CLINICAL STUDY

Late effects of anticancer therapy on kidney function in children with acute lymphoblastic leukemia

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Abstract

The current state: **Children with curable cancer are potentially at risk of long-term renal sequelae. The nephrotoxicity is considered dose related and includes a variable reduction of glomerular filtration rate along with tubular dysfunction.**
Subjective: **The aims of the present study were: to analyse kidney damage as well as the clinical course in children treated for ALL, to determine what type of nephrotoxic damage is most frequent in relation with the used treatment, to determine possible risks of acute and chronic nephropathy of anticancer therapy, to standardise evaluation of kidney function in children after their complex antitumourous treatment has finished.**
Methods and material: **We examined a group of 36 children (21 boys, 15 girls, average age at diagnosis of ALL 6.9 years)) treated for ALL using the therapeutical protocol ALL BFM 90.The average period after the treatment had finished was 48 month. The following parameters were examined: urinalysis and urine sediment, clearance of creatinine, tubular resorption, ultrasound of kidneys, 24 hrs proteinuria (PU) and urine concentration of albumine, transferine, alpha-1-microglobuline and Tamm-Horsfall protein. Concentration function of kidneys was examined by test with DDAPV.**
Results: **After finish of cytostatic therapy had 19 patients (52.8 %) PU. Glomerular PU was found in 3 children (15.8 %), in 3 children (15.8 %) was found mixed PU and 13 children (68.4 %) had tubular PU. Reduction of GFR had 5 patients (13.9 %) and 19 patients (52.8 %) had reduction of DDAPV test.**
Conclusion: **Sensitive laboratory analysis of proteinuria is required for timely detection of the most frequent type of kidney damage in the course of treatment with cytostatics but also other concurrently administered drugs. Thus we can reliably detect mainly patients with glomerular/mixed proteinuria who are potentially imperilled by the risk of the development of chronic renal failure. If there is higher level of glomerular/mixed proteinuria even after the treatment has finished, the patients have to undergo another nephrological monitoring.** ***(Tab. 3, Ref. 20.)***
Key words: nephrotoxicity, acute lymphoblastic leukemia, proteinuria, kidney function.

The acute lymphoblastic leukemia (ALL) is the most frequent oncological disease in child's age. Since 1989 children with this diagnosis are treated according to the standard curative regimen BFM and about 80 % of patients survive more than 5 years in the present. On the one hand, the number of children who are totally cured from the oncological disease increases, on the other hand at the same time the group of children with the risk of late morbidity becomes larger (19). Alteration of the kidney function as a consequence of cytostatic therapy is well known as from literary data as from the clinical practice (2, 15, 17). Under physiological conditions the kidney is an organ with relatively high metabolic turnover. Its regular function is a limiting factor in maintaining the integrity and homeostasis of the inner environment. The kidneys metabolise the majority of drugs, which are then excluded in urine. The impairment of the kidneys due to the cytostatic therapy occurs via the direct effect of the administered drugs on the one hand, or by an indirect effect on the other. The clinical symptoms of the renal impairment may be manifested as acute failure of the kidneys or may be expressed as manifestations of their chronic impairment.

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Tab. 1. Laboratory parameters before chemotherapy.

Patient	Urine			C_{kr}	TR	USV
	urinanalysis	microscopy	proteinuria	ml/min/1,73m^2	%	
1	negative	2Le	43	115,7	98,7	negative
2	negative	negative	22	101,6	98,8	negative
3	B+	3Le,2Ery	65	123,4	99,2	negative
4	negative	negative	38	128,2	99,0	negative
5	negative	4Le	37	98,7	97,6	negative
6	B+	2Le	45	100,2	98,0	negative
7	negative	3Le,2Ery	32	97,5	97,7	negative
8	negative	2Le,3Ery	38	102,3	98,8	negative
9	B+	3Le	49	123,7	99,3	pelvis duplex l.sin.
10	B+	3Le,2Ery	46	115,3	98,8	negative
11	negative	negative	37	122,6	98,9	negative
12	negative	negative	36	103,5	99,1	negative
13	negative	3Le	28	115,6	98,8	negative
14	B+	3Le,3Ery	37	100,1	98,0	negative
15	negative	negative	44	118,7	99,5	negative
16	negative	2Le	35	98,7	97,8	negative
17	negative	2Le,3Ery	30	99,8	98,0	negative
18	negative	2Le	27	102,7	98,6	negative
19	B+	negative	65	125,8	99,5	negative
20	negative	negative	48	105,4	98,7	negative
21	B+	negative	94	134,2	99,4	sy of upper ren.calyx l.sin
22	B+	3Ery	88	142,3	99,2	negative
23	negative	negative	55	111,7	98,8	negative
24	negative	negative	45	100,2	99,3	negative
25	negative	2Le	48	112,7	98,5	negative
26	negative	negative	55	123,6	99,1	negative
27	B+	3Le	22	98,7	97,4	negative
28	negative	negative	39	82,4	97,6	negative
29	negative	negative	41	97,8	98,0	negative
30	B+	negative	96	132,8	99,2	negative
31	negative	2Le	33	81,8	97,6	negative
32	negative	negative	37	89,6	97,7	negative
33	negative	3Le	44	93,6	98,2	negative
34	negative	2Le	42	88,3	97,8	negative
35	negative	negative	37	97,8	98,4	negative
36	negative	2Le	43	102,3	98,7	negative

