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Results of treatment of acute lymphoblastic leukemias in adults by the modified program "M-Hyper-CVAD-L-Asp-HD-Mtx-HD-Ara-C"

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Abstract: A comparative analysis of the efficacy of treatment of 2 groups of patients with acute lymphoblastic leukemia was carried out according to the standard Hyper-CVAD-HD-Mtx-HD-Ara-C protocol (34 patients) and a modified protocol with the addition of L-Asparaginase "m-Hyper- CVAD-L-Asp-HD-Mtx-HD-Ara-C "(32 patients) with a reduced dose of cytarabine up to 2000 mg / m2. The results of the treatment showed a statistical improvement in the parameters of achieving primary remission, total and disease-free 3-year survival in the group of patients receiving the modified protocol, without increasing the incidence of induction mortality.

Keywords: acute lymphoblastic leukemia, treatment, Hyper-CVAD, modification.

Introduction. Treatment of acute lympholastic leukemia in adults remains an urgent problem of modern hematology. Unlike children's ALL, acute adult lymphoblastic leukemia remains an incurable disease in a large percentage of cases, even despite high-dose chemotherapy programs and transplantation of stem hemopoietic cells. Given the encouraging experience of foreign researchers on the use of the protocol "Hyper-CVAD-HD-Mtx-HD-Ara-C" [2,4,5,6,7,8], which can be a universal and highly effective program for both B-celled ALL , T-ALL, Ph / BCR / ABL positive forms of ALL, relapses of ALL, we decided to implement and evaluate the effectiveness of the above-mentioned adult ALL treatment program.

At the beginning of 2015, the Hyper-CVAD-HD-Mtx-HD-Ara-C program, with some corrections introduced by us, was introduced into the practice of adult hematological units of NIIG and PC of

Uzbekistan in the treatment of acute adult lymphoblastic leukemia. L-Asparaginase is enzyme preparation is one of the basic drugs in the treatment of acute lymphoblastic leukemia. The program "Hyper-CVAD-HD-Mtx-HD-Ara-C" is included L-Asparaginazane. The experience of adding L-Asparaginase to the Hyper-CVAD protocol was proposed by FaderlS et al. (2011) in adult patients with relapsed ALL [1]. Given the importance and necessity of using L-Asparaginase in the treatment of ALL, we considered it expedient to add it to the protocol.

Purpose of the study. The purpose of our study was to evaluate the efficacy, toxicity and tolerability of the modified Hyper-CVAD-L-Asp-HD-Mtx-HD-Ara-C protocol with the addition of L-Asparaginase enzyme preparation in comparison with the standard Hyper-CVAD-HD- Mtx-HD-Ara-C. "

Materials and methods. All in all, 66 (100%) primary patients with ALL (36 men and 30 women) aged 16 to 50 years (mean 33 + 17 years) were included in the study. Translocation t(9:22) was detected in 12 (18.1%) from 66, by the D-FISH method. 34 patients received treatment according to the standard Hyper-CVAD-HD-Mtx-HD-Ara-C protocol, and 32 patients underwent a modification of the m-Hyper-CVAD-L-Asp-HD-Mtx-HD-Ara- C ":

Block A:

- Cyclophosphamide 300 mg / m2 1-3 days, 2 times a day IV,
- Vincristine 1.4 mg / m2 on the 4th and 11th days of the IV,
- Dexamethasone 40 mg / m2 1-4, 11-14 days,
- Doxorubicin 50 mg / m2 4 and 11 days. (In the standard protocol, doxorubicin is administered in block A only 1 time on day 4. In our study, doxorubicin was administered 2 times).
- L-Asparaginase 6000 U / m2 6.7.8 days (it is not in the standard protocol)

Block B (started after recovery of blood values - Hb more than 90 g / l, Leukocytes - not less than 2.0 x 106 / l, platelets not less than 80.0 x 106 / l):

- Methotrexate 1500 mg / m2 on the 22nd day or after restoration of blood values after block A, in the form of daily administration followed by the administration of the antidote of calciumafolinate at 12 mg / m2 iv and in, 6 hours after the end of methotrexate administration, every 6 hours for 4 days),
- Cytarabine 2000 mg / m2 23.24 days. (The dose of cytarabine in the original protocol is 3000 mg / m 2 In our study, the dose of cytarabine was reduced to 2000 mg / m2).

