Are elevated serum levels of IGFBP-2 after intensive chemotherapy of childhood acute lymphoblastic leukemia a risk factor of relapse?

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Abstract

Introduction: In the study we investigated the association between IGFs, their binding proteins and pathogenesis as well as prognostic factors of relapse of childhood ALL.

Material and methods: In 43 children suffering from ALL, we observed 7 cases of relapse. We studied the serum levels IGF-I, IGF-II, IGFBP-3 and IGFBP-2 (expressed in SDS) in a subgroup with relapse (A) and in a subgroup without relapse (B) at diagnosis (1), after induction of remission (2) and after intensive chemotherapy (3). All comparisons were made with age-and sex-matched controls.

Results: It was found that in subgroup A, the values of IGFBP-2 remained high at each stage of the investigation: 3.92±2.50 (1) 3.68±0.99 (2) 3.52±1.26 (3), whereas in the subgroup B they underwent a significant reduction from 3.87±1,86 (1) 3.45±1.25 (2) 2.15±1.84 (3), p=0.02. In comparison to a control group, the correlations between IGF-I and IGFBP-3, and IGF-I and IGFBP-2 were disturbed for the whole group of children at each stage of the investigation. However, at diagnosis we obserwed a negative correlation between IGFBP-2 and hemoglobin (r=-0.57 p=0.0001).

Conclusion: Increased values of IGFBP-2 after intensive chemotherapy in children who subsequently underwent a relapse of the disease, suggest that IGFBP-2 levels might constitute a prognosis factor. However, this requires verification with a larger group of children. The negative correlation between values of hemoglobin and IGFBP-2 observed at diagnosis might further suggest the involvement of this protein in the process of leukemogenesis in children.

Key words: IGFBP-2, acute lymphoblastic leukemia, children, relapse.

Abbreviations: ALL acute lymphoblastic leukemia; AML – acute myeloblastic leukemia; IGF – insulin-like growth factor; IGFBP – IGF binding protein; IGFBP-rP – IGFBP related protein; ALS – acid labile subunit; BFM – Berlin-Frankfurt-Münster; NHL – Non-Hodgkin lymphoma; BMI – body mass index; GH – growth hormone.

Introduction

Insulin-like growth factors – IGFs, belong to a family of peptides involved in the proliferation and differentiation of cells. They also have an insulin-like metabolic effects. Together with their binding proteins (IGF binding proteins – IGFBPs), proteases of IGFBPs, activators and inhibitors of these proteases, as well as two cell-surface receptors mediating the biological activity of IGFs, they constitute a system of great significance within physiology and pathology [1-5].

The primary function of IGFBPs is the modulation of the biological activity of IGFs, through prolongation their half-life and the influence on their bioavailability (1,9-11). The physiological activity of IGFBPs is based on two mechanisms: IGF-dependent and IGF-independent. The function of IGFBPs in the mechanism IGF-dependent, is the transport of IGFs across the capillary barrier, enhance or inhibit the presentation of IGFs to their receptor. The regulation of the growth, migration and metabolism of cells, through IGFBPs, also occurs in the mechanism independent on IGFs [4,6,10-12].

Recent studies have confirmed the involvement of the IGF system in the pathogenesis of cancers (breast, prostate, lung, ovarian, bladder cancer, childhood acute lymphoblastic leuke-

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mia, Wilms tumour, neuroblastoma), and have verified their significance in prognosis [13-21].

The aim of the study was to investigate the involvement of IGF-I and IGF-II, and their binding proteins IGFBP-3 and IGFBP-2 into the pathogenesis of acute lymphoblastic leukemia (ALL) in children, as well as learn if the investigated factors play a role in relapse prognosis.