proteinuria - mg/24hrs
B - proteinuria (dipstick testing: 0, +, ++, +++, ++++)
Le - leukocytes ; Ery - erytrocytes ; C_{kr} - creatinine clearance
TR - tubular resorption ; USV - ultrasonography

Tab. 2. Laboratory parameters after chemotherapy.

Patient	Urine			C_{kr}	TR	USV
	urinanalysis	microscopy	proteinuria	ml/min/1,73m^2	%	
1	negative	negative	87	137,4	99,2	negative
2	B++	2Le	238	112,6	88,6 ββ	negative
3	negative	negative	65	128,7	98,5	negative
4	B+	negative	287	115,8	87,6 ββ	negative
5	negative	negative	43	98,6	97,8 ββ	negative
6	negative	negative	54	103,2	98,4	negative
7	B++	2Le	253	98,6	85,4 ββ	negative
8	negative	3Le	44	115,4	98,4	negative
9	B+	2Le,0-2Ery	66	129,5	98,8	pelvis duplex l.sin
10	B++	negative	312	88,6 β	88,6 ββ	negative
11	negative	negative	46	128,8	98,8	negative
12	B++	3Le,0-2Ery	386	87,4 β	87,6 ββ	negative
13	negative	negative	89	135,0	98,7	negative
14	negative	2Le	48	98,7	98,7	negative
15	B++	2Le,0-2Ery	356	90,3 β	89,0 ββ	negative
16	B++	negative	288	105,5	88,8 ββ	negative
17	negative	3Le	47	98,7	99,2	negative
18	B++	2Le,2Ery	320	112,5	88,7 ββ	negative
19	B++	2-3Le,0-2Ery	315	98,5	97,8 ββ	negative
20	B++	negative	287	103,4	90,2 ββ	negative
21	B++	3Le,0-2Ery	256	137,5	93,6 ββ	sy of upper ren.calyx l.sin
22	K+	5Ery	96	138,9	99,5	negative
23	B++	3Le,2Ery	347	95,6 β	91,0 ββ	negative
24	B++	negative	284	92,3 β	88,7 ββ	negative
25	negative	3Le	105	118,7	98,7	negative
26	B++	3Le	317	116,8	89,7 ββ	negative
27	negative	negative	66	98,6	98,2	negative
28	B++	negative	225	102,0	98,6	negative
29	B++	negative	194	115,6	98,8	negative
30	B++	negative	314	123,7	98,7	negative
31	negative	negative	98	98,6	99,2	negative
32	negative	negative	90	123,6	98,7	negative
33	negative	negative	87	98,6	98,8	negative
34	B++	negative	336	112,7	98,4	negative
35	negative	negative	65	102,3	99,2	negative
36	B++	negative	290	115,7	98,7	negative

proteinuria - mg/24hrs
B - proteinuria (dipstick testing: 0, +, ++, +++, ++++)
Le - leukocytes ; Ery - erytrocytes ; C_{kr} - creatinine clearance
TR - tubular resorption ; USV - ultrasonography
β - decreased C_{kr} ; ββ - decreased TR

Material and methods

We analysed a group of 36 children (21 boys and 15 girls) treated for ALL. At the time of diagnosing the disease the average age of the children was 6.9 years (in the range of 1.5 to 17.3 years). The children were treated according the therapeutic regimen ALL BFM 90. Considering the determined degree of the ALL risk 7 children (20.0 %) were treated according to the regimen for standard risk, 26 children (72.2 %) according to the regimen for medium risk and 3 children (7.8 %) according to the regimen for high risk. Before the onset of the oncological therapy, taking into consideration possible nephrotoxic effects, in all children usual examinations given in Table 1 were carried out. Control examinations of all children were performed in the course of a short-term hospitalisation within in average 48 months (in the range of 24 months to 96 months and 3 weeks) after the termination of the antitumour therapy. The results obtained are given in Tables 2 and 3. At the control examination all children were in the clinical and hematological remission of ALL.

