Comparative analysis of toxicity of treatment protocols ALL-BFM-95m and ALL-MB-2008 for acute lymphoblastic leukemia in children in Uzbekistan

Bakhramov S.M. Center for Professional Development of Medical Workers, Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan

Ibragimova S.Z. Center for Pediatric Hematology, Oncology and Clinical Immunology Tashkent, Uzbekistan

ABSTRACT

Over the past two decades, significant progress in the treatment of children with acute lymphoblastic leukemia has been made in many countries, also in low- and middle-income countries (LMICs), but survival rates remain significantly lower than in developed countries [2,5,6]. Inadequate Accompanying therapy and the resulting high mortality from toxicity are important reasons for treatment failure in children with acute lymphoblastic leukemia in LMICs

Keywords: lymphoblastic leukemia

Introduction. Over the past two decades, significant progress in the treatment of children with acute lymphoblastic leukemia has been made in many countries, also in low- and middle-income countries (LMICs), but survival rates remain significantly lower than in developed countries [2,5,6]. Inadequate Accompanying therapy and the resulting high mortality from toxicity are important reasons for treatment failure in children with acute lymphoblastic leukemia in LMICs. Early lethality and rates of death in remission are considered important criteria for adequate supportive therapy, and the effectiveness of therapy is also assessed by them [1, 4]. This is also confirmed by literature data, in developing countries, mortality rates up to 15%, which is a fairly high rate, while in European countries and the United States this figure is only 3% [1, 3].

Material and methods. This paper analyzes the results of treatment of primary patients with ALL who received therapy according to the ALL-BFM-95m and ALL-MB-2008 protocols registered since 1999. to 2016 in the clinic of Center for Pediatric Hematology, Oncology and Clinical Immunology **(**Tashkent) the age of 1 to 15 years. The sample of subjects included 375 patients aged 1 to 15 years, of which 229 (61.5%) were boys, 146 (38.5%) were girls.

Discussion.

Were analyzed such indicators as hematological toxicity, frequency and severity of infectious episodes, the need for transfusions, liver toxicity. The analysis revealed that anemic syndrome was more often observed during treatment on the ALL-BFM-95m protocol at the stages of induction and consolidation compared with the ALL-MB-2008 protocol (11.8% and 9% versus 49.9% and 28.2% on ALL-BPM-95m), including episodes

of thrombocytopenia (16.7% and 9.3% versus 39.6% and 21.2% on ALL-BPM-95m). As a result, transfusion dependence was higher on the ALL-BFM-95m protocol (the amount of erythromass and thromboconcentrate per 1 patient on the ALL-BFM-95m protocol was more than 2 times less than on ALL-MB-2008). The feasibility of the intensive phase of therapy (remission induction) was significantly worse on the ALL-BFM-95m protocol, due to the large amount of chemotherapy (2 injections more anthracyclines, 8 injections of asparaginase), which may have affected the final results of treatment. The ALL-MB-2008 protocol has a lower toxicity compared to the ALL-BFM-95m protocol with a higher efficiency (71% and 48%). (See Table 1.)

Table 1.
Comparative analysis of hematological toxicity of protocols ALL-BFM-95m and ALL-MB-2008

Stages of therapy		Hemoglobin < 70 g/l			Platelets < 20x10⁹/l			Myelotoxic agranulocytosis		
MB n=223	BFM n=145	MB	BFM	p	MB	BFM	p	MB	BFM	p
Induktion	Ia	35 %	41%	0,01	39,6 %	46,3 %	0,12	61,2 %	74,3 %	0,12
Consolidation I	Ib	11%	49,9 %	<0, 0001	13%	19%	0,003	25%	34%	0, 004
Consolidation II	M	9%	28,2 %	0,0001	6%	12%	0,003	15%	23%	0, 001
Consolidation III	II	7%	12%	0,01	4%	16%	0,01	10%	34%	<0,0001

Due to the greater number of transfusions with blood components, 31% (45) of patients who received PCT according to ALL-BFM-95m had viral hepatitis B and C, and only 11.2% (25) of patients receiving treatment according to the ALL-MB-2008 protocol , which increased liver toxicity in the form of hepatomegaly, hyperbilirubinemia, increased activity of aminotransferases during protocol M with high doses of methotrexate, which only 71.2% (103) of patients managed to complete in full. In the majority of patients who received therapy, deviations were observed in the indicators of the activity of liver enzymes (ALT, AST) and bilirubin. According to the ALL-BFM-95m program in 87.3% (126) patients, according to the ALL-MB-2008 program in 75.1% (167) patients (Table 2).