Material and methods

Patients and control

Forty-three children with newly diagnosed ALL (30 males and 13 females), from Department of Pediatric Oncology in Bialystok were studied prospectively from February 2000 to January 2004. The patients were investigated at three different points: at diagnosis (n=43), after induction of remission (n=32) and after the end of intensive chemotherapy (n=38). Thirty-seven of the patients (86%) suffered from B-precursor cell ALL, whereas four (9.3%) suffered from T-cell ALL. The immunophenotype ALL-common with coexpression of the myeloid markers was determined in two patients (4.65%). Initial leukocytes count ranged from 1.200 to 540.000 $x10^9$/l. According to the protocol ALL IC-BFM 2002 children with initial leukocytosis over 20 000 /mm^3 face higher risk of relapse. In analysed group 14/43 (30,23%) of the patients had initial leukocytosis >20 000/mm^3 and only 3/14 (21,42%) of them presented the relapse of ALL – *Tab. 1*. The median age of the patients was 4.66 (range 1.5-16) at the start of chemotherapy. Three of the patients died at the time induction remission (as the consequence of severe infection during bone marrow aplasia), one continued the treatment in another department. Clinical data of the children at diagnosis explain *Tab. 1*. Among 43 studied patients, seven developed recurrence, on average 26 months after diagnosis – *Tab. 2*. Children were divided into two subgroups: A-subgroup with relapse and B-subgroup without relapse. The control group included 42 healthy children (the age range from 1.33 to 16.83, median =5.58, 31 males and 10 females).

Therapy

Twenty-seven patients were treated according to the protocol ALL-BFM-90 (for low risk group), six – according to the New York II protocol (for high risk group) and ten – according to the ALL IC-BFM 2002 protocol (3 – standard risk group, 6 – intermediate risk group, 1 – high risk group).

Blood Sampling

Blood samples were collected at diagnosis (1), after induction remission – (after protocol I in the protocols BFM and after protocol of the induction remission, part one of the consolidation of the remission according to the New York II protocol) (2) and after finishing the intensive chemotherapy (3); on average 6-8 months after diagnosis. Serum was stored at -80°C until analysis. The blood samples of the children who had severe infections (fever, elevated CRP) and impairment of liver function (s-aminotransferases as abnormally high levels as 5x the above normal limit) were excluded.

Methods

Anthropometric parameters. Linear growth was measured on a wall-mounted Harpenden stadiometer. The weight was measured and the BMI (body mass index) calculated at all study points. Data were transformed to SDS using Polish reference values [22].

Biochemical measurements. IGF-I analysis was performed after acid–ethanol extraction, by radioimmunoassay (RIA, Biosource Europe S.A., Belgium KIP1589). Inter-assay coefficient of variation was 9.8, 9.6 and 8.1% at 38.8 ng/ml, 160.8 ng/ml and 664 ng/ml respectively.

IGF-II was also determined after acid-ethanol extraction, by IRMA (DSL, Webster, Texas, USA DSL-9100). Inter-assay coefficient of variation was 9.5, 6.3 and 10.4% at 74 ng/ml, 427 ng/ml and 1295 ng/ml respectively.

IGFBP-3 concentration was measured using a commmercially available radioimmunoassay kit (DSL, Webster, Texas, USA DSL--6600). Inter-assay coefficient of variation was 1.9%, 0.5% and 0.6% at 76.9 ng/ml, 21.51 ng/ml and 8.03 ng/ml respectively.

IGFBP-2 concentration was evaluated by RIA (DSL, Webster, Texas, USA DSL-7100). Inter-assay coefficient of variation was 7.4%, 4.5% and 7.2% at 2.7 ng/ml, 13.2 ng/ml and 69.7 ng/ml respectively.

The values of IGF-I, IGF-II, IGFBP-3 and IGFBP-2 were age-adjusted by calculating the standard deviation score (SDS) [23-25].

Statistical Analysis

All values are presented as the mean and SD of the age and sex-independent standard deviation score (SDS). All comparisons were made with age-and sex-matched controls. Statistical procedures were performed using SPSS for windows (STATISTICA 6.0 PL). The statistical difference between the values of two independent groups was tested by the U Mann-Whitney test. Changes in the parameters were assessed for three periods: at diagnosis, after the induction of remission and after intensive chemotherapy. The significance of the changes was analyzed by Friedman, Wilcoxon and ANOVA tests. The correlations were performed using Spearman correlation analysis. The significance was chosen as $p<0.05$.

All the investigations were strictly made in accordance with the guidelines of the medical ethics committee in Białystok.

Results

The values of IGF-I SDS in both subgroups exceeded -2 SD score and rested unchanged during the analysis. Those values were lower comparing to control group – *Tab. 3*. We did not find any differences between mean values of IGF-II SDS in both subgroups at any point of analysis – *Tab. 3*.