The basic chemical examination of urine was performed by means of test stripes. Always the fresh morning urine was analysed. The urine sediment was evaluated in microscope after centrifugation (1000 r.p.m. for 2—3 min) using usual enlargement (10x or 40x). Urine for the examination of proteinuria (PU) was collected for 24 hours and PU was determined using immunoturbidimetry after denaturing proteins by means trichloroacetic and hydrochloric acids. The value of 150 mg per 24 hours was taken as the upper limit of quantitative aPU. Urine concentrations of albumin, transferrin, alpha$_1$-microglobulin and Tamm-Horsfall protein were used for distinguishing the types of PU. Glomerular filtration (GF) was determined by means of clearance of endogenous creatinine. For the analysis a urine sample from complete 24-hour diuresis was taken. Blood for determining the serum concentrations of laboratory parameters was obtained from a vein, always on an empty stomach in morning hours at the end of the period of urine collecting. The concentration ability of the kidneys was determined by a DDAPV test (1-deamino-8-D-arginine-vasopressine) in modification according to Janda using the preparation Adiuretin SD drops. This test was used only in the control examination of the children group investigated, since it is not a standard part of the examination regimen before the onset of therapy with cytostatics. In all children the kidneys were examined by ultrasonography using an Acuson 128 XP/100 apparatus with 3.5 or 5 MHz probe. In the course of the control hospitalisation blood pressure was monitored (ABPM method) in all children for 24 hours. The data obtained were processed statistically using the method of simple classification according two markers and Fischer factorial test, which makes it possible to verify the hypothesis of independence even at small frequencies.

Tab. 3. Analysis of proteinuria, ADH test and hypertension after chemotherapy.

	Proteinuria					
	albumin	transferin	alfa-1microglob.	T-H protein	ADH test	
Patient	mg/24hrs	mg/l	mg/24hrs	mg/24hrs	mmol/kg	Hypertension
2			24	78	890	0
4			38	87	875	0
7			36	82	870	0
10			45	94	860	0
12	51	3,4	49	97	827	0
15	46	2,9			830	0
16			37	91	887	0
18			39	93	885	0
19			36	89	923	0
20			38	88	868	0
21			36	82	895	0
23	49	3,1	46	89	894	0
24	39	2,7	42	88	878	0
26			39	89	880	0
28			31	84	902	0
28			26	73	920	0
29					917	0
30	39	2,7			898	0
34	44	2,9			880	0
36			29	70	887	0

alfa-1microglob. - alfa-1microglobulin ; T-H protein - Tamm-Horsfall protein
ADH test - test with desmopressin, urine osmolality
+, 0 - present/absence of hypertension

Results

According to the respective medical regimens in no child a important renal pathology was found at the onset of ALL therapy. The values of standard biochemical and microscopic analysis were within normal limits, as well as parameters of the functional examination of the kidneys. In two children (patients 9 and 21) the ultrasonographic examination revealed an anomaly of the outer urinary tract, quite silent up to that time.

At the control check-up the standard chemical examination showed PU in 20 children (55.6 %) and microscopic hematuria in one child. Considering the upper estimated limit of PU/24 hours an increased excretion of proteins was found in 19 children (52.8 %). The range of values of PU/24 hours was 105—386 mg. The detailed analysis of PU showed the glomerular type in 3 children, mixed type in other 3 children and tubular type in 13 children (68.4 %). The functional examination of the kidneys revealed decreased values of GF in total in 5 children. All these patients had slightly increased serum concentration of creatinine, but in none of them the criteria of chronic renal failure were met. A decreased value of tubular resorption was found in 15 children (41.7 %). The detailed analysis of concentration ability of the kidneys carried out by the ADH test demonstrated a decrease of this function in 19 children (52.8 %). The range of maximum reached values of urine osmolality was 827—923 mmol/kg. Hypertension was not demonstrated in any child of the group investigated during the 24-hour monitoring of the blood pressure.

The ultrasonographic examination showed only the morphological anomalies of the extrarenal passages detected earlier.

Nephrotoxicity of the cytostatic therapy at the control examination was evaluated statistically for the group of 36 children. The calculated predicative guess of nephrotoxicity development lay at the level of 94.4, which means that the patients will sustain a renal impairment due to the cytostatic therapy with nearly 95 % probability. The relationship between the PU type and the curative regimen used with consideration of the risk group was also evaluated statistically. Statistical analysis did not prove any statistically significant relationship between the PU type and the curative protocol used. This indicates that one cannot predict what PU type could appear after the termination of the treatment.

