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Central Neurotoxicity as a Complication of Acute Childhood Leukemia

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Abstract Over the past decades, significant progress has been made in the treatment of acute leukemia through the use of risk-adapted software regimens of antitumor therapy, but neurological complications still represent a significant problem of modern protocols for the treatment of hematological onco-diseases in children. Neurological complications can be primary due to the spread of tumor cells to the central nervous system, or secondary due to indirect or long-term consequences of cancer, as well as as a result of treatment of the disease, such as radiation and chemotherapy, which causes neurotoxicity of the latter. The literature review reveals the latest achievements of science and clinical practice in identifying risk factors and pathogenetic mechanisms for the development of adverse events of neurotoxicity associated with both the disease itself and chemotherapeutic drugs widely used in acute leukemia. A better understanding of the biology and pathogenesis of CNS leukemia is necessary to develop more effective methods for the prevention and treatment of this unfavorable complication of hematological onco-diseases in children. Identification of the neurotoxicity characteristics of chemotherapy is a prerequisite for further reducing the frequency of side effects of chemotherapy treatment in a patient using individualized treatment options for acute leukemia.

Keywords Acute leukemia, Lymphoblastic leukemia, Myeloid leukemia, Neurotoxicity, Methotrexate, Chemotherapy

The most common malignancy diagnosed in children is acute leukemia – AL, an aggressive hematological onco – pathology characterized by the proliferation of immature blast cells in the bone marrow, which grow uncontrollably and do not have the ability to differentiate into mature cells [1]. Almost all leukemias in the pediatric population are acute types. At the same time, in patients under 15 years of age, the dominant variant is acute lymphoblastic leukemia (ALL), cases of which are registered approximately 5 times more often than acute myeloid leukemia (AML) – the pathology occupies 80% of hemoblastoses and 25% of all childhood tumors [2].

According to the estimates of Russian authors, the prevalence of ALL in the pediatric population is recorded at the level of 3-4 cases per 100 thousand people among the Russian child population under the age of 18, while the peak incidence is observed at the age of 2-5 years. Over the past 10 years, the incidence of ALL in children from 0 to 17 years of age in the Russian Federation has increased by 30 % [3,4], which justifies the need for regular revision of diagnostic and treatment protocols in order to develop safer therapy strategies while maintaining the level of therapeutic effect.

ALL is primarily a malignant neoplasm of the bone marrow and blood, but other hematopoietic and lymphatic tissues, including the spleen, thymus, and lymph nodes, can also be affected [5]. In addition, ALL cells are found in non-blood-forming and non-lymphatic tissues, primarily in the central nervous system (CNS), as well as in the testes, skin, eyes, bones, chest, muscles, and abdominal organs [6]. ALL is divided into B-line, T-line, and rare NK cell line variants that are morphologically indistinguishable [1]. According to the changes of the World Health Organization (WHO) and the International Consensus Classification (ICC) from 2022, the classification of the main subtypes of ALL includes four separate objects: B-ALL/LBL, not otherwise specified (NOS), B-ALL/LBL with recurrent genetic abnormalities, T-ALL/LBL and NK-ALL/LBL.

1. CNS Lesion in ALL

CNS damage occurs with a particularly high frequency both at thetime of diagnosis (8-13%) and in relapse (10-30%) [7, 8]. It is one of the main clinical problems of both the disease itself and chemotherapy. Early autopsy studies showed that CNS damage develops during the disease in a larger proportion of patients with ALL [9]. In general, according to the results of a studyconducted by Anastasopoulou S. etal. [10] 9.2% of patients experienced at least one CNS toxicity during the course of ALL treatment. Most cases of CNS toxicity occurred during the first 6 months of treatment. The total incidence of CNS toxicity was 4.8% at 2 months, 7.5% at 6 months, and 8.7% at 1 year. According to Thas

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trup M. etal. neurotoxic adverse events were reported in 12% of pediatric patients with ALL in the form of seizures, stroke-like syndrome, posterior reversible encephalopathy syndrome, or prolonged neurocognitive deficits [8]. As part of a comprehensive Parasole R study. etal. [11] studied the incidence of neurological complications during ALL treatment in 48 pediatric patients. According to the data obtained by the authors, complications of ALL from the central nervous system included posterior reversible leukoencephalopathy syndrome, stroke, temporal lobe epilepsy, high-dose methotrexate toxicity, syndrome of inadequate antidiuretic hormone secretion, and other unclassified events.

