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THE EFFECTIVENESS OF THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN THE STANDARD RISK GROUP BY PROTOCOL ALL-MB-2008

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Abstract. The results of a multicenter randomized trial of the effectiveness of treatment by protocol ALL-MB-2008 of children with acute lymphoblastic leukemia (ALL), the standard risk group (SRG). The primary analysis included 350 patients with ALL, registered in the Scientific Research Institute of Hematology and Blood Transfusion in Children's Department (Tashkent, Uzbekistan), which were included in the study during the period from 01.09.2009 till 31.11.2014. In the observation group were attributed the standard risk group to the 114 patients (32.5%). Overall survival rate (OS) was 89.5%, incomplete remission (CCR) are 99 patients (86.8%).
Keywords: acute lymphoblastic leukemia, children, survival, immunophenotyping, chemotherapy.

Introduction. Leukemia is a common name for malignant tumors of the hematopoietic tissue with damage to the bone marrow. The causes of tumor diseases are poorly understood. Leukogenesis in humans appears to be multifactorial, with external factors such as radiation exposure and viral infections interacting with constitutional or genetic ones. Leukemias are the most common cancers in children; their share is 1/3 of new cases of tumor diseases that occur annually in children. Acute lymphoblastic leukemia (ALL) occurs in 76–82% of the total number of leukemias [1,2]. Currently, no true leukemia-associated markers have been found. In most acute leukemias, leukemic cells have immunophenotypes comparable to normal hematopoietic cells of similar stages of differentiation. In acute leukemia, blast cells are considered as malignant analogues of normal cells in the early stages of lymphopoiesis and myelopoiesis. Due to the ambiguity of the therapeutic effect and various outcomes of the disease, the information obtained by immunophenotyping of leukemic cells, together with other factors, contributes to the determination of the aggressiveness of the tumor process and is important in studying the prognostic significance of the immunological characteristics of tumor cells. In the 70s, long-term remissions (more than 5 years) were observed only in 5% of children with acute leukemia. The successes achieved in hematology in the last decade have made it possible to radically change the outcomes of acute leukemia, which until recently were considered absolutely fatal diseases. Remission in acute lymphoblastic leukemia is achieved in 95% of patients. In 70–75% of children with ALL, it is possible to obtain such long-term remissions that they can be considered cured [2,3]. L-asparaginase (ASP), derived from certain strains of Escherichia coli (COLI-ASP), is an original biological drug used in the treatment of acute lymphoblastic leukemia (ALL) in children since 1970 [1, 2]. COLI-ASP catalyzes the hydrolysis of L-asparagine (ASN) to aspartate and ammonium, resulting in low levels of ASN in plasma and cerebrospinal fluid. In turn, ASN deficiency inhibits protein synthesis in leukemic cells and causes their death. At the same time, normal cells are less

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sensitive to ASN deficiency due to their ability to synthesize it by activating the ASN enzyme. Causing a pronounced antitumor effect, COLI-ASP in its mechanism of action is an enzyme, and not a "real" cytostatic agent and has minimal myelotoxicity. The intensive study of asparaginase was started in 1953 by J.G. Kidd [4], but the first works on the use of COLI-ASP in the treatment of human leukemias and lymphomas appeared in 1967 [3]. Initially, COLI-ASP was part of induction therapy in the form of short courses of 2-3 weeks with an interval of 2-3 days, which increased the rate of achieving complete remissions from 85-90 to 98%. Thus, in the induction of remission protocols of the BFM group (Berlin-Frankfurt-Munster), COLI-ASP was used at a single dose of 10,000 IU/m21 every 3 days, the course included 8 injections. Significant progress in optimizing COLI-ASP therapy has been made possible by research at the Dana Farber Cancer Institute (DFCI) in the United States, when a long-term COLI-ASP regimen was proposed as part of the 77-01 protocol. It turned out that in the group of children who received long-term COLI-ASP therapy, the 5-year event-free survival (EFS) was 72%, while in the group of children who did not receive such treatment, only 47%. The authors associated the high efficiency of the program with a long-term regimen and a large cumulative dose of COLI-ASP [4]. In 1991, when creating the first Russian protocol for the treatment of ALL in children "Moscow-Berlin-91" (ALL-MB-91), an analysis of the results of studies of ALL therapy conducted by the main cooperative groups of the world was used. The long-term COLI-ASP regimen made it possible to completely abandon the elements of high-dose chemotherapy without reducing its effectiveness [5, 6].

