person's organs and tissues. After therapy, only a small percentage of children may experience long-term or severe side effects. Treatment kind and duration are two variables that can impact the child by raising the risk of treatment-related complications. How old the kid is when they start receiving treatment. Body part attended to. The gender of the kid. Health in general for the youngster.

There are two types of side effects that can occur as a result of medical treatments: those that are considered "long-term effects" and those that are considered "late effects," which do not manifest for quite some time following therapy. Among the consequences are: Decrease in red blood cell count: Chemotherapy is classified as myelosuppressive when it inhibits the body's ability to produce red blood cells, either directly or indirectly. Chemotherapy can have the following adverse effects on various types of blood cells. Most diseases and disorders cause a decrease in haemoglobin and red blood cell counts, a condition known as anaemia. As a result, the youngster experiences symptoms such as increased weakness, fatigue, and lethargy, as well as headaches, shortness of breath, pale complexion, rapid heartbeat, and temperature changes. This occurs because, for a short period of time, chemotherapy can cause myelosuppression, which means that it stops the bone marrow from making blood cells. Because of this, treatment is postponed or the amount of chemotherapy drugs is reduced. Neutropenia is the condition Another symptom is a drop in the number of neutrophils, the main kind of white blood cell, which is defined as 1X109/L or below 1. This is a major health concern because neutrophils are responsible for fighting infections. There has to be a decrease in chemotherapy dosage as a result of the lower Absolute Neutrophil Count (ANC) ratio. The most common signs of an infection in children include a high temperature, chills, and a generally sickly appearance. Neupogen, neulasta, and leukine are a few of the medications that can be used to manage this illness. The immune systems of the majority of the children undergoing chemotherapy do not work as intended, leading to infections. The youngster becomes ill as a result of an invasion of numerous bacteria, viruses, and fungus. A child's condition can deteriorate rapidly due to infections. Antibiotics are used to treat children who experience fever and chills. Infection can occur for a variety of causes, including: Youngsters' contact with sick individuals Potential entry points for microbes into the body through surface wounds. Complications, such pneumonia, have caused problems to emerge. Sores in the mouth, throat, and intestines allow the body's naturally occurring germs to enter the bloodstream.

In addition to the issues already mentioned, a decrease in platelets was also noted, which makes bruising and bleeding more common. Problems with constipation, a hard toothbrush, or nosebleeds can all cause hard bowel movements, which can contribute to bleeding gums. Platelet transfusion may be necessary in some instances. Patients often experience a low platelet count for 7–10 days after chemotherapy begins, and it takes many days to weeks for the body to achieve appropriate levels.

Gene Transfer for Immunotherapy: CAR and TCR

In order to steer effector immune cells away from TAAs, synthetic T-cell receptors (TCR) have been developed. High affinity artificial TCRs generated from α and β chains obtained from patients were

introduced into engineered T-cells. One kind of chimeric T cell receptor is the chimeric antigen receptor (CAR), which gets its extracellular domain from an antibody that is coupled to a T-cell domain. T cells are isolated from the patient's blood and modified in a lab so that they express certain receptors as part of this treatment [31]. By binding to proteins on the surface of leukaemia cells, these receptors can trigger a specific immune response from T-cells that are subsequently expanded in a lab and reinfused into the patient. This method has demonstrated encouraging outcomes against certain advanced instances of ALL in preliminary clinical studies. Extremely low blood pressure and extremely high fevers were among the severe side effects reported in youngsters receiving this medicine. Controlling these adverse consequences is a primary area of research, and progress is being made in this direction. Only a few number of prominent healthcare facilities now offer CAR T-cell treatment through clinical studies.