Currently, known risk factors for CNS damage in ALL include peripheral hyperleukocytosis at diagnosis and T-cell immunophenotype [12]. With AL-B cell precursor (BCP)-ALL certain cytogenetic changes, such as translocation of t(1;19) and t(9;22), are associated with a higher incidence of CNS leukemia [13,14]. Thus, in preB-ALL, translocation t (1;19), which causes BCR-ABL1 fusion, is a risk factor for CNS relapse, and these cells were found to express the Mer kinase Mer. Mer-positive ALL blasts enter the G0/G1 phase when co-cultured with cells originating from the central nervous system [15].

In ALL with t (1; 19) translocation, a frequently occurring rearrangement of E2A-PBX1 is found with increased IL7R expression on the surface of blasts and the frequency of CNS leukemia development [16]. CNS metastases are observed in all subtypes of ALL. In the absence of preventive treatment, CNS damage occurs in 30-70% of patients with AL. Specific neurological manifestations vary depending on the structures, neural component, and neuroanatomic localization. The addition of neurological symptoms not only reduces the child's quality of life, but also contributes to changes in the patient's treatment tactics, which significantly affects the prognosis of the underlying disease [17]. Relapse of CNS ALL predicts poor outcomes, but treatment options remain limited.

2. Anatomical Structures Potentially Involved In Leukemic Infiltration

In recent years, several approaches have been proposed that provide a more detailed understanding of the anatomical pathways used by leukemic cells to enter the central nervous system.

In the context of leukemic infiltration of the central nervous system, the most relevant are the endothelial blood-brain barrier (BBB), hemato-leptomeningeal barrier (HLMB) and hematolytic barrier (HLB). The BBB is formed by endothelial cells, astrocytes, and pericytes in and around microvessels that reach the CNS parenchyma.

The capillary endothelium is the anatomical basis of the BBB due to the tight junctions between endothelial cells that prevent the passage of cells and macromolecules, as well as due to the limited ability of endothelial cells to pinocytosis. HLMB is formed by a thin layer of soft mater cells covering the surface of non-fenestrated microvessels of the subarachnoid space. HLB is located in the vascular plexus of the ventricles of the brain [18]. It consists of epithelial cells of the choroid plexus, which are connected by dense junctions, and meningeal postcapillary venules, which contain fenestrated endothelium. In addition to the vascular system of the brain, studies have revealed the dural lymphatic system inside the meninges, which runs along the sinuses of the dura matter and provides drainage of macromolecules and cells from the deep parenchyma of the central nervous system [7]. Accordingly, the potential hematodural lymphatic barrier (HMLB) may hypothetically play a role in CNS infiltration in addition to BBB, HLMB, and HLB.

Histopathological data show that in the final stages of CNS damage, leukemic cells can spread along the perivascular spaces that reach the brain parenchyma (Virchow-Robin space) and eventually break through the piaglial membrane and enter the cerebral cortex [12].

Study conducted after implantation of the GFP-labeled Nalm-6 ALL cell line using intravital microscopy showed that, similar to models of metastatic solid malignant tumors, ALLcells are retained in the branches of microvessels shortly after injection. However, unlike disseminated carcinoma cells, leukemia cells cannot enter the brain parenchyma [18].

In vivo studies on xenograft models (PDX) - ALL made it possible to detect cells that infiltrate the central nervous system in the subarachnoid space of leptomeninges near the venous sinuses of the dura matter. The brain parenchyma is rarely infiltrated by ALL cells and this occurs mainly in the last stages of CNS leukemia [19,20,21]. These observations may be limited by the artificial origin of the model systems. However, they confirm the results of the in vitro study, which found arachnoid membrane involvement and parenchymal involvement in 17 out of 126 brain samples obtained at autopsy, and only in patients with late-stage disease [8].

In the early stages of leukemia, the spread of ALL cells was limited to the surface arachnoid and subarachnoid spaces. It was also found that Nalm-6 cells xenografted to NSG mice circulated and persisted for a short time persisted in the leptomeningeal vasculature, but did not cross the GLMB.

According to Yao H. etal. it was also found that the vascular plexus is free of leukemic cells until the late stages of the disease, which contradicts the penetration of ALL into the central nervous system through GLMB or GMLB. In the search for alternative pathways, the authors found small cavities that directly intersect the bone marrow and subarachnoid space. It was suggested that they correspond to connective vessels and that mechanisms mediated by integrin-laminin are necessary for interaction with these vessels [22].

