Journal Homepage: - www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI: 10.21474/IJAR01/9954
DOI URL: http://dx.doi.org/10.21474/IJAR01/9954
ISSN NO. 2320-5407

RESEARCH ARTICLE

A REVIEW ARTICLE OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA.

Ghaida'a Saleh Almohammadi.
MBBS, Medical Intern, College of Medicine, Taibah University, Saudi Arabia.

Manuscript Info

Manuscript History
Received: 18 August 2019
Final Accepted: 20 September 2019
Published: October 2019

Key words:-
Childhood acute lymphoblastic leukemia; incidence; risk factors; treatment; long-term outcomes.

Abstract

Background: Childhood acute lymphoblastic leukemia is a malignant disorder that originates in a single B or T lymphocyte progenitor. Worldwide, it is the most common childhood cancer. It accounts 25% of all childhood cancers and approximately 75% of all cases of childhood leukemia. Although contemporary treatments have been effective in curing more than 80% of children with acute lymphoblastic leukemia; however, some patients develop fatal acute and delayed complications as a result of side effects from the medications requiring more aggressive management.

Objective: Detect the recent incidence of childhood acute lymphoblastic leukemia and causes of that. Also discuss the treatment strategies of childhood acute lymphoblastic leukemia and their late possible effects.

Methods: The data was collected from PubMed, Medline, SDL, Up to date and Springer databases. The search terms were childhood acute lymphoblastic leukemia, incidence, classification, biology, pathophysiology, clinical manifestations, causes, risk factors, treatment, survival rate, long-term outcomes, worldwide and Saudi Arabia.

Conclusion: Childhood acute lymphoblastic leukemia incidence rates are generally higher in developed than in developing countries. The risk factors of childhood acute lymphoblastic leukemia are environmental and genetic factors. The late effects of acute lymphoblastic leukemia treatment mainly are increasing of cardiovascular morbidity and mortality, neurocognitive impairment, endocrine dysfunction and metabolic abnormalities. There are multiple new treatments that might improve the overall response of patients like molecular therapies that target genetic abnormalities of the leukemic cells and their affected signaling pathways.

Introduction:-

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer worldwide. It accounts for 25% of all childhood cancers and approximately 75% of all cases of childhood leukemia.[1,2] In Saudi Arabia childhood ALL accounting 71.1% in male and 70.8% in female of all types of leukemia.[3] All over the world incidence of childhood ALL is higher among male than female.[4,5] The highest incidence rate appears in the birth to age 4 years group.[6]

Corresponding Author:-Ghaida'a Saleh Almohammadi.
Address**:**-MBBS, Medical Intern, College of Medicine, Taibah University, Saudi Arabia.

In this research we will answer the following questions:
1. What the risk factors and pathophysiology of childhood ALL?
2. What the management of childhood ALL?

This type of cancer is very important to study it because high incidence of occurrence and the age of occurrence, especially Saudi Arabia because 37.2% of the population is under 14 years of age.[1,3] Subsequently, the majority of the population are at risk of childhood cancer specifically ALL.[6]

Objectives:-

1. Detect the incidence of childhood ALL worldwide and in Saudi Arabia.
2. Recognize the classification of childhood ALL and the most common type.
3. Describe the biology and pathophysiology.
4. Determine the causes and the risk factors of childhood ALL.
5. Discuss the management of this type of cancer.
6. Find methods to increase the survival rate and improve prognosis in children with ALL.

Methodology:-

The data was collected from PubMed, Medline, SDL, Up to date and Springer databases. The search terms were childhood acute lymphoblastic leukemia, incidence, classification, biology, pathophysiology, clinical manifestations, causes, risk factors, treatment, survival rate, long-term outcomes, worldwide and Saudi Arabia. Journal articles were retrieved from diverse fields: epidemiology, biomedical research, hematology, pediatric, oncology and cancer prevention.