Concentrated Treatment Although conventional cancer treatments like radiation, chemotherapy, and surgery are still in use, newer protocols such as immunotherapy and molecular directed therapy (targeted therapy) have greatly improved treatment efficacy by reducing nonspecific toxicity caused by chemotherapeutic drugs. Among the most significant treatments for acute promyelocytic leukaemia (APL) and acute myeloid leukaemia (AML) is targeted therapy. An APL treatment using all-trans-retinoic acid (ATRA) resulted in a 70-80% cure rate or disease-free survival rate. The expression of the PML/RAR-α fusion transcript on chromosome 15 of the PML gene determines the intensity of ATRA, which differentiates APL blasts. Capillary leak syndrome is a serious issue that can be treated with chemotherapy or corticosteroids. It comes with adverse effects such as cardiac/respiratory failure, fever, and renal impairment. Only a quarter of people with an elevated white blood cell count experience this issue. Additionally, a combination of ATRA and gemtuzumab ozogamicin (GO), an antibody conjugated with calicheamicin (a plant cytotoxic antibiotic), was discovered to induce a response against the CD33 marker, which is expressed by 90% of leukemic blasts. Because GO causes deadly hepatic venoocclusive disease when used alone or with other drugs, researchers are trying to figure out how to incorporate it into induction and consolidation treatments. There are a number of mutations and translocations that contribute to AML, and these could be the focus of directed therapy. The focus shifts to AML blasts, which exhibit an up-regulation of tyrosine kinases as a result of mutations. Leukemic blast replication is enabled by some of the tiny compounds that lead to blocking signalling pathways. Mutations in c-kit and flt3, which are blocked by drugs like SU5416 and SU6668, are the most common in AML. Some proteins, including as Ras proteins, activate downstream of tyrosine kinases when they are influenced by the enzyme farnesyl transferase. Tipifarnib is the first line of defence against AML because it inhibits farnesyl transferase [32], an enzyme that has been associated with relapse in some individuals. Intense chemotherapy regimens, stem cell transplantation, and comprehensive supportive care have all contributed to advancements in the treatment of acute lymphoblastic leukaemia (ALL). Additional progress has been achieved by the use of antibody treatment and molecular targeting with kinase inhibitors. When used in conjunction with cyclophosphamide, vincristine, dexamethasone, and doxorubicin, rituximab effectively targets the CD20 marker, which has been shown to be useful in treating B-cell ALL and Burkitt's lymphoma.

Variation in response was also observed for other surface antigens that antibodies target, including as CD19, CD22, CD25, and CD 52. In chronic myeloid leukaemia (CML), a tyrosine kinase protein called BCR-ABL is inhibited. One of the most important medicines that acts as a signal transduction inhibitor is imatinib mesylate. After the failure of INF-α therapy, imatinib was Side effects of imatinib include headache, rash, nausea, diarrhoea, myelosuppression, and fluid retention; nonetheless, it was discovered to increase survival rate. Researchers are looking at ways to enhance molecular remission, such as using high dosage treatment. cancer that is not Hodgkin's A cure rate of over 75% has been achieved by the use of radiation treatment and multidrug chemotherapy. Increases in patient survival have resulted from the introduction of targeted therapy, which is based on a knowledge of cancer cell biology and its microenvironment.

Conclusion:

The taxonomy of ALL has been greatly revised by comprehensive sequencing and integrated genomewide analysis, leading to the discovery of novel entities with therapeutic and prognostic implications. Diverse genetic abnormalities in ALL converge on particular pathways, each of which

causes a unique pattern of gene expression. Clinical diagnostic workup for ALL must use gene expression techniques to identify these pathways, which are critical for therapeutic targeting. Drug sensitivity testing of panels of chemotherapeutic drugs ex vivo and functional genomic screens are two examples of mutation-agnostic methods that show promise for discovering new therapeutic vulnerabilities and effective combinations.149 Improving patient survival and reducing side effects would be the ultimate goal of such an intervention, which would lead to new therapeutic regimens that incorporate immunotherapy, reduced-intensity conventional chemotherapy, and personalised mutation-directed targeted therapy. Blood cancers account for almost 40% of all childhood cancers. One of the major achievements of the twentieth century is the substantial improvement in the treatment of these types of cancer. There have been tremendous advancements in the treatment of most childhood cancers, with acute lymphoblastic leukaemia (ALL) being the most notable. More than 80% of children survive childhood thanks to improvements in the last several decades. Clinical trials carried out by many research groups, including those specialising in paediatrics and oncology, have contributed to these advancements. These were complemented by the substantial contributions made by the discovery of efficient therapeutic agents when combined with different chemotherapeutic drugs. Cure rates for non-lymphoblastic leukaemia have barely reached 50%, despite the overall survival rate of malignancies improving to 90%. Additionally, stem cell transplantation and other intensified regimens have improved outcomes; yet, contemporary therapies are linked to several acute and late complications, and related consequences seem to be on the rise. Haematological cancers can be better treated and patients can have a better chance of survival if our knowledge of the genes and processes that cause them grows. Advances in molecular biology have greatly enhanced our capacity to detect and prevent illness recurrence, monitor how patients react to various treatment plans, make more accurate predictions about their prognoses, and personalise their treatments. In order to develop effective treatments for subsets of children with haematological malignancies, the paediatric oncology and allied research communities must first identify and confirm the most significant therapeutic targets.