The integrin family of genes encodes alpha and beta proteins that are part of heterodimeric receptors that transmit signals in response to a variety of extracellular ligands. Some of the main integrins found on immune cells are β2 in complex with AL (LFA-1) or αm (Mac-1), which bind intracellular cell adhesion (ICAM) molecules and various extracellular matrix (ECM)molecules, as well as α4β1 andα4β7 [23]. Although integrins are involved in a wide range of biological

processes, their direct role is usually associated with cell adhesion or migration. In leukocytes, integrins are used in a well-organized manner together with chemokine receptor signaling to achieve extravasation from the blood through the endothelial cell wall to inflamed tissue [24].

In hematopoietic and epithelial cells, integrin adhesion to stromal cells or components of the extracellular matrix (ECM) induces signaling necessary for cell survival, proliferation, and migration. Integrins are also vital for cancer cells, which use integrins for their own survival, invasion and migration within tissues, binding of endothelial cells, extravasation and metastatic colonization of distal organs [25].

In hematological cancers, integrin a7 expression has been shown to be associated with AML with granulocytic sarcoma, and integrin αa4:β1 (VLA-4) is an independent prognostic factor in lymphoblastic leukemia and has been associated with chemoresistance. Thus, integrin-mediated chemoresistance is perceived as a form of adhesion-mediated drug resistance (CAM-DR).

ALL cells are disseminated into the central nervous system using connective vessels, but migrate to the abluminal endothelial site using integrin α6 to attach to laminin. By using this non-hematogenic pathway, ALL cells have bypassed the need to pass the BBB or GLMB of the choroid plexus, since they are delivered directly to the outer layers of the meninges and then to the cerebrospinal fluid.

Thus, to access the central nervous system, leukemic cells can move along the walls of vascular channels connecting the bone marrow of the skull and vertebrae with thepachymeningae, cross the vascular endothelium by transendothelial migration or destruction of the endothelium, diffusely infiltrate the arachnoid membrane, migrate and intensively proliferate in the cerebrospinal fluid and, as a result, infiltrate the perivascular spaces and the brain parenchyma (the Virchow-Robin space) [26,27,28].

The dural lymphatic system is a further route for transporting lymphocytes, and it is quite possible that ALL cells enter the lymphatic vessels of the central nervous system. This hypothesis is of particular interest in the context of relapse of CNS AL, since leukemic cells can re-enter the systemic circulation. It should be noted that none of the above-mentioned studies demonstrates evidence of exclusivity of one or another pathway of ALL penetration into the central nervous system. Therefore, it is possible that ALL cells can use several different pathways for simultaneous penetration into the CNS-BBB, GLMB, GLB, emissary veins and lymphatic vessels of the brain [29].

Moreover, the pathways of entry into the central nervous system may differ depending on the subtype of ALL (B-cell precursor, T-cell or different cytogenetic background), so there is a need for additional research. Disclosure of the details of the mechanisms of entry of ALL cells into the central nervous system is a prerequisite for accurate and effective treatment of the involved integrins as a possible supplement to standard prevention in order to prevent CNS damage and relapse of ALL.

3. Cellular Features that Contribute to the Penetration and Survival of ALL in the Central Nervous System

It remains a matter of debate whether the ability to enter the central nervous system is a common feature of ALL cells, or whether some cells have a particularly high propensity to cause CNS leukemia due to their molecular characteristics.

For example, several studies have examined whether ALL cells entering the central nervous system exhibit a high migration potential, for example, due to activation of chemokine receptors and/or adhesion molecules. Among lymphocytes, T cells are more likely to enter the central nervous system than other lymphocytes. T cells in the cerebrospinal fluid express high levels of P-selectin adhesion molecules, glycoproteinligand 1 (PSGL-1), and lymphocyte function-related antigen-1 (LFA-1), by which they attach to P-selectin and the intercellular adhesion molecule. Moreover, T cells in the cerebrospinal fluid express chemokine receptors, including CXCR3, CCR5, CCR6, and CCR7, and the corresponding CCR7, CCL19 and CCL21 ligands were found in the choroid plexus epithelium. This may also apply to T-ALL, and the interaction of T-ALL cells with the choroid plexus and subarachnoid vessels through chemokine adhesion and signaling chemokine may represent an important mechanism of CNS pathology in ALL. CCR7-mediated binding of T-ALL cells to CCL19 and CCL21 in the choroid plexus epithelium has been demonstrated as a likely axis of infiltration of central nervous system by T-ALL cells [18].

In BCP-ALL, the overall ability of leukemic cells to cause CNS leukemia in preclinical models was confirmed in the Williams MTS study etal., in which 23 out of 29 samples administered to immunodeficient mice (79%) caused CNS leukemia in leptomeningas, regardless of their cytogenetic background and the corresponding CNS status. They also found that chemokine receptor signaling does not lead to CNS entry in BCP-ALL, because they did not find differential expression of chemokine receptors between BCP-ALL cells without CNS and cells with CNS, which confirms the mechanisms of CNS infiltration of T-ALL, but is not necessarily applicable to BCP-ALL [21].

A study using high-throughput sequencing methods showed that the clonal architecture of BCP-ALL in the CNS and bone marrow is similar [30]. Overall, these data support the hypothesis that CNS HRV-ALL share common characteristics and that almost all clones can spread to the CNS. In addition, they suggest that relapses of CNS ALL are inherently biologically indistinguishable, often arise from the same subclones in two locations, or move freely between compartments during relapse, which contradicts the hypothesis of the existence of clones with a specific CNS tropism. However, another study revealed increased expression of traffic/adhesion markers, including CXCR3 and PSGL-1, in populations of BCP-ALL isolated from the central nervous system, compared with cells obtained from

bone marrow [31].

Cytometric testing showed that a subpopulation of BCP-ALL cells (>1%) with a "CNS protein profile" was present in the bone marrow at the time of diagnosis in patients who later developed isolated CNS relapse, while this subpopulation was <1% or absent in all other patients. These data indicate that the presence of a (small) subpopulation of BCP-ALL cells with a "CNS protein profile" at diagnosis is associated with isolated CNS relapse. In addition, α6-integrin signaling has been shown to enhance the migration of BCP-ALL cells to cerebrospinal fluid samples in in vitro, which may be the molecular basis for ALL migration through connective vessels [22].

In the research of Bazarny V.V. etal. it was shown that patients with ALL who developed neurotoxic complications during chemotherapy showed changes in the CSF cytokine profile. In pediatric patients with advanced neurological disorders, the most noticeable increase in the level of CXCL12 (SDF-1a) and stem cell factor, as well as an increase in the blood content of CXCL10 (IP-10), was observed in comparison with the control group. On this basis, the authors suggest identifying these indicators as potential markers of chemo-induced neurological disorders of ALL [32].

Some studies suggest an oncogenic role of IL-15 in hematological malignancies. IL-15 exhibits pleiotropic functions by targeting various immune cells, including natural killer cells (NK). NK cells are a subset of innate immune system lymphocytes that play an important role in immune cancer surveillance due to their ability to recognize and kill transformed cells without prior sensitization. Cytotoxicity mediated by NK cells is regulated by the balance of signals transmitted by activating and inhibiting receptors when interacting with the target cell. NK cell development, survival, and activation are predominantly regulated by IL-15. Moreover, IL-15 has been shown to enhance the cytotoxicity of NK cells against tumor cells by enhancing the expression of NKG2D and NKp44 receptors on NK cells, as well as the expression of cytotoxic effector molecules.

An association has been reported between increased interleukin-15 (IL-15) mRNA expression in ALL blasts and an increased risk of CNS damage. IL-15 can enhance leukemia cell growth in a growth factor-poor CSF environment [33,34,35]. Activation of NK cells by leukemia cells expressing IL-15 can lead to control of residual disease in the periphery, but to a lesser extent in the central nervous system due to the lack of penetration of NK cells into the brain. This may explain the association between IL-15 expression and relapses of ALL in the central nervous system and, importantly, suggests the need for CNS-directed prevention in anti-leukemic therapy protocols using NK cells.

This information can be used to develop new diagnostic and treatment strategies aimed at preventing relapses of CNS ALL with reduced toxicity. Finding the best treatment for ALL is an ongoing challenge, leading to the constant development of new therapeutic approaches. Among them, immunotherapy stands out, using the patient's immune system to target cancer cells, improving survival and reducing the toxicity of chemotherapy. The main methods of immunotherapy include the use of bispecific antibodies, CART or CARNK cells, as well as antibody-drug conjugates, which show important results, primarily in the treatment of B-ALL. CART or CARNK cells and antibody therapy are also promising for the treatment of T-ALL. However, the significance of chemokine adhesion and signaling chemokines, as well as the role of IL in the mechanisms of BCP-ALL cell penetration into the central nervous system, is not fully understood and requires further study.

4. Features of Neurotoxicity and Chemotherapeutic Drugs

Thanks to recent advances in anti-leukemic drugs and supportive care, as well as risk-based approaches to therapy, chemotherapy-based protocols for treating AL have now been developed and are being used, ensuring a patient's probability of recovery in the range of 80-90% in ALL and 60-70% in AML [33-6]. This has led to a shift in focus from strengthening treatment to achieving a cure with fewer side effects. Progress is being made through the use of minimal residual disease (MRD) monitoring to adjust treatment intensity according to clinical response, and more recently through the introduction of targeted immunotherapy.

However, serious problems remain. One particularly challenging area is how best to prevent and/or treat recurrent leukemia affecting the central nervous system. Detection of leukemic blasts in the central nervous system by cytology is more common in patients with a higher number of white blood cells at the time of diagnosis, ALL T-lines, and high-risk cytogenetics. At the same time, delivery of effective anti-leukemic agents to the central nervous system is considered necessary for the treatment of ALL in children.

Current CNS-focused therapy includes diagnostic and drug-assisted early combination of intrathecal and high-dose systemic chemotherapy to destroy leukemia cells that potentially exist in the central nervous system at the time of diagnosis, as well as to prevent relapse, accompanied by repeated intrathecal procedures up to 26 times within 2-3 years. Studying the results of a diagnostic spinal puncture reduces the risk of localization of AL in the central nervous system from 50% to 5%, but the method is traumatic, associated with low sensitivity and poor specificity [37].

The question of the timing of performing a diagnostic lumbar puncture also remains controversial. It is assumed that the delay of the first lumbar puncture is associated with a lower frequency of traumatic lumbar punctures and a lower number of CNS relapses [38]. However, no randomized comparisons have been made, and some practitioners are concerned that delayed LP may affect CNS staging. This is especially important for protocols that use CNS status for CNS stratification and intensity of systemic therapy. More sensitive biomarkers are needed before this question can be answered correctly [39].

All current ALL protocols use a combination of systemic therapy and intrathecal therapy against CNS leukemia, with some research groups also using radiation therapy for certain high-risk groups. This preliminary CNS therapy is sometimes referred to as "CNS prevention", which reflects the goal of preventing CNS relapse. At the same time, despite the fact that some chemotherapeutic agents and new methods of immunotherapy provide excellent control of systemic leukemia and CNS leukemia, chemotherapy itself can be highly neurotoxic. While the balance between adequate treatment to prevent relapse and minimizing the effects of chemotherapy to reduce side effects is especially important when it comes to a child's developing brain.

Treatment-related complications are among the causes of deaths among children with oncohematological pathology and can cause violations of the treatment protocol, cancellation or reduction of the dose of drugs. Violations in the treatment protocol, in turn, can reduce the effectiveness of treatment and increase the frequency of relapses of the underlying disease [40]. Treatment-related complications are classified as "early acute complications" when they develop in the first 2 weeks after starting treatment, as "complications during therapy" when they develop 2 weeks after starting treatment, and as "late complications" when they develop after recovery from the last dose of chemotherapy [41]. At the same time, the time of occurrence of neurotoxic complications, their variety and severity are individual for each patient.

Another major obstacle to improving treatment is that it is not possible to accurately identify children at risk of CNS relapse or monitor their response to treatment due to the lack of sensitive biomarkers. The problems are obvious: there is no way to measure the leukemic load on the central nervous system, studies have failed to establish the most effective CNS treatment regimens, and non-toxic approaches for patients with relapses, refractoriness, or intolerance are not available.

The current concept of pathogenesis of neurotoxicity of chemotherapeutic drugs is based on several types of effects on the nervous system: direct neurotoxicity, immune-mediated response, and DNA damage [42]. Methotrexate and vincristine have the most pronounced effect on the nervous system. It is believed that methotrexate can have a direct toxic effect on the central nervous system, damaging neuronal tissue. Moreover, the drug is involved in the folate metabolic pathways and causes biochemical changes in excitatory amino acids, homocysteine, S-adenosylmethionine /S-adenosylhomocysteine, adenosine, and biopterins, which can lead to neurological symptoms [43].

Risk factors include high-dose intravenous administration, intrathecal administration, adolescence, and a history of radiation therapy. Therefore, for example, if the overall prevalence of neurotoxic complications with intravenous administration of methotrexate is about 10%, then with intraventricular administration of the drug, the prevalence of complications reaches up to 40%. High doses of methotrexate (1.5-8 g/m^2) and age >10 years were associated with an increased risk of transient encephalopathy in children with ALL. Radiation therapy increases the neurotoxicity of methotrexate several times [44]. Several studies have reported a high prevalence of subacute methotrexate neurotoxicity among Latin American patients with ALL, suggesting that sensitivity to methotrexate therapy may vary by race and ethnicity [45,46,47].

The neurotoxicity of methotrexate can be divided into acute, subacute and chronic. Acute or subacute neurotoxicity may be manifested by stroke-like symptoms, such as aphasia, muscle weakness, sensory disturbances, and ataxia, occurring within 2-14 days after starting methotrexate [4-8]. Neurological symptoms are usually transient. On the contrary, the chronic type can cause slow-developing leukoencephalopathy and progress to irreversible neurological dysfunction [44-9]. The greatest frequency of this type of damage is observed among preschool children. The level of consciousness can be altered, causing confusion, disorientation, hallucinations, or lethargy.

Other symptoms that may occur in the acute stage of leukoencephalopathy include seizures, headache, vision loss, hemiparesis, and aphasia. There may be a subacute onset of dementia with impaired intellectual development and learning difficulties. White matter damage is a particular risk when intrathecal methotrexate is combined with cranial radiation therapy [50]. Stopping taking methotrexate for a short period of time can help speed up recovery. In rare cases, disseminated coagulation necrosis may occur, which has a more serious prognosis. Aseptic meningitis, a well-known complication of intrathecal use of medications such as methotrexate, may present with headache, stiff neck muscles, fever, and vomiting.

Treatment with L-asparaginase can lead to vascular complications, including hemorrhagic or ischemic stroke, which can often affect the venous sinuses. Vascular events usually occur after the first 14 days of treatment [51]. Cytarabine and 5-fluorouracil have been shown in studies to cause damage to the cerebellum, which is manifested by ataxia, titubation, outstretched arm tremor, nystagmus and dysarthria. The mild reversible type is more common in children than in adults over 50 years of age, who tend to have severe Purkinje cell damage [52].

Vincristine peripheral polyneuropathy is one of the most frequent neurotoxic complications of chemotherapy (from 30 to 100%) [53]. The main clinical manifestations of the disease are characterized by individual disorders or a combination of motor, sensory and vegetative symptoms of varying severity and duration. Typical is distal symmetrical sensorimotor neuropathy with predominant damage to the peroneal nerves, peroneal muscle paresis, and chronic neuropathic pain [54,55].

Thus, despite the improvements made in the diagnosis and treatment of both forms of acute leukemia: lymphoblastic (ALL) and myeloid (AML), CNS damage still limits long-term treatment, remaining one of the most severe complications and the main cause of death. Treatment-related mortality remains high – life-threatening or permanently disabling treatment-related side effects occur in 40% of surviving children, and 10-15% of patients have relapses of the disease

[56]. Patients at high risk of CNS infiltration receive additional cranial radiation in some protocols, which further increases the risk of neurocognitive deficits and secondary malignancies. Early detection of neurotoxicity is important because of its possible similarity to metastatic disease, paraneoplastic syndrome, or comorbid neurological disorders that do not require dose reduction or discontinuation of the prescribed drug.

5. Conclusions and Promising Areas of Research

Although current AL treatment regimens provide high survival rates, 1/5 of pediatric patients continue to experience relapses of the disease. In addition, the development of neurological complications of ALL is an unsolved problem in the treatment of ALL. This is due to the fact that modern therapy, for example, aimed at the central nervous system, is non-specific. At the same time, despite the active study of neurological complications of the pathology itself, there is a steady increase in the neuro-toxic effects of chemotherapy drugs prescribed in the framework of AL therapy protocols.

Currently, the issues of standardizing the management of such patients remain unresolved, the values of laboratory markers for predicting and early diagnosis of neurotoxic complications have not been determined, which focuses attention on the need for further study of the problem considered in the literature review. To develop new diagnostic and therapeutic strategies, it is increasingly important to understand the pathogenetic mechanisms of CNS infiltration in ALL. This direction should include further investigation of ALL pathways of entry, survival pathways, and cellular behavior in the CNS.

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