BIOMARKERS OF KIDNEY INJURY IN CHILDREN WITH LEUKEMIA AFTER ANTICANCER THERAPY

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Abstract. *The paper deals with the problem of kidney injury in children with leukemia after anticancer therapy. It is stated that cancer incidence has a steady growing trend all over the world, including the children population of Russia. It is reported that a significant proportion of childhood cancer survivors suffer serious late complications, including heart failure, neurotoxicity, nephrotoxicity, growth failure, hormonal disorders, and secondary cancers. Therefore, current research is focused on the problems of early diagnosis even in the "asymptomatic" period of the disease. Special attention is paid to early diagnosis of kidney disorder in children with leukemia who have received anti-cancer treatment. The aim of research was to study the markers of kidney damage after completion of polychemotherapy and radiation therapy. The results obtained demonstrate that in the first two years after completion of anticancer therapy children with acute lymphoblastic leukemia (ALL) had an increased level of urinary kidney damage-1 molecule (KIM-1). It is highlighted that further long-term follow-up studies are necessary to assess the significance of the urinary KIM-1 and cystatin C in the blood serum and their relationship to kidney damage after anticancer treatment in childhood.*

Keywords: *leukemia, children, anticancer therapy, nephrotoxicity, biomarkers, kidney damage, CKD.*

Cancer incidence has a steady growing trend all over the world, including the children population of Russia. Implementation of the National Project "Healthcare" (the federal project "Fight against Cancer"), significantly improved results of anticancer treatment and accompanying support in children. The project has also resulted in a wider introduction of anticancer drugs into clinical practice, progress in studying the molecular biological features of the disease, search for the main immunological, cytogenetic and molecular targets for epigenetic therapy, contribute to the survival of patients with cancer [1-4]. Up to 40% of childhood cancer survivors suffer serious late complications, including heart failure, neurotoxicity, nephrotoxicity, growth failure, hormonal disorders, and secondary cancers [5]. Cancer survivors are at risk for early and late renal side effects, including CKD and kidney failure, impaired (estimated) GFR, proteinuria, hypomagnesaemia, hypophosphatemia, impaired tubular phosphate reabsorption, and hypertension. The prevalence of long-term renal outcomes ranges from 0 to 84% [6]. Green DM. et al. 2021 found that 2.1% of 2753 adult childhood cancer survivors diagnosed ≥10 years ago had stage 3-5 CKD according to the KDIGO 2012 criteria [7]. Anticancer chemotherapy is associated with nephrotoxic side effects that affect long-term consequences, and their study is of particular relevance [8]. Late complications not only seriously impair the quality of life of patients and cause higher rates of hospitalization, but in 15% of cases become the direct cause of patient death [9-11]. Therefore, current research is focused on the problems of early diagnosis even in the "asymptomatic" period of the disease. Early diagnosis of kidney disorder in children with leukemia who have received anti-cancer treatment is essential in prevention of development and progression of chronic kidney disease. Currently the new diagnosic approach is the assessment of kidney function using new biomarkers that are more sensitive and specific in relation to the functional state of the kidneys compared to blood creatine. The presence of markers of kidney damage is possible in the early stages from the onset of the development of the pathological process to establish the level of

manifestation of the nephron. It is worth noting that biomarkers are detected in children with severe early injury and recovery before proteinuria or serum creatinine reveal irreversible expansion and disappearance of the nephron [12]. The aim of our research was to study the markers of kidney damage after completion of polychemotherapy and radiation therapy.