The reason for the modification was the fact that in our subjective opinion, the intensity of Block A is not aggressive enough, and Block B is unreasonably intense. Therefore, we decided to apply L-Asparaginase in a dose of 6,000 units / m2 on 6.7.8 days on day A, additionally, doxorubicin 50 mg / m2 was administered on the 11th day, and in block B the dose of cytarabine was reduced from 3000 mg / m2 up to 2000 mg / m2. Thus, the intensity of both blocks is relatively equalized.

Table. №1. Characteristics of patients.

Indicators	Standard protocol "Hyper-CVAD-HD-Mtx-HD-Ara-C" n = 34		Modified protocol "M-Hyper-CVAD-L-Asp-HD-Mtx-HD-Ara-C" n = 32	
	Абс.	%	Абс.	%
Initial hyperleukocytosis more than 30.0 x 106	7	20.5	6	18.7
Neuroleukemia in the onset	1	2.9	0	0
Splenomegaly	4	11.7	3	9.3
Hepatomegaly	4	11.7	4	12.5
B-cell immunophenotype	33	97	32	100
T-cell immunophenotype	1	2.9	0	0
BCR / ABL mutation t (9; 22)	7	20	5	15.6
Mutation MLL or t (4:11)	0	0	0	0
Mutation C-MYC or t (8:14)	0	0	0	0

As can be seen in Table 1, both groups were comparable in both quantity and initial data.

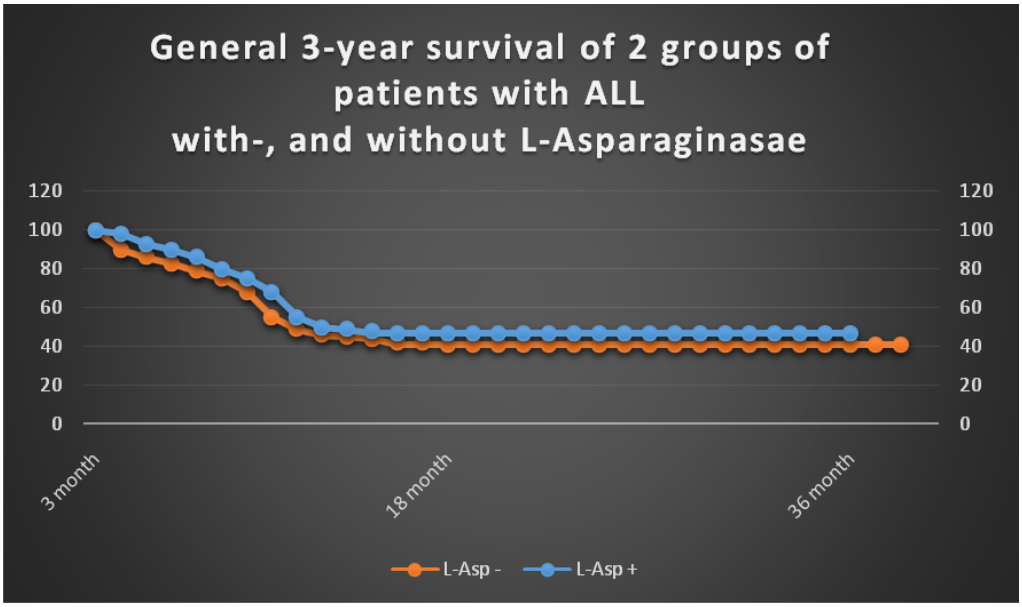
All patients with proven F (9:22) FISH or BCR / ABL PCR-realtime oncogen (Ph + ALL) on-orally received imatinib 400 mg / day during the entire course of treatment, except for the period of deep myelotoxic aplasia of hematopoiesis. Before each block of the protocol, intrathecal administration of cytostatics (cytarabine 30 mg, methotrexate 15 mg, dexamethasone 4 mg) was carried out. A control analysis of the bone marrow was carried out after the first induction block A. When was detected resistance, patients switched to protocols for the treatment of resistant forms.