Values of IGF-II SDS increased significantly in the group without relapse (B) p=0.001 by ANOVA. In subgroup A the values did not differ statistically at any the time of the observation. In comparison to control group (0.57±1.04), we found lower IGF-II SDS at diagnosis in subgroup B (p=0.009) – *Tab. 3*. In other points of analysis there were no differences between control and the subgroups.

Table 1. **Hematologic parameters of the patients at diagnosis**

	immunophenotype	Sex F/M	age	initial leukocyte (x109/l)	blast count (x109/l)	Hb (G/l)	Karyotype of blasts
1.	ALL-common	M	4.56	2.80	0.28	8.1	normal
2.	ALL-common*	M	14.40	33.90	27.12	11.8	normal
3.	ALL-common	F	4.40	32.70	25.06	7.9	normal
4.	ALL-common	M	2.00	4.90	0.29	9.1	normal
5.	ALL-common	M	5.00	11.00	3.30	13.2	abnormal**
6.	ALL-common*	F	6.40	80.00	72.00	7.4	normal
7.	ALL-common	M	3.00	540.00	507.60	8	normal
8.	ALL-common	M	8.08	4.80	0.96	7.9	normal
9.	ALL-common*	M	2.24	3.50	3.50	6.8	normal
10.	ALL-common	M	3.56	7.50	1.27	11.2	normal
11.	ALL-common	M	13.72	1.60	0.00	7.7	normal
12.	ALL-common	F	3.00	7.00	1.40	8.4	normal
13.	ALL-common*	M	5.80	79.80	71.80	9.1	t (9;22)
14.	ALL-common	M	2.75	1.70	0.51	8.9	normal
15.	ALL-common	M	13.16	1.40	0.00	5.7	normal
16.	ALL-common	M	3.16	30.60	18.48	10.2	normal
17.	ALL-common*	F	4.64	9.10	0.91	7.2	normal
18.	ALL-common	M	10.16	2.80	0.84	9.8	normal
19.	ALL-common*	M	5.80	56.00	45.36	6.8	normal
20.	ALL-common	F	3.91	2.70	0.54	10.2	normal
21.	ALL-common	M	4.40	11.50	9.43	3.6	normal
22.	ALL-common	M	1.56	3.10	0.31	7	normal
23.	ALL-common	M	16.00	2.70	0.00	8.4	normal
24.	ALL-common	F	4.83	6.60	2.54	9.3	normal
25.	ALL-common	F	12.58	2.40	0.38	9	normal
26.	ALL-common	F	14.33	2.30	2.02	10.4	normal
27.	ALL-common	M	2.83	8.70	4.52	10.3	normal
28.	ALL-common	M	2.75	26.50	24.38	7.1	normal
29.	ALL-common	M	6.50	6.50	1.43	9.8	normal
30.	ALL-common	M	4.66	5.60	1.51	6.7	normal
31.	ALL-common	M	4.33	30.90	28.42	7.8	normal
32.	ALL-common	M	2.33	5.10	2.28	3.3	normal
33.	ALL-common	M	4.60	31.10	7.46	5.5	normal
34.	ALL-common	F	1.75	9.90	6.33	7	normal
35.	ALL-common	M	6.08	4.90	2.05	8.9	normal
36.	ALL-common	F	2.91	23.90	5.97	4.9	normal
37.	ALL-common	M	14.16	3.40	0.13	8.3	hyperdiploidia
38.	ALL-common + coexpression CD15*	F	13.64	9.80	9.80	9.9	normal
39.	ALL-common + coexpression CD33	F	13.40	12.30	8.65	8.9	normal
40.	ALL-pre T	M	6.750	107.50	80.00	3.3	47XY+ mar[3]
41.	ALL-T	M	7.40	66.80	37.07	12	normal
42.	ALL-T	F	2.75	6.00	0.00	6	normal
43.	ALL-T	M	7.58	1.200	0.48	6.7	t(8;10), t(7:14)

* – children with relapse; ** – 44-46,XY,del(1)(q42),del(3)(q32),del(5) (?p11),?del(7)(?q31?q34),r(?),-19,-21[cp19]/46,XY[20]

Table 2. **Characteristics of patients with relapse**

F/M	relapse	time after diagnosis (month)	program of treatment
F	early bone marrow	21	New York II
M	early bone marrow	28	New York II
F	early bone marrow	26	BFM-90
M	early bone marrow	30	BFM-90
F	late mixed (bone marrow+CNS)	40	BFM-90
M	very early testicular	7	BFM-90
M	late mixed (bone marrow and testicular)	30	New York II