References:

1. Noetzli L, Lo RW, Lee-Sherick AB, et al. Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia. Nat Genet. 2015;47(5):535-538.
2. Mullighan CG, Goorha S, Radtke I, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007;446(7137):758-764.
3. Gu Z, Churchman ML, Roberts KG, et al. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nat Genet. 2019;51 (2):296-307.
4. Churchman ML, Qian M, Te Kronnie G, et al. Germline genetic IKZF1 variation and predisposition to childhood acute lymphoblastic leukemia. Cancer Cell. 2018;33(5):937-948.
5. Kuehn HS, Boisson B, Cunningham-Rundles C, et al. Loss of B cells in patients with heterozygous mutations in IKAROS. N Engl J Med. 2016;374(11):1032-1043.
6. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature. 2008;453(7191):110-114.
7. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009;360(5):470- 480.
8. Zhang J, McCastlain K, Yoshihara H, et al. Deregulation of DUX4 and ERG in acute lymphoblastic leukemia. Nat Genet. 2016;48(12):1481-1489.
9. Brown AL, Arts P, Carmichael CL, et al. RUNX1-mutated families show phenotype heterogeneity and a somatic mutation profile unique to germline predisposed AML. Blood Adv. 2020;4(6):1131-1144.
10. Feurstein S, Godley LA. Germline ETV6 mutations and predisposition to hematological malignancies. Int J Hematol. 2017;106 (2):189-195.
11. Gocho Y, Yang JJ. Genetic defects in hematopoietic transcription factors and predisposition to acute lymphoblastic leukemia. Blood. 2019;134(10):793-797.
12. Papaemmanuil E, Hosking FJ, Vijayakrishnan J, et al. Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with

risk of childhood acute lymphoblastic leukemia. Nat Genet. 2009;41(9):1006-1010.
13. Trevino LR, Yang W, French D, et al. Germline genomic variants associated with childhood acute lymphoblastic leukemia. Nat Genet. 2009;41(9):1001-1005.
14. Perez-Andreu V, Roberts KG, Harvey RC, et al. Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse. Nat Genet. 2013;45(12):1494-1498.
15. Qian M, Xu H, Perez-Andreu V, et al. Novel susceptibility variants at the ERG locus for childhood acute lymphoblastic leukemia in Hispanics. Blood. 2019;133(7):724-729.
16. Qian M, Zhao X, Devidas M, et al. Genome- wide association study of susceptibility loci for T-cell acute lymphoblastic leukemia in children. J Natl Cancer Inst. 2019;111 (12):1350-1357.
17. de Smith AJ, Lavoie G, Walsh KM, et al. Predisposing germline mutations in high hyperdiploid acute lymphoblastic leukemia in children. Genes Chromosomes Cancer. 2019;58(10):723-730.
18. Pouliot GP, Degar J, Hinze L, et al. Fanconi- BRCA pathway mutations in childhood T- cell acute lymphoblastic leukemia. PLoS One. 2019;14(11):e0221288.
19. Winer P, Muskens IS, Walsh KM, et al. Germline variants in predisposition genes in children with Down syndrome and acute lymphoblastic leukemia. Blood Adv. 2020;4(4):672-675.
20. Greaves M. Pre-natal origins of childhood leukemia. Rev Clin Exp Hematol. 2003;7(3):233-245.
21. Grulich AE, Vajdic CM, Falster MO, et al. Birth order and risk of non-hodgkin lymphoma—true association or bias? Am J Epidemiol 2010; 172(6): 621-30.
22. Carozza SE, Li B, Wang Q, Horel S, Cooper S. Agricultural pesticides and risk of childhood cancers. Int J Hyg Environ Health 2009; 212(2): 186-95.
23. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006; 107(1): 265-76.
24. Li J, Thompson TD, Miller JW, Pollack LA, Stewart SL. Cancer incidence among children and adolescents in the United States, 2001-2003. Pediatrics 2008; 121(6): e1470-7.
25. Burkhardt B. Paediatric lymphoblastic T-cell leukaemia and lymphoma: one or two diseases? Br J Haematol 2010; 149(5): 653-68.
26. Bolarinwa RA, Ndakotsu MA, Oyekunle AA, Salawu L, Akinola NO, Durosinmi MA. AIDS-related lymphomas in Nigeria. Braz J Infect Dis 2009; 13(5): 359-61.
27. Kuriakose P. Targeted therapy for hematologic malignancies. Cancer Contr 2005; 12(2): 82-90.
28. Caryn E. Sorge, Jenny K. McDaniel and Ana C. Xavier. Targeted Therapies for the Treatment of Pediatric Non-Hodgkin Lymphomas: Present and Future. Pharmaceuticals 2016; 9: 28.
29. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. JAMA 2003; 290(12): 1583-92
30. Gurney JG, Kadan-Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 2003; 97(3): 663-73.
31. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 2001; 19(13): 3163-72.
32. Mertens AC, Yasui Y, Liu Y, et al. Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study. Cancer 2002; 95(11): 2431-41.
33. Wallace WH, Blacklay A, Eiser C, et al. Developing strategies for long term follow up of survivors of childhood cancer. BMJ 2001; 323(7307): 271-4.