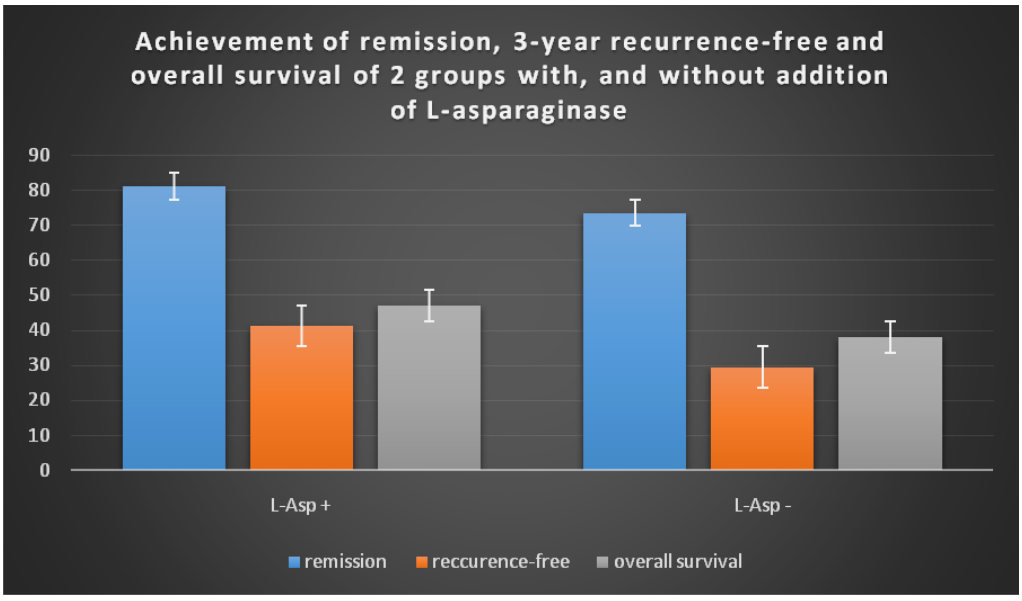
Discussion of the results. In a comparative analysis of the standard and modified protocols, we obtained the following data presented in Table 2.

Table №2. Results of treatment of patients with primary ALL standard and modified protocol "m-Hyper-CVAD-L-Asp-HD-Mtx-HD-Ara-C"

Indicators	Standard protocol "Hyper-CVAD-HD-Mtx-HD-Ara-C" n = 34		Modified protocol "M-Hyper-CVAD-L-Asp-HD-Mtx-HD-Ara-C" n = 32	
	abs	%	abs	%
Achievement of primary remission	25	73.5	26	81.2
Primary resistance	3	8.8	2	6.2
Early mortality	1	2.9	1	3.1
Late mortality	3	8.8	2	6.2
Relapse early	2	5.8	2	6.2
Late relapse	4	11.7	1	3.1
Overal 3-year survival rate	14	41.1	15	46.8
Disease-free 3-year survival	10	29.4	12	37.5
* - Dose of cytarabine 2000 mg / m2 At P≥ 0.05				

As can be seen from the table, in a comparative analysis of two approaches to the treatment of acute lymphoblastic leukemia in 2 comparable treatment groups, we obtained a statistically significant improvement in the parameters for achieving primary remission, total and disease-free survival in the group of patients who underwent a modified protocol supplemented with L-Asparaginase. Later relapses were greater in the group without the addition of L-Asparaginase. After each course of chemotherapy, all patients developed hematological toxicity, with the development of febrile neutropenia, clinically significant thrombocytopenia, deep anemia. This required appropriate accompanying therapy in both groups. There were no statistically significant differences with respect to hematological and organ toxicity.





We did not get the desired result, which is described in the literature [3], which refers to 55% of 3-year recurrence-free survival. The addition of L-asparaginase to the protocol did not increase the organ toxicity and thrombotic episodes. At the same time, we obtained a statistically significant improvement in the indices of general and disease-free survival in the group of patients with the addition of L-Asparaginase to treatment.

Conclusions: Thus, when analyzing the results of treatment of 2 comparable groups of patients with lymphoid forms of acute leukemias treated with the modified Hyper-CVAD-HD-Mtx-HD-Ara-C protocol supplemented with L-Asparaginase, to establish a statistically significant improvement in the rates of primary remission, total and disease-free survival, in favor of a modified protocol without increasing hematological and organ toxicity.

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