Material and research methods

The analysis included primary patients of the standard risk group (SGR) of ALL, registered in the children's department of the Research Institute of G and PC (Tashkent), who entered the ALL-MB-2008 study in the period from 09/01/2009 to 11/31/2014. Criteria Patients included in the analysis were:

• age at the time of diagnosis from 1 to 15 years;

• compliance with the criteria of the standard risk group (RGR): initial leukocytosis less than 30.0x109/l; age over 1 year; no initial CNS lesion; non-T cell immunology and/or absence of initial anterior mediastinal involvement; absence of translocations t(4;11) and/or t(9;22); achievement of remission on the 36th day of therapy;

• complete implementation of the consolidation phase in accordance with the protocol.

Diagnosis and definition of events.

• All patients at the time of diagnosis underwent a standard clinical examination, general and biochemical blood tests.

• The diagnosis of ALL was established on the basis of morphological, cytochemical, immunological and molecular genetic studies of the bone marrow in patients with >25% blast cells with lymphoblastic cytochemical and immunological characteristics of the tumor substrate.

The scheme of the ALL-MB-2008 protocol is shown in fig. one.

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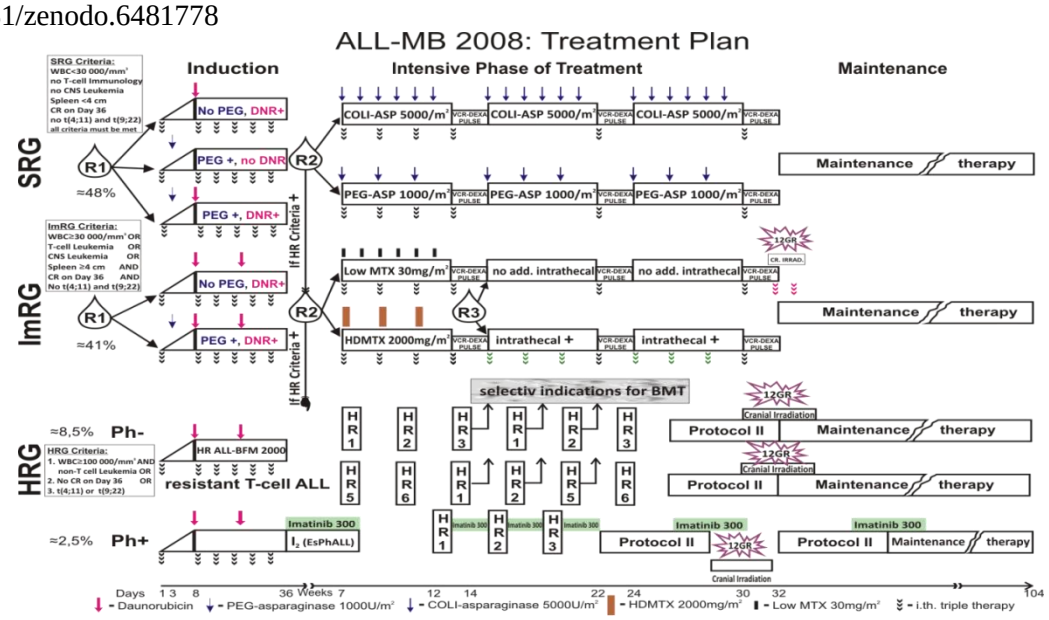

Fig.1. General scheme of the ALL-MB-2008 protocol

According to this protocol, the choice of therapy for ALL is determined by the risk group. For patients with GHR, treatment consists of phases of remission induction, post-induction consolidation therapy, and maintenance therapy. All patients at the time of registration in the study, regardless of risk group, one of the induction steroid therapy regimen (DEXA at a dose of 6 mg/m2 per day). Induction therapy in GHR continued from weeks 1 to 7 and included 6 weekly injections of vincristine (VCR) at a dose of 1.5 mg/m2 and intrathecal therapy, a single application of daunorubicin (DNR) at a dose of 45 mg/m2 and daily dexamethasone . The general scheme of consolidation therapy is shown in fig. 2.