We observed significant increase of the values of IGFBP-3 SDS in both subgroups; in group A p=0.005 by ANOVA and in subgroup B p=0.00035 by ANOVA. After induction remission the mean values of IGFBP-3 SDS were lower in subgroup A, than in subgroup B, p=0.01. The mean value of IGFBP-3 SDS in control group differed statistically from group A at diagnosis (p=0.006) and after induction remission (p=0.01). After the end of intensive chemotherapy we did not find the differences between subgroup A and control. In subgroup B, IGFBP-3 SDS values were lower than in control group only at diagnosis (p=0.009).

At diagnosis and after induction remission the mean values of IGFBP-2 SDS did not differ significantly between subgroup A and subgroup B (p=0.95, p=0.98 respectively). However, after the end of intensive chemotherapy we observed tendency to lower values of IGFBP-2 SDS in subgroup B comparing to subgroup A (p=0.06) – *Tab. 3*. The values of IGFBP-2 SDS declined significantly during the observation in subgroup B (p=0.02 by ANOVA) whereas in subgroup A they stayed unchanged (p=0.84 by ANOVA). Those values were higher than in control group at diagnosis and after induction remission. However, after the end of intensive chemotherapy we found the difference between control and subgroup A (p=0.001) but there was not difference between control and subgroup B (p=0.77).

We did not find the differences in IGF-I, IGF-II, IGFBP-3 and IGFBP-2 expressed as SD score at any point of analysis between the group of children with initial leukocytosis >20 000 /mm^3 and <20 000/mm^3.

We observed the correlation between IGF-I SDS and IGF-II SDS in control group (r=0.38 p=0.01), and similarly in subgroup B: at diagnosis (1) r=0.41 p=0.01 and after induction remission (2) r=0.42 p=0.01. We did not find such correlation at any point of analysis in subgroup A. We found the correlation between IGF-I SDS and IGFBP-3 SDS in subgroup A at diagnosis (r=0.75 p=0.04) and after induction remission (r=0.94 p=0.004) similarly to control (r=0.53 p=0.0003) but there was no such correlations in subgroup B – *Tab. 4*. There was no correlation between IGF-I SDS and IGFBP-2 SDS at any stage of analysis. The correlation between IGF-II SDS and IGFBP-3 SDS in subgroup without relapse were similar to control r=0.44 p=0.008 (1), ns (2) and r=0.46 p=0.008 (3), whereas in patients with relapse it was not observed. We did not find any correlation between IGF-II SDS and IGFBP-2 SDS in analyzed subgroups, whereas in control it was observed – *Tab. 4*. We found the negative correlation between IGFBP-2 SDS and hemoglobin (-0.57 p=0.0001), between IGFPB-2 SDS and total protein at the time of diagnosis -0.45 p=0.003 and after induction remission -0.46 p=0.03. However, in our study we did not observe any corelation between initial leucocytosis and platelets and count of blast cells.

Discussion

The amount of leucocytosis (>20 000/mm^3), the age of the child and genetic changes within the karyotype of the lymphoblasts at the time of diagnosis are recognised as the risks of ALL relapse. There are other factors of relapse such as the response

Table 3. **Values of the components the IGF-system, expressed as SDS (subgroup A, B and C-control): 1 – at diagnosis, 2 – after induction remission, 3 – after intensive chemotherapy, p – difference between subgroup A and subgroup B; p*difference between control and subgroup A – p<0.05, p**difference between control and subgroup B – p<0.05**