Review:

1. Different subtypes of ALL were identified based on their genetic lesions such as: their lineage (T- versus B-cell), chromosome number, or the presence or absence of chromosomal translocations. These genetic lesions account for about 75% of ALL patients, and they significantly influence the approach of the treatment. [7]
2. In Saudi Arabia, the precursor B-cell lymphoblastic leukemia and precursor T-cell lymphoblastic leukemia are account for 37.8%, 44.5% in male and female, and 9%, 4.5% in male and female subsequentlly.[3]
3. The subtype of precursor B-cell ALL is more prevalence among children with Down syndrome.[8] Prevalence of ALL is increased in children with some congenital anomalies.[9] Results of study find the congenital anomalies are increased in siblings and maternal family of ALL patients.[10]
4. Although, the environmental risk factors play a role in development of ALL, but in most cases exhibited no obvious evidences associate these factors with leukemogenesis. For example, the incidence of ALL among children of high socioeconomic status is higher than others and has been associated with a delayed exposure to common childhood infections.[11]

Reported childhood leukemia incidence in England and Wales continues to be higher in relatively wealthy communities. Possible explanations include under-diagnosis of leukemia in children from poor community.[12] Fortunately, another study assumes that folate supplementation during pregnancy decreases the risk of childhood ALL.[13] Treatment of ALL has 4 stages. First stage is induction (to attain remission) therapy, second stage is intensification (consolidation), Third stage is central nervous system (CNS) prophylaxis or CNS preventive therapy and fourth stage is maintenance therapy.[14] The most intensive form of treatment for ALL is allogeneic hemopoietin stem-cell transplantation. Nonetheless, allogeneic transplantation clearly benefits several subgroups of patients with high-risk ALL, such as individuals with Philadelphia chromosome-positive disease and those with a poor initial response to treatment.[15] Findings of study suggest that outcome among high-risk pediatric patients with ALL after hematopoietic stem-cell transplantation was not affected by donor type either sibling donors or matched unrelated donors.[16]

Recently, greater than 95% of newly diagnosed children who have ALL achieve a complete remission of leukemia.[9] Although the 5-year event-free survival rates of childhood ALL increased to 82%[17], many studies have yielded that survivors of childhood ALL exhibit early mortality and morbidity. Survivors who treated with radiation therapy or had a leukemia relapse are at greatest risk for adverse outcomes.[18] Also survivors are at significant risk of cardiovascular events, obesity, growth hormone deficiency, insulin resistance, muscle weakness, peripheral neuropathy, impaired balance & neurocognitive impairment.[19]

Incidence

Childhood ALL is an acute form of leukemia. It accounts for one fourth of all childhood cancer and three fourth of all newly diagnosed leukemia[14.] Childhood cancer incidence rates are generally higher in developed than in developing countries. It is probably due to the difficulty of measuring the incidence accurately in developing countries, where cases are often unreported due to the greater rate of deaths from infectious diseases and malnutrition. However, the great majority of children, and 80% of children with cancer lives in developing countries.[1]

Several studies have reported that the incidence of childhood leukemia increases specially in England, Wales[12] and Canada. [20, 21]

Risk factors

Despite the prevalence childhood ALL worldwide, there are only few known risk factors such as: sex, age, race, exposure to ionizing radiation, and some congenital diseases, like Down syndrome and neurofibromatosis. Some researchers suggest that this type of cancer is mainly due to environmental rather than genetic risk factors. Some investigators confirmed that exposure to magnetic fields < 0.4 micro Tessla, pesticides, solvents, benzene are considered important environmental risk factors, as well as maternal alcohol consumption, contaminated drinking water, infections, and high birth weight.[22,23]

A meta-analysis was performed to investigate the association between maternal solvent, paint, petroleum exposure, as well as smoking during pregnancy and risk of childhood ALL. This study revealed significant association between these materials and risk of childhood ALL.[24] While other study revealed that no association between maternal infection during the pregnancy and risk of leukemia.[25]

Some investigators reported that children with Down syndrome exhibit increased in risk of ALL.[8] Also another study showed no increase in risk of relapse in children with Down syndrome but the survival and event free survival were lower in comparing with other children.[26] Parallel to these results, a recent study at King Abdulaziz Medical City regarding this issue found significant association between genetics lesions and development of childhood ALL particularly among children in industrialized countries, probably due to some industrial pollutants.[27]

Pathophysiology

Childhood ALL is a malignant cancer that arises from recurrent genetic alterations that block precursor B- and T-cell differentiation and drive aberrant cell proliferation and survival. ALL is characterized by the accumulation of malignant, immature lymphoid cells in the bone marrow and, in most cases, also in peripheral blood.[28]