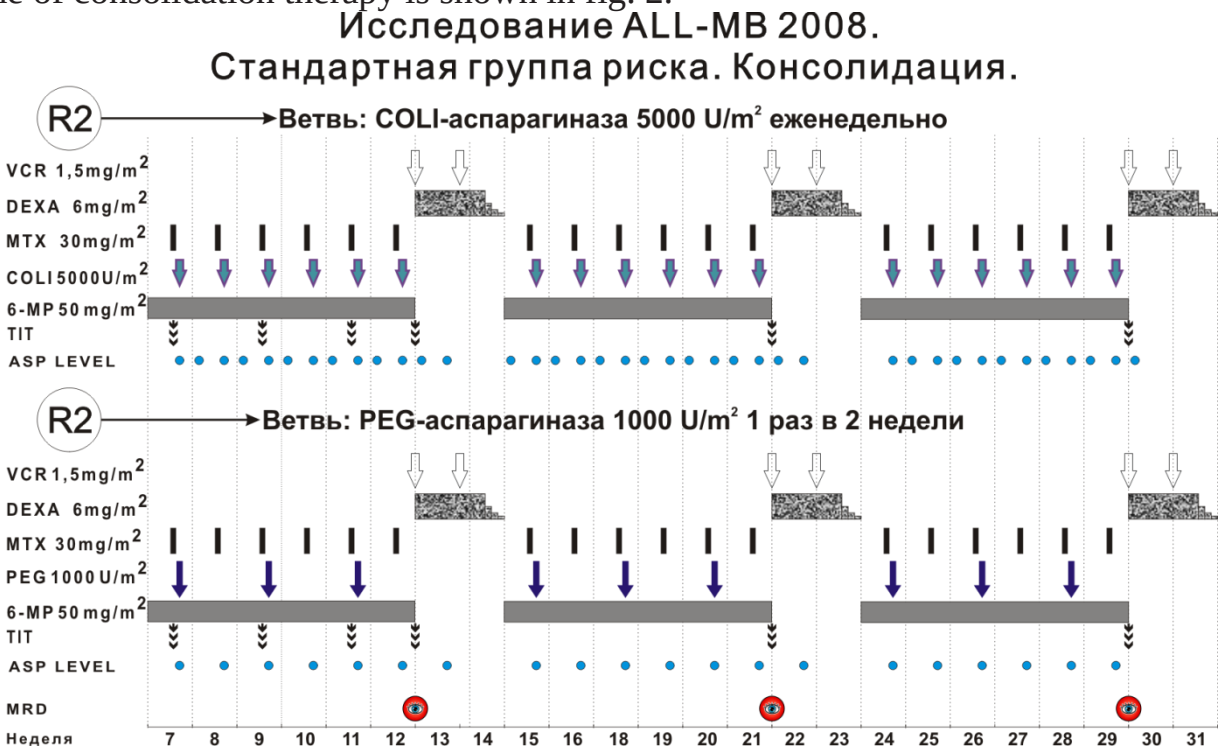

Fig.2 The general scheme of therapy for the consolidation of a standard risk group

Consolidation consists of 3 phases: S1, S2, 6 weeks of 6-MP daily and weekly injections of MTX and COLI-ASP followed by 2 weeks of reinduction (DEXA +

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VCR + intrathecal administration of 3 drugs). COLI ASP was administered intramuscularly once a week one day after the introduction of MTX. After consolidation was completed, patients were given standard maintenance treatment (6-MP and MTX) for 1.5 years, interrupted every 6 weeks. reinduction courses VCR and DEXA. The results of ALL therapy were assessed by the frequency of achieving complete remissions, the number of relapses, deaths in complete remission and the number of patients in complete long-term remission (CPR), as well as OS (overall survival), EFS (event-free) and DFS (relapse-free) . Statistical data processing was carried out using Microsoft Access, Paradox, GraphPad Prism 3.0, and STATISTICA 7.0 programs.

Differences between the compared parameters were considered statistically significant at $p \leq 0.05$.

Research results and discussion.

Until the 1990s, non-programmed polychemotherapy was carried out in Uzbekistan, and in this case, the DFS was 5-10%. Since the end of the 90s, the ALL-BFM-95m PCT program with a reduced dose of methotrexate 1g/m2 has been started, but stratification into risk groups has not been fully carried out due to the lack of immunophenotyping and molecular genetic studies. And it was not possible to carry out therapy according to the protocol in full, due to the large number of toxic and infectious complications. The indicators of OS and RFS remained low and did not exceed 50%. To improve the results of therapy for acute lymphoblastic leukemia, it was necessary to introduce new methods of diagnosis and treatment. Since September 2009 the children's department of the clinic of the Research Institute of G and PC began to participate in the research protocol for the treatment of children with acute lymphoblastic leukemia ALL-MB-2008. The ALL-MB-2008 study was successfully completed in 2014. In total, 4241 patients from clinics in Russia, Belarus, Armenia and Uzbekistan were registered in the protocol, but only 3461 patients were included in the analysis (patients from the clinic of the Research Institute of G and the PC of the Ministry of Health of the Republic of Uzbekistan are not included here , since they did not participate in randomization), 86% of patients are alive; EFS was 81%. There were 1711 patients (49.4%) of the standard risk group.

Out of 350 patients with acute lymphoblastic leukemia who received treatment in the pediatric department of the Research Institute of G and PC (Tashkent, Uzbekistan) according to the ALL-MB-2008 protocol, 114 patients (32.5%) were classified as SGR. A smaller number of patients in the standard risk group, compared with the protocol as a whole (49.4%), is due to the lack of information on the results of immunophenotyping and molecular genetic testing. Clinical and hematological remission was achieved in 109 patients (95.6%). Primary resistance was found in 1 patient (0.8%), 1 patient (0.8%) died during induction, 3 (2.63%) patients were lost from observation. Isolated bone marrow early relapses were observed in 5 patients (4.38%). The cause of death in 5 (4.38%) patients in complete remission was infectious complications that developed against the background of myelotoxic agranulocytosis. Overall survival (OS) was 89.5%, 99 patients (86.8%) are in complete long-term remission (CPR). Of the 99 patients in PPR, 45 patients (45.5%) completed maintenance therapy.

In general, according to the ALL-MB-2008 study (clinics of Russia, Belarus, Armenia), death in induction was 1.6%, death in remission was 2%, lost from observation - 0.6%, isolated bone marrow early relapses were observed in 3.7% of patients, 91.9% of patients of the standard risk group are in the PPR [6,7,8].

Despite the success achieved in the treatment of acute lymphoblastic leukemia in children in Uzbekistan, a number of problems were identified during the implementation of therapy according to the ALL-MB 2008 protocol. First of all, high mortality was noted at the stage of induction therapy and in remission compared with other clinics participating in the study. The frequency of deaths in remission was quite significant and amounted to 4.38%. The reasons for the high mortality rates were the relatively late diagnosis of acute lymphoblastic leukemia, untimely diagnosis of infectious complications. It is noteworthy that the significance of relapses is 4.38%, which is associated with interruptions in polychemotherapy due to infectious episodes.

Conclusion

Thus, the introduction of the new ALL-MB 2008 polychemotherapy protocol in Uzbekistan led to an increase in the event-free survival of children with acute lymphoblastic leukemia of the standard risk group (ALL) up to 86.8%. The key components of this progress were: the use of new diagnostic methods, such as immunophenotyping and molecular genetic testing, which allowed for risk-adapted therapy, 3–4-component induction therapy (remission achieved in 98–99% of patients); prevention of CNS damage (decrease in the frequency of neurorelapses); intensive phase of therapy; long-term maintenance therapy.

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