Methods. We examined 39 children with acute lymphoblastic leukemia (ALL) after anticancer therapy (22 boys and 19 girls) aged 10,7 ± 3,7 years. They received anticancer therapy according to approved treatment protocols. The examination period from the end of anticancer therapy ranged from 2 weeks to 6,5 years. The patients were divided into 3 groups: Group I - patients with a period of 2 weeks to 2 years from completion of the therapy; Group II - patients with a period of 2 years to 4 years from completion of the therapy, and Group III - patients with a period of 4 to 6.5 years from completion of the therapy. The control group included 50 children (25 boys and 25 girls) at the age of 10,7 ± 4,8 years of I-II health groups. All children in the control group had estimated glomerular filtration rate (eGFR) > 90 ml / min / 1,73 m2, urine tests and kidney ultrasound data were normal, SDS BMI was from -1 to +1. Formulas based on serum creatinine and cystatin C concentrations (CKiD U25 using age-dependent coefficient) were used to calculate eGFR. Lipocalin associated with neutrophilic gelatinase (NGAL), β2-microglobulin (β2-m), kidney damage-1 molecule (KIM-1), interleukin 18 (IL-18), in blood serum - cystatin C were studied by ELISA method. The results were presented as a median and interquartile range [IQR]. Comparison between groups was performed using the Mann-Whitney U test.

Results. Children of Group I had the level of urinary KIM -1 - 323.19 pg / ml [150.43-888.55], which was significantly higher according to the control group: 162.35 pg/ml [95.85-253.95], p=0.009. Urinary β2-m /UCr - 0.85 mkg / mg [0.35-7.55], urinary IL -18 /UCr - 26.36 pg/mg [17.32-39.05] were even lower than in control group; β2-m /UCr - 4.63 mkg/mg [1.75-9.43], p=0.035, IL-18 /UCr - 44.86 pg/mg [35.03-58.15], p= 0.018. All urinary markers in children from Group II and Group III did not differ from those in the control group. The level of cystatin C in blood serum in all three groups of patients was higher than in the control group 0.47 mg/l [0.43-0.53]: 1-st group - 0.62 mg/l [0.54-0.86], p<0.001; 2-nd group - 0.6 mg/l [0.48-0.64], p=0.024; 3-d group - 0.57 mg/l [0.51-0.63], p=0.004.

Discussion. The influence of anticancer treatment, especially radiotherapy and nephrotoxic agents such as ifosfamide and cisplatin, on kidney function is well known in patients with ALL treated in childhood. Bárdi E. et al., 2004, found that the level of serum cystatin C remains elevated after the end of specific therapy [13]. In a study by Grevtseva E., 2017, children were identified with persistent elevated levels of cystatin C and interleukin-18 in the blood serum after the end of specific therapy [14]. Zubowska et al., 2013, studied the role of IL-18, IMT-1, and beta2-microglobulin in the detection of chronic kidney disease in cancer patients after the end of treatment. The author concluded that beta2-microglobulin and especially IL-18 can be used as early markers of chronic damage to the proximal tubules in children after chemotherapy [15]. Latoch E et al., 2021, evaluated urinary beta2-microglobulin levels in children with leukemia. The authors found a significantly higher concentration of beta2-microglobulin in the urine in children with a longer follow-up period (more than 5 years after treatment) [16]. In another study by the same authors, it was shown that children 5 years after the end of treatment had higher levels of KIM-1, NGAL compared with those whose time from the end of therapy did not exceed 5 years at the time of the study [17].

But there are studies demonstrating that in children with ALL these markers remain normal after anticancer therapy. Krawczuk-Rybak M et al. reported that after the completion of specific therapy, renal function in children returned to normal, despite previous use of nephrotoxic drugs. Cystatin C in blood serum, beta2-microglobulin and cystatin C in urine after the end of specific therapy were the same in the analyzed and control group of healthy children [18]. Kaya Z et al. concluded that renal toxicity for low-risk ALL resolves

slowly, leaving almost no significant late nephrotoxicity in survivors [19].

In the current study we tried to find out whether biomarkers are elevated in survivors of childhood ALL patients compared to control group.

There are several limitations of this study. It was a single-center analysis, with a relatively small number of patients. We did not evaluate the levels of biomarkers before the start of treatment, during exposure to chemotherapy or at the end of therapy. The strengths of our research include the homogenous group of acute lymphoblastic leukemia survivors, relatively long follow-up time and no ethnic diversity.

Conclusions. In the first two years after completion of anticancer therapy children with ALL had an increased level of urinary KIM -1. The level of cystatin C in the blood serum after completion of the polychemotherapy and radiation therapy remains elevated during 6 years. Further long-term follow-up studies are necessary to assess the significance of the urinary KIM-1 and cystatin C in the blood serum and their relationship to kidney damage after anticancer treatment in childhood.

References

1. Torre L.A., Siegel R.L., Ward E.M., Jemal A. Global cancer incidence and mortality rates and trends-an update. Cancer Epidemiol Biomarkers Prev. 2016. 25: 16-27.

2. Nada A., Jetton, J.G. Pediatric onco-nephrology: time to spread the word. Pediatr Nephrol 36, 2227–2255 (2021). https://doi.org/10.1007/s00467-020-04800-3

3. Porta C., Bamias A., Danesh F.R., Dębska-Ślizień A., Gallieni M., Gertz M.A., Kielstein J.T., Tesarova P., Wong G., Cheung M, Wheeler D.C., Winkelmayer W.C., Małyszko J. Conference Participants. KDIGO Controversies Conference on onco-nephrology: understanding kidney impairment and solid-organ malignancies, and managing kidney cancer. Kidney Int. 2020 Nov. 98 (5): 1108-1119. doi: 10.1016/j.kint.2020.06.046. PMID: 33126977.

4. Национальный проект «Здравоохранение»

5. Geenen M.M., Cardous-Ubbink M.C., Kremer L.C.M. et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer // Journal of the American Medical Association. 2007. Vol. 297, №24, pp. 2705–2715,

6. Kooijmans E.C., Bökenkamp A., Tjahjadi N.S., Tettero J.M., van Dulmen-den Broeder E., van der Pal H.J., Veening M.A. Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev. 2019 Mar 11. 3 (3): CD008944. doi: 10.1002/14651858.CD008944.pub3. PMID: 30855726. PMCID: PMC6410614.

7. Green D.M., Wang M., Krasin M., Srivastava D., Onder S., Jay D.W., Ness K.K., Greene W., Lanctot JQ, Shelton K.C., Zhu L., Mulrooney D.A., Ehrhardt MJ, Davidoff A.M., Robison L.L., Hudson M.M. Kidney Function after Treatment for Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study. J Am Soc Nephrol. 2021 Mar 2. 32 (4): 983–93. doi: 10.1681/ASN.2020060849. Epub ahead of print. PMID: 33653686. PMCID: PMC8017532.

8. Онконефрология: поражения почек при использовании противоопухолевых препаратов. Обзор литературы - Часть 1. Нефрология и диализ. 2020. 22(3): 383-395. DOI: 10.28996/2618-9801-2020-3-383-395

9. Lupuşoru M., Lupuşoru G., Ailincăi I., Frăţilă G., Andronesi A., Micu E., Banu M., Costea R., Ismail G. Renal replacement therapy in cancer patients with acute kidney injury (Review). Exp Ther Med. 2021 Aug. 22 (2): 864. doi: 10.3892/etm.2021.10296. Epub 2021 Jun 11. PMID: 34178137; PMCID: PMC8220659.

10. Mulrooney D.A., Dover D.C., Li S.et al., "Twenty years of follow-up among survivors of childhood and young adult acute myeloid leukemia: a report from the Childhood Cancer Survivor Study," Cancer. 2008. vol. 112, № 9, pp. 2071–2079.

11. Kurt B.A., Nolan V.G., Ness K.K., Neglia J.P., Tersak J.M., Hudson M.M., Armstrong G.T., Hutchinson R.J., Leisenring W.M., Oeffinger K.C., Robison L.L., Arora M. Hospitalization rates among survivors of childhood cancer in the Childhood Cancer Survivor Study cohort. Pediatr Blood Cