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Olga Troyanovska[1], Sergiy Nyankovsky[2], Volodymyr Loginskiy[3], Leonid Dubey[3]

Analysis of infective complications during the program chemotherapy of Acute lymphoblastic leukemia in children in Ukraine

[1]Lviv Regional Specialized Childrens Clinic
[2]Lviv National Medical University
[3]Lviv Institute of blood pathology and transfusion medicine

Establishment of intensive chemotherapeutic regimens for the treatment of acute lymphoblastic leukemia /ALL/ in children in Ukraine have led to improved survival of patients. Because the main cause of mortality of children with ALL are life-threatening infective complications, we have assessed the regularity of development of severe infectious diseases during the program chemotherapy and their relation with explored changes of cellular and humoral immunity and neutropenia.

Key Words: acute lymphoblastic leukemia in chjldren, cellular and humoral immunity, neutropenia, program chemotherapy, infective complications.

Abbreviations:ALL, acute lymphoblastic leukemia; G-CSF, granulocyte colony- stimulating factor.

Acute lymphoblastic leukemia (ALL) – the most common cancer in childhood, makes 30% of pediatric tumours[1]. Any questions related to ALL are important due to increase of the frequency of oncohematological diseases all over the world and also in Ukraine [2]. Establishment of modern chemotherapeutic regimens for ALL treatment had crucial impact on ALL outcome: 70-80% of patients stay in complete long-lasting remission. In Ukraine from the early 90-th of the last century have been started the treatment of childhood ALL according to the uniform program GLL-DGLU-93/95 – modified regimens of original German ALL-BFM-program. It markedly improved ALL outcome. [3]. Event- free survival of children with ALL in Ukraine is 0,75. Meantime, the main cause of mortality (75%) in these patients are life- threatening infections [4]. Prevention of infective complications is a reliable way to improve ALL treatment results [5]. In the last years the etiology and clinical features of infections in the course of leukemias were studied by many researches [6 ,7 ,8, 9, 10, 11, 12, 13, 14]. Numerous investigations have been done to explore different changes of immune system in patients with ALL as a pathogenetic basis for increased susceptibility to infectious diseases [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25].

The aim of the present study was to assess the regularity of development of infective complications during the treatment of ALL in children according to the common in Ukraine chemotherapeutic regimens (GLL-DGLU-93/95) and their relation with the explored changes of cellular and humoral immunity and neutropenia.

PATIENTS AND METHODS

The cohort of 87 patients with ALL, treated in the Hematological Department of Lviv Regional Specialized Children's Clinic, and diagnosed

January 1995 to May 2002 determined. 50 boys 57%/ and 37 girls/42,9%/ with 79 cases of B-/lineage ALL and 8 cases of T-lineage ALL age from 1,1 to 13,9 years. All patients were treated according to the GLL-DGLU-93/95 intermediate protocol regimens.

The freguency of infective complications in children with ALL during the program chemotherapy

Complications	Protocol I, days			Protocol M	Protocol II, days	
	1 – 20	21 – 40	41 – 64		1 – 20	21 – 49
local infections	16 (18,4 %)	32 (36,8 %)	36 (41,4 %)	49 (56,3 %)	17 (19,5 %)	77 (88,5 %)
generalized infections	0	0	0	0	0	9 (10,3 %)
febrile neutropenia	2 (2,3 %)	4 (4,6 %)	12 (13,8 %)	0	0	9 (10,3 %)
lethal outcomes	0	4 (4,6 %)	0	0	0	5 (5,7 %)

risk group branch/,which included 3 protocols /I,M,II/ and maintenance chemotherapy /6-MP, Mtx/ of 2 years general duration.

Investigations of hematological and immunological changes started on day 33 of the Protocol Iafter the completion of induction therapy, before the consolidation treatment. The next examinations were performed prior to the reinduction therapy /Protocol II/ and before the maintenance chemotherapy. The plan of immunity exploration included: examinations of peripheral blood neutrophils and lymphocytes level, the total quantity of T-lymphocytes /CD3+/ and their subsets /CD4+, CD8+/, the quantity of B-lymphocytes /CD19+/ and NK-cells /CD16/56+/: investigation of serum immunoglobulins /IgA, IgM, IgG/. Examinations were performed using modern equipment: hematological analyzer SYSMEX KX-21, Flow Cytometer FACScan /Becton Dickinson/, ICS-Analizer II for serum immunoglobulins investigation.

RESULTS

The results of analysis of infective complications in children with ALL during the program chemotherapy are demonstrated in Table I.

The treatment according to the Protocol I characterized with gradual increase of frequency of infective complications. If before the day 20 of the Protocol I 20% of patients developed infectious diseases and most of them were localized /otitis, enteritis, stomatitis etc./, then from day 21 to 40 of the protocol treatment 53% of children developed infections, moreover in 6,9 % of paients diseases manifested as generalized process /sepsis, septicopyemia/ and in 4,6% of them had lethal outcome. Starting from day 41 and to the end of Protocol I the frequency of infective complications was still high /55,2%/ but the processes were mainly localized. Infections of low intensity and short durations were typical for the Protocol M. The onset of Protocol II (days 1–20) characterized by low level of infections /19,5% but starting from day 21 their frequency markedly increased, in 10,3% of patients diseases were life- threatening and in 5,7% had lethal issue.

DISUSSION

Analysis of infective complications during the program chemotherapy of ALL in children established 2 critical periods of high risk of life-threatening bacterial and fungal infections: days 21–40 of Protocol I and 21–49 of Protocol II.

Investigation of the immune system of children with ALL during the program treatment showed 2 critical points of immunosuppression: after the completion of induction treatment according to the Protocol I and during the completion of reinduction treatment according to the Protocol II. These periods characterized with low level of CD3+-lymphocytes /0,4-0,5x10/9/l/ and their subsets – CD4+lymphocytes /0,2-0,3x10/9/l/,CD8 +-lymphocytes /0,18-0,2x10/9/l/. The level of CD19+-lymphocytes dropped to 0,2x10/9/l. The level of CD16/56+-lymphocytes decreased lower than 0,1x10/9/l.Invastigation of humoral immunity at the critical points of immunosuppression showed low levels of IgA 60-70mg/100ml, IgM 60-80mg/100ml and IgG 560mg/100ml. Deep neutropenia 0,4-0,6x10/9/l was typical for the periods of immunosuppression.

CONCLUSIONS

1. During the program treatment of childhood ALL according to the common in Ukraine chemotherapy regimens GLL-DGL-93/95 were established 2 crytical periods of the development of life-threatening bacterial and fungal complications with high risk of lethal outcome: days 21–40 of Protocol I and 21-49 of Protocol II.

2.The periods of high risk of infective complications corresponded to the critical points of immnosupprssion including cellular,humoral immunity and deep neutropenia.

3. Wide spectrum antibiotics, antimicotics and immune correction using i.v.immunoglobulins, G-

CSF should be recommended during the periods of high risk of life-threatening infective complications during the program treatment of ALL in children [26, 27, 28].

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Olga Troyanovska
Lwów