		A n	mean	range	standard deviation	B n	mean	range	standard deviation	p	C n	mean	range	standard deviation	p*,**
IGF-I SDS	1	7	-2.10	-2.79 - (-1.18)	0.61	36	-2.02	-4.59 - 1.10	1.15	ns					
	2	7	-2.16	-3.13 - (-0.98)	0.77	27	-2.08	-4.47 - 1.14	1.43	ns	41	-0.31	-2.93 - 12.01	2.50	p*,**
	3	7	-2.24	-3.62 - 0.03	1.12	31	-1.60	-3.96 - 1.58	1.10	ns					p*,**
IGF-II SDS	1	7	0.30	-1.66 - 4.31	2.08	36	-0.19	-2.85 - 2.62	1.33	ns					p**
	2	7	0.30	-1.19 - 1.07	0.84	27	0.40	-1.90 - 3.76	1.48	ns	41	0.57	-1.33 - 3.17	1.04	ns
	3	7	0.09	-1.94 - 2.90	1.81	31	0.77	-3.16 - 6.09	1.77	ns					ns
IGFBP-3 SDS	1	7	-0.78	-1.98 -1.80	1.29	36	-0.08	-4.50 - 7.79	2.29	ns					p*,**
	2	7	-0.74	-1.80 - 0.20	0.83	27	1.13	-1.53 - 4.53	1.72	p=0.01	41	0.92	-1.99 - 6.39	1.72	p*
	3	7	1.12	-1.54 - 5.80	2.41	31	1.96	-1.26 - 11.28	2.72	ns					ns
IGFBP-2 SDS	1	7	3.87	1.32 - 6.15	1.86	36	3.92	-3.69 - 8.44	2.50	ns					
	2	7	3.68	2.64 - 5.41	0.99	27	3.45	0.22 - 5.84	1.25	ns	41	1.34	-2.03 - 4.31	1.37	p**, p*,**
	3	7	3.52	1.54 - 5.36	1.26	31	2.15	-1.22 - 5.89	1.84	p=0.06					p*

Table 4. **Correlation between components of the IGF-system: 1 – at diagnosis, 2 – after induction of remission, 3 – after intensive chemotherapy, c – control**

corelation r Spearman		IGF-II SDS	IGFBP-3 SDS	IGFBP-2 SDS
IGF-I SDS	1	0.37 p=0.01	ns	ns
	2	0.44 p=0.01	ns	ns
	3	ns	ns	ns
	c	0.38 p=0.01	0.53 p=0.0003	-0.56 p=0.0001
IGF-II SDS	1		0.43 p=0.004	ns
	2		ns	-0.41 p=0.01
	3		0.47 p=0.002	ns
	c		0.46 p=0.002	-0.40 p=0.008
IGFBP-3 SDS	1			ns
	2			-0.38 p=0.03
	3			ns
	c			ns

to induction therapy and the presence of minimal residual disease in the 12th week of chemotherapy treatment. Despite appropriate allocation of children to therapeutic programs, there is a group of children in which the relapse of the disease may occur. Unfortunately, the treatment of the second attack of the disease involves a high risk of failure. This is why the efforts of the researchers within this area are concentrated upon investigating unfavourable factors affecting prognosis, in order to intervene early enough to prevent a relapse of the disease.

During the current study, the relapse occurred in seven children (out of 43). Only three out of seven were classified into the high risk group, based on the classical risk factors of relapse and received more intensive chemotherapy treatment. The remaining four were treated with protocol ALL BFM-90 for the low risk group.

In both of the subgroups – with and without relapse, a significant increase of the level of IGFBP-3 SDS was observed in subsequent phases of the study. In the subgroup without relapse it was observed a significant increase of IGF-II SDS, whereas in the subgroup with the relapse, mean values of insulin-like growth factors (IGF-I SDS and IGF-II SDS) as well as IGFBP-2 SDS remained relatively constant throughout the time of the analysis (therefore no significant changes were observed).

No statistically significant differences in the mean values of IGF-I SDS, IGF-II SDS were observed between the subgroups at any stage of the investigation. The subgroup which relapsed displayed higher mean values of IGFBP-2 SDS in comparison to the group without relapse, following intensive chemotherapy p=0.06. It should be noted that the mean values of IGFBP-2 SDS, both at diagnosis and after the induction of remission were nearly identical in both subgroups p(1)=0.95 and p(2)=0.98. The presence of significant differences between both subgroups in the mean values of IGFBP-2 SDS was noted only after the end of intensive chemotherapy. Therefore, the high level of IGFBP-2 SDS at the end of intensive treatment might be an independent risk factor for the relapse of the disease in children with ALL.