Signs and symptoms

The signs and symptoms of ALL are variable and they are mainly due to infiltration of blasts in the bone marrow, lymphoid system, and extramedullary sites, such as the CNS, but the majority of patients present with a sudden onset of fatigue, or spontaneous bleeding. Malaise, lethargy, weight loss, fevers, night sweats, as well as bone and joint pain due to infiltration of blast cells in the marrow cavity and periosteum. These symptoms more frequently in children than adults. Young children may have also difficulty in walking [29.30]

Treatment and late effect

Many studies have shown that, childhood ALL treatment is composed of four main components: remission induction, consolidation, continuation, and treatment of subclinical CNS leukemia. The only exception is B cell ALL, that requires a specific therapy with high-dose cyclophosphamide, methotrexate, cytarabine and intensive intrathecal therapy. [31]

More than 80% of children with ALL have been cured by using that previous treatment; however, 20 % of patients developed acute and delayed complications as a result of side effects from the medications.[32] For this reason, some researches reached for multiple new treatment that might improve the prognosis in children with ALL. These include new anti metabolites and nucleoside analogues, changing the formulations of known chemotherapeutic agents, molecular therapies targeting the leukemic cells genetic composition and their affected signaling pathways as well as monoclonal antibodies against leukemia-associated antigens.[32] Furthermore, allogeneic hemopoietin stem-cell transplantation is the most promising form of the new treatment strategies. This treatment is of benefit to those subgroups of patients with an increased risk of developing ALL, such as individuals who show poor response to

initial treatment and children with Philadelphia chromosome-positive disease.[15, 16] On the other side, children with T-cell ALL is best treated with stem-cell transplantation. [33] A recent study has suggested that the rational combination therapies may reduce the toxicity and lead to synergistic antileukemic activity.[34] While other investigators have reported that the effective treatment for patients with non-high-risk ALL is the combination of IV medium high-dose methotrexate (2 g/m2 times three), triple intrathecal therapy in the first year of maintenance treatment, the use of dexamethasone for induction and pulses during maintenance treatment.[35] For childhood ALL, Berlin-Frankfurt-Munster and Dana-Farber Cancer Institute consortia's treatment strategies are widely applicable. A previous study compared the monetary costs and health effects of hospital treatments for these two treatment strategies for 2 years, and they found that there was no difference in both treatment protocols. So current Berlin-Frankfurt-Munster or Dana-Farber Cancer Institute strategies should represent conventional therapy for the next economic evaluation of treatments for childhood ALL.[36]

Various late effects of the treatment are nowadays well acknowledged, and the survivors have increased cardiovascular morbidity and mortality. While the treatment of ALL may have direct toxic effects on various organ systems, lifestyle factors affect the cardiovascular risk of the survivors as well.

There is a previous study of 16 to 30 years old childhood ALL survivors, the following results were obtained: the cardiovascular risk factor status was equally poor in ALL survivors and age and sex-matched controls. Insufficient physical activity was alarmingly common in ALL survivors as one third of the ALL survivors reported less than one hour of moderate activity weekly. Physical fitness was lower in ALL survivors compared with the controls, and especially female survivors performed poorly. Endothelial function was attenuated in ALL survivors compared to the controls, and this was seen especially in males. Subclinical attenuations in cardiac function were found in ALL survivors compared to controls with both tissue Doppler imaging and velocity vector imaging echocardiographic methods. The exercise program improved insulin sensitivity, fitness and endothelial function as well as echocardiographic tissue Doppler imaging and velocity vector imaging measures.

Despite the rather similar cardiovascular disease risk factors status in ALL survivors and controls, the number of survivors who already had at least one established cardiovascular risk factor (62 %) at this young age underlines the importance of cardiovascular risk factor status in this population, as their risk for cardiovascular morbidity and mortality may also be increased due to the independent effects of sedentary lifestyle and anthracycline treatment on e.g. vascular endothelium. Insufficient physical activity and poor physical fitness were alarmingly common especially among female survivors. While the present findings on the effects of exercise on endothelium are encouraging, larger studies with controlled interventions would be needed to further clarify the somewhat different findings on endothelium in males and females. In addition, controlled interventions would be needed to confirm whether the effect of exercise on endothelium is equal in ALL survivors and controls.[37] Large study of clinically evaluated ALL survivors recognized a high prevalence of metabolic syndrome, obesity and cardiovascular disease, particularly in those who have received cranial radiotherapy, underscoring the need for screening and aggressive reduction of modifiable risks.[38]