Discussion

Prior to the commencement of the ALL therapy using the appropriate regimen, the knowledge of the biochemical examinations of urine and urine sediment and serum concentrations of urea, creatinine and uric acid are usually fully sufficient in standard clinical practice. Further, it is necessary to carry out ultrasonographic examination of the kidneys and their tubular system (3, 20). If these parameters are monitored in the course of the cytostatic therapy, the acute impairment of the kidneys can be diagnosed in time. However, it must be mentioned that these parameters including the clearance of endogenous creatinine (as determined by total collection of urine during 24 hours or calculated using Schwartz formula) characterize mostly the excretion renal function and may also have a false negative telling value. A question therefore appears of whether in the initial phases of cytostatic therapy another biochemical parameters should be monitored, which would signalise "finer" changes in the glomerular and/or tubular renal functions (4, 5, 7, 8, 9, 11). Few literary data (12, 13) state that the renal tubule is that part of nephrone, which is impaired in the initial phase of the cytostatic therapy. In these cases the tubulopathy induced by cytostatics is manifested in particular by tubular PU (i.e. by the presence of proteins abwith molecular mass lower than 50 000 D, e.g. alpha$_1$-microglobulin, beta$_2$-microglobulin, retinol-binding protein) or by mixed proteinuria (i.e. the presence of proteins with molecular mass higher than 50 000 D, e.g. albumin, transferrin, dimers of microglobulins and Tamm-Horsfall protein). In the described case the basal glomerular membrane was damaged only scarcely, which was also indicated by less frequent PU of the glomerular type. The described changes were mostly reversible and after the termination of the therapy the parameters of urine returned to the normal. The detection and analysis of proteins were performed by highly sensitive laser densitometry, however. When using this method, a hypothetical question occurs of how to proceed in the case of a given patient in the standard curative regimen. Should one decrease the doses of cytostatics, extend the interval of their administration or administer some scavengers of oxygen radicals?

Just because the reversibility of the changes described no specific therapeutic measures were adopted. It is only recommended to monitor these patients thoroughly as they represent a risk group for the development of possible irreversible changes of renal functions. Up to now only a small part of hematooncological clinics, including pediatric ones, have the possibility such dynamics of nephrotoxicity analyse and monitor by laboratory techniques. In our group of children with ALL we had not this possibility and before the commencement of the administration of cytostatics we used the standardly accessible laboratory examinations. Only in two children we detected by ultrasonography a development anomaly, which did not represent a contraindication of the antitumour therapy.

Besides the manifestations of the acute renal impairment connected with cytostatics therapy one should consider also possible late nephrotoxic effects of this therapy. They are even more im-

portant, because their manifestation occurs usually after a longer time interval (of years) after the termination of therapy of the tumour disease. Moreover, they can be demonstrated only with use of targeted and highly sensitive laboratory methods. Economic factors play the non-negligible role in the accessibility of these methods even in developed countries (1, 14).

"Chronic nephropathy" observed after the termination of cytostatic therapy has in most cases the pattern of damage to some of the tubular renal functions. The corresponding laboratory finding is usually tubular PU, but also impairment of the concentration ability of the kidneys. These changes need not indicate a heavy alteration of renal functions, however. We obtained similar findings when analysing our group of patients, in which practically no child fulfilled criteria of chronic renal failure and in no child hypertension was proved. On the contrary, cytostatics-induced "chronic nephropathy" manifested by glomerular/mixed PU represents a more consequential situation, indicating a greater damage to the kidneys. In our group this type of PU was found in 6 children. It is therefore necessary to follow these patients carefully further and monitor their dynamic renal functions, including blood pressure.

However, it must be taken into consideration that not only cytostatics have to play the principal role in the relationship to renal impairment. The majority of children treated for hemoblastosis/tumour disease are often exposed to a wide spectrum of nephrotoxic drugs, in particular some antibiotics (6, 16, 18). This was the case of our group of children, who nearly all received antibiotics with potential to damage the kidneys in different phases of the therapy. The reason for the administration was in particular the development of febrile neutropenia, but also therapy of intercurrent infections. In standard clinical practice it is impossible to distinguish these initiating factors and recognize specifically whether the primary role is played by the cytostatic or by another drug. It would be possible only then, if the complex cytostatic therapy were monitored by highly sensitive methods with respect to renal functions.

On the basis of accessible literary data and our own experience we suppose that the standard and expected complication of the curative regimen ALL BFM 90 is represented by the nephrotoxic effect of the complex antitumour therapy with late manifestations appearing after months or even years after termination of the treatment. The most frequent finding signalising the renal impairment is PU, which is glomerular, tubular or mixed. Isolated glomerular PU has a good prognosis and usually is not accompanied by serious renal dysfunction. In children treated for ALL the development of chronic renal failure occurs only rarely. In the context of the above discussion and on the basis of our experience we suppose that the curative regimen ALL BFM 90 was safe with regard of the nephrotoxicity and that no heavier impairment of renal functions occurred. These data are important for the construction of new curative regimens and evaluation of their side effects, since the regimen ALL BFM 90 was substituted by the regimen ALL BFM 95 and a new regimen ALL BFM 2000 will be introduce in the year 2001.

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