Mohnike et al. found that the values of IGFBP-2 SDS normalise in children with ALL in remission [26]. Vorwerk et al. observed that the expression of the IGFBP-2 gene in mononuclear cells in children with ALL is the same at the time of diagnosis and during the 33rd day of the treatment (i.e. at the time of remission). In children who later experienced a relapse of the disease, there was a higher proportion of cells expressing the IGFBP-2 gene at the time of diagnosis, compared to the rest of the children. Vorwerk et al. investigated the expression of the following genes: IGF-I, IGF-II, IGF-IR, IGF-IIR, IGFBP-1 to 5, IGFBP-rP1 and IGFBP-rP2. They found that the significant differences in IGFBP-2 and IGFBP-3 gene expression between the group which relapsed and the remaining children [27].

Wex et al. showed a positive correlation between the expression of the IGFBP-2 gene in mononuclear cells obtained from children with ALL (from bone marrow or peripheral blood) and the concentration of IGFBP-2 in the serum. They concluded that higher concentration of IGFBP-2 in the serum was related to its abnormally high production by neoplastic cells [28]. Dawczynski et al. observed relapse after a blood marrow transplantation in AML-patients with increase of IGFBP-2 at day 100 after a blood marrow transplantation. The authors suggest the high possibility of relapse and poor outcome in patients with IGFBP-2 higher then 4.5 SDS [29].

It has also been noted that the concentration of IGFBP-2 in the blood serum is correlated with the stage of the disease and can serve as a marker for reccurrence of solid tumours. In patients with ovarian cancer, in whom a continuously increased level of IGFBP-2 was observed during post-operative treatment, a relapse of the disease subsequently occurred [30]. Likewise, in patients with colorectal cancer, high values of IGFBP-2 correlated with recurrence and degree of dissemination of the disease [31].

We found strong negative correlation between IGFBP-2 SDS and hemoglobin (g/L) at diagnosis (r=-0.57, p=0.0001). It indicates that IGFBP-2 level is proportional to degree of anemia at diagnosis due to elimination of precursors of normal erythropoiesis by leukemic clone. The high level of IGFBP-2, observed during fetal development, might suggest that in patients with ALL the increase of IGFBP-2 is connected with proliferation of early hematopoietic progenitors [29,32]. The decrease of IGFBP-2 values during the treatment, described in malignant disease by other authors, indicates their role in leukemogenesis [26,30].

Petridou et al. found that high levels of IGFBP-3 at the time of diagnosis of ALL in children decrease the risk of death from the disease [33]. Vorwerk et al. showed that high values of

IGFBP-2 and low values of IGFBP-3 at the time of diagnosis increase the risk of relapse [34].

In the current study, at diagnosis the mean levels of IGFBP-3 SDS were lower in both analyzed subgroups comparing to control. However, these values rose during the treatment. Similarly, Mohnike et al. found that low values of IGFBP-3 at diagnosis increased after induction remission [26]. It has suggested that increased IGFBP-3 proteolysis might be responsible for the enhanced growth of IGFBP-2 – over expressing tumors *in vivo* [18]. In our study, in the group with relapse, the increase of IGFBP-3 SDS was less intensive. After induction remission, we found the difference in IGFBP-3 SDS between the group with and without relapse. Dawczynski et al. observed the increase of IGFBP-2 with simultaneous decrease of serum IGF-I and IGFBP-3 100 days after bone marrow transplantation [29]. In our opinion, the differences in correlations between IGF-I SDS and IGFBP-3 SDS, IGF-II SDS, in the group with and without relapse, indicate different mechanisms of regulation and their possible role in leukemogenesis. It is suggested that IGFBP-3 has antiproliferative and proapoptotic action.

Values of IGFBP-2 rested elevated for the group which relapsed throughout the whole analysis. Following the end of intensive chemotherapy, they were higher in comparison to the group without relapse, in which they decreased by 41%. It may suggest the local production of IGFBP-2 by residual blasts. The small group of children with relapse might perhaps prevent the formulation of definite conclusions and these findings therefore require verification with a larger group. Increased values of IGFBP-2 in children may be a risk factor for relapse.

Conclusion

The differences in the levels of insulin-like growth factors and their binding proteins between healthy children and those with acute lymphoblastic leukemia at the time of diagnosis, as well as the changes observed during therapy and in particular differences in the group of patients who relapsed, suggest the involvement of IGFs and IGFBPs in the process of leukemogenesis. The continuously increased values of IGFBP-2 after the end of intensive chemotherapy in the group of children who subsequently experience a relapse of the disease, suggest that high values of IGFBP-2 might constitute a prognostic factor in ALL. However, this requires verification with a larger group of children.

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