Some researchers found significant association between energy expenditure and body fat in prophylactic cranial irradiation recipients specially in female patients, so the most of survivors of ALL are overweight and this became worsen with increasing length of follow up. [39]

It is found that prophylactic 18 Gy cranial irradiation plus chemotherapy for childhood ALL can effectively prevent central nervous system relapse and is unlikely to produce clinically significant late effects, despite it may cause slight pituitary hormone abnormality.[40] Previous study revealed that many factors can lead to several side effects including, direct cardiac damage, obesity, endocrine dysfunction, metabolic abnormalities, reduced muscle strength, poor sensation and impaired balance. All these previous factors also probably contribute to the high rates of poor cardiac fitness observed among ALL survivors.[19] In addition, other study revealed that the CNS can also be damage due to treatment of childhood ALL, which contributes to decreasing in cognitive function. As a result of neurocognitive deficits in survivors, important life outcomes have been affected in the form of lower educational achievement, unemployment, lower likelihood of marrying and lack of independent living. This problem occurred for not only children who were received cranial radiation, but also for children who treated only with chemotherapy.[19]

Conclusion:-

Childhood ALL is more prevalence in developed than in developing countries. Possible explanations include under-diagnosis of leukemia in children from poor communities, and/or association of high socioeconomic status with hypothesized risk factors. The risk factors of childhood ALL are environmental and genetic factors. They include sex, age, race, exposure to ionizing radiation, and some congenital diseases, like Down syndrome and neurofibromatosis. Also, exposure to magnetic fields < 0.4 micro Tessla, pesticides, solvents, benzene, maternal alcohol consumption, contaminated drinking water, infections, and high birth weight. There are higher frequencies of ETV6-RUNX1 positive childhood ALL mostly in more industrialized countries, probably due to some industrial pollutants or westernized lifestyle. There are multiple new treatments that might improve the overall response of those children. These include new antimetabolites and nucleoside analogues, changing the formulations of known chemotherapeutic agents, molecular therapies targeting the leukemic cells genetic composition and their affected signaling pathways as well as monoclonal antibodies against leukemia-associated antigens. The late effects of ALL treatment include increasing of cardiovascular morbidity and mortality, pituitary hormone abnormality, obesity, metabolic abnormalities, poor physical fitness, impaired balance, poor sensation and neurocognitive impairment.

Acknowledgment:-

I thank my supervisor Dr. Zeineb Elsawaf for her effort that helped me in writing this review article.

Figure 1:-Proposed Sequential Acquisition of Genetic Alterations Contributing to the Pathogenesis and Relapse of ALL. As shown in Panel A, either common inherited variants or, rarely, deleterious germline mutations confer a predisposition to ALL. Initiating lesions, commonly translocations, are acquired in a lymphoid progenitor. Secondary sequence mutations and structural genetic alterations contribute to an arrest in lymphoid development and perturbation of multiple cellular pathways, resulting in clinically manifest leukemia. PI3K denotes phosphatidylinositol 3-kinase. As shown in Panel B, ALL is commonly genetically polyclonal at diagnosis. Initial therapy suppresses or eliminates more proliferative predominant clones, leaving subclones that harbor or acquire mutations that confer resistance to specific chemotherapeutic agents. Less commonly, relapse clones share no genetic alterations with diagnosis clones and probably are a second leukemia in persons with a genetic predisposition.[41]

Table 1:-Recently approved agents in ALL

Study	Dose schedule (daily x 5 days)	Number of patients	CR* (%)	OR‡ (%)	Refs
Clofarabine (CLOLAR; Genzyme)§					
Phase I Pediatric	11.25–70 mg per m^2	17	4 (24)	8 (47)	49
Phase II Pediatric	52mgperm^2	61	12 (20)	18 (30)	50
Nelarabine (Arranon; GlaxoSmithKline) — in patients with T-cell ALL only¶					
Phase I Pediatric	5–75 mg per kg	26	7 (27)	11 (42)	54
Phase II Pediatrics	(1st relapse)				55
	900 mg per m^2	6	2 (33)	2 (33)	
	650 mg per m^2	33	16 (48)	18 (55)	
Phase II Pediatrics	(2nd relapse)				55
	≥900mgperm^2	10	3 (30)	3 (30)	
	650 mg per m^2	30	7 (23)	8 (27)	
Phase II Pediatrics	Central nervous system positive				55
	900 mg per m^2	1	0	0	
	650 mg per m^2	6	1 (17)	1 (17)	
	400 mg per m^2	21	5 (24)	7 (33)	

*Complete remission (CR) refers to marrow remission irrespective of peripheral blood-count recovery in all studies. ‡Overall response (OR) refers to complete and partial remissions. §Associated with hepatic-skin toxicity. ¶Associated with neurotoxicity.[32]

References:-

1. Global cancer facts & figures 2nd edition, 2008. American Cancer Society, Inc. 2011; No.86181.
2. Rana ZA, Rabbani MW, Sheikh MA, Khan AA. Outcome of childhood acute lymphoblastic leukemia after induction therapy--3 years experience at a single pediatric oncology centre. Journal of Ayub Medical College Abbottabad. 2009; 21(4):150-153.
3. Al-Eid HS and Garcia AD. Cancer incidence report, Saudi Arabia, 2009. Saudi Cancer Registry. 2012.
4. ALBakr RB, Khojah OT. Incidence trend of the leukemia reported cases in the kingdom of Saudi Arabia, observational descriptive statistic from Saudi cancer registry. International journal of biomedical research. 2014; 5 (8): 522-524.
5. Bhutani M, Kochupillai V & Bakhshi S. Childhood acute lymphoblastic leukemia: Indian experience. Indian journal of medical & pediatric oncology. 2004; 25: 3-8.
6. Al-Mutlaq HM, Bawazir AA, Jradi H, Al-Dhalaan ZA, Al-Shehri A. Patterns of childhood cancer incidence in Saudi Arabia (1999- 2008). Asian pacific journal of cancer prevention. 2015; 16(2):431-435.
7. Forero RM, Hernandez M, Hernandez-Rivas JM. Genetics of Acute Lymphoblastic Leukemia, Leukemia. 2013. Available from: http://www.intechopen.com/books/leukemia/genetics-of-acute-lymphoblastic-leukemia.
8. Buitenkamp T, Izraeli S, Zimmermann M, Forestier E, Heerema N, van den Heuvel-Eibrink M et al. Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. Blood. 2014;123(1):70-77.
9. Hutter JJ. Childhood Leukemia. Pediatrics in review. 2010; 31(6): 234-241.
10. Infante-Rivard C, Amre DK. Congenital anomalies in children with acute lymphoblastic leukemia and in their family. International journal of epidemiology. 2001; 30 (2): 350-352.
11. Odenike OM, Michaelis LC, Stock W. Acute lymphoblastic leukemia. Oncology. 2006: 1182-1209.
12. Kroll M, Stiller C, Murphy M, Carpenter L. Childhood leukaemia and socioeconomic status in England and Wales 1976–2005: evidence of higher incidence in relatively affluent communities persists over time. Br J Cancer. 2011;105(11):1783-1787.
13. Thompson J, Gerald P, Willoughby M, Armstrong B. Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukemia in childhood: a case-control study. The Lancet. 2001;358(9297):1935-1940
14. Arya LS. Acute lymphoblastic leukemia: current therapy. Indian journal of medical and pediatric oncology. 2004; 25(5): 11-17.
15. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukemia. Lancet 2008; 371:1030–1043.
16. Peters C, Schrappe M, Stackelberg VA, Schrauder A, Bader P, Ebell W et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: A prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. Journal of Clinical Oncology. 2015; 33(11): 1265-1274.
17. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC et al. Treatment of childhood acute lymphoblastic leukemia without prophylactic cranial irradiation. New England journal of medicine. 2009; 360(26): 2730–2741.
18. 18-Mody R, Li S, Dover D, Sallan S, Leisenring W, Oeffinger K et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood. 2008;111(12):5515-5523.
19. Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukemia: general overview and implications for long-term cardiac health. Expert review of hematology. 2011; 4(2):185-197.
20. Borugian MJ, Spinelli JJ, Mezei G, Wilkins R, Abanto Z, McBride ML. Childhood leukemia and socioeconomic status in Canada. Epidemiology. 2005; 16(4):526-31.
21. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukemia: a review. Int J Epidemiol. 2006 Apr;35(2):370-84.
22. Chang JS. Parental smoking and childhood leukemia. Methods Mol Biol. 2009; 472:103-37.
23. McNally RJ, Parker L. Environmental factors and childhood acute leukemias and lymphomas. Leuk Lymphoma. 2006; 47(4):583-98.