Hyperfermentemia of the 1st degree was noted (22.4%/28 and 30.2%/50, respectively). Most often, their increase corresponded to the 2nd degree of toxicity - 46.3% (58) (on the ALL-

BFM-95m protocol and 51.7% (86) on the ALL-MB-2008 protocol. On the ALL-BFM-95m protocol more often 3rd degree toxicity was observed - 31.3% (40 patients) compared with the ALL-MB-2008 protocol - 18.1%.

Table 2.

Comparative analysis of liver toxicity

Name	I degree	p	II degree	p	III degree	p	IV degree	p
Bilirubin BFM	36,3% (46)	0.003	40,1% (50)	0.2690	18.6% (23)	0. 0001	5% (7)	0.004
Bilirubin MB	48,2% (107)	0.003	45% (101)	0.2690	6,8% (15)	0. 0001	-	0.025
Enzymes (ALT, AST) BFM	22,4% (28)	0.065	46,3% (58)	0.0615	31,3% (40)	0.0001	-	0.065
Enzymes (ALT, AST) MB	30,2% (50)	0.065	51,7% (86)	0.0615	18,1% (31)	0. 0001	-	

An increase in transaminase levels by more than 5 times, that is, the 3rd degree of toxicity, required a temporary cessation of chemotherapy and the appointment of infusion therapy in combination with hepatotropic drugs (Heptral, Essentiale H).

Hyperbilirubinemia due to the fraction of direct bilirubin during chemotherapy of the 1st degree of severity was observed in 46 patients (36.3%) on the ALL-BFM-95m protocol and in 107 patients (48.2%) on the ALL-MB-2008 protocol an increase in bilirubin level up to the 2nd degree was observed in 50 patients (40.1%) on the ALL-BFM-95m protocol and in 101 patients (45%) on the ALL-MB-2008 protocol of the 3rd degree was noted in 23 patients (18.6%) on the ALL-BFM-95m protocol and in 15 patients (6.8%) on the ALL-MB-2008 protocol. In 7 patients (5%) on the ALL-BFM-95m protocol, bilirubinemia of the 4th degree of toxicity was noted, in all patients hepatitis C infection was noted, according to the ALL-MB-2008 protocol, there were no such patients (Table 2).

Conclusion.

A comparative analysis of the results showed that the ALL-MB-2008 protocol turned out to be more reproducible and effective in the conditions of Uzbekistan. 10-year disease-free survival according to the ALL-MB-2008 protocol was 71±3% compared to 48.8±4% according to the ALL-BFM-95m protocol. The percentage of achieving remissions was also much higher on the ALL-MB-2008 protocol (95.1% - 213 patients) compared to the ALL-BPM-95m protocol (90.3% - 131 patients) (p=0.0765). It should be noted that induction mortality was high in patients of the first group (6.9%) compared with the second group (1.8%, p=0.0121). There is also a high TRD of 11.2%±2.6% compared to 8.8%±1.9%. There were no significant differences in the number of non-responder patients. Significantly lower hematological and hepatic toxicity of therapy according to the ALL-MB-2008 protocol compared to the ALL-BFM-95m protocol was proven. Also, the possibility of achieving higher

efficiency when using the protocol with a lower intensity at all stages of treatment has been proven, and most of the therapy is carried out on an outpatient basis. This significantly reduces the toxicity of therapy, and as a consequence, mortality in induction and remission. The ALL-MB-2008 protocol can be recommended for the treatment of primary patients with ALL in Uzbekistan.

References.

1. 1. Hematology/oncology of childhood. ed. Rumyantseva A.G., Samochatova E.V. M.: ID MEDPRAKTIKA, 2014; 792 p. , pp.125-178. (rus.)
2. 2. Karachunsky A.I., Rumyantseva Yu.V., Rumyantsev A.G. Evolution of ALL treatment in children: critical use of world experience in Russia // Problems of hematology/oncology and immunology in pediatrics, 2011; 10(2):15–32. (rus.)
3. 3. Rumyantsev, A.G. Accompanying therapy and infection control in hematological and oncological diseases / A.G. Rumyantsev, A.A. Maschan, E.V. Samochatova. M.: Medpraktika-M, 2016. - 504 p., p. 225-256. (rus.)
4. Agulnik A, Mora Robles LN, Forbes PW, et al. Improved outcomes after successful implementation of a pediatric early warning system (PEWS) in a resource-limited pediatric oncology hospital. *Cancer* 2017; 123(15): c.65–74.
5. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). *The Lancet* 2015; 385(9972): 977–1010.
6. Demanelis K., Sriplung H., Meza R., et al. Differences in childhood leukemia incidence and survival between Southern Thailand and the United States: a population-based analysis // Pediatr Blood Cancer. 2015 Oct;62(10):1790-8.