24. Zhou Y, Zhang S, Li Z, Zhu J, Bi Y, Bai Y, Wang H. Maternal Benzene Exposure during Pregnancy and Risk of Childhood Acute Lymphoblastic Leukemia: A Meta-Analysis of Epidemiologic Studies. PLoS One. 2014; 9(10): e110466.
25. Bzhalava D, Hultin E, Arroyo Mühr LS, Ekström J, Lehtinen M, de Villiers EM, Dillner J. Viremia during pregnancy and risk of childhood leukemia and lymphomas in the offspring: Nested case-control study. Int J Cancer. 2016 May 1;138(9):2212-20.
26. Chessells J, Harrison G, Richards S, Bailey C, Hill F, Gibson B, Hann I. Down's syndrome and acute lymphoblastic leukaemia: clinical features and response to treatment. Arch Dis Child. 2001 Oct; 85(4): 321–325.
27. Aljamaan K, Aljumah TK, Aloraibi S, Absar M, Iqbal Z. Low frequency of ETV6-RUNX1 (t 12; 21) in Saudi Arabian pediatric acute lymphoblastic leukemia patients: association with clinical parameters and early remission. Asian pacific journal of cancer prevention. 2015; 16(17):7523-7527.
28. Teitell MA and Pandolfi PP. Molecular genetics of acute lymphoblastic leukemia. Annu Rev Pathol. 2009; 4:175-98.
29. Larson R, Anastasi J. Acute Lymphoblastic Leukemia: Clinical Presentation, Diagnosis, and Classification. Acute Leukemias. 2008:109-118.
30. Esparza SD, Sakamoto KM. Topics in pediatric leukemia – acute lymphoblastic leukemia. MedGenMed. 2005; 7(1): 23.
31. Rubnitz JE and Pui CH. Childhood Acute Lymphoblastic Leukemia. The Oncologist 1997; 2:374-380.
32. Pui CH, Jeha S. New therapeutic strategies for the treatment of acute lymphoblastic leukemia. Nat Rev Drug Discov. 2007 Feb; 6(2):149-65.
33. Schrauder A, Reiter A, Gadner H, Niethammer D, Klingebiel T, Kremens B, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results from ALL-BFM 90 and 95. J Clin Oncol. 2006 Dec 20;24(36):5742-9.
34. Gutierrez A, Look AT. Molecular Targeted Therapies in T-Cell Acute Lymphoblastic Leukemia. Molecularly Targeted Therapy for Childhood Cancer. 2010; 19-30.
35. Veerman AJ1, Hahlen K, Kamps WA, Van Leeuwen EF, De Vaan GA, Solbu G, Suciu S, Van Wering ER, Van der Does-Van der Berg A. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia. Results of protocol ALL VI from the Dutch Childhood Leukemia Study Group. J Clin Oncol. 1996 Mar;14(3):911-8.
36. Rae C, Furlong W, Jankovic M, Moghrabi A, Naqvi A, Sala A, et al. Economic evaluation of treatment for acute lymphoblastic leukemia in childhood. Eur J Cancer Care (Engl). 2014 Nov; 23(6):779-85.
37. Jarvela L. CARDIOVASCULAR HEALTH AND FITNESS AFTER CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA. 2015.
38. Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia - From the St. Jude Lifetime Cohort. Br J Haematol. 2014 May; 165(3):364-74.
39. Warner JT. Body composition, exercise and energy expenditure in survivors of acute lymphoblastic leukaemia. Pediatr Blood Cancer. 2008 Feb; 50(2 Suppl):456-61; discussion 468.
40. Hata M, Ogino I, Aida N, Saito K, Omura M, Kigasawa H, et al. Prophylactic cranial irradiation of acute lymphoblastic leukemia in childhood: outcomes of late effects on pituitary function and growth in long-term survivors. Int J Cancer. 2001; 96 Suppl:117-24.
41. Hunger S, Mullighan C. Acute Lymphoblastic Leukemia in Children. New England Journal of Medicine. 2015;373(16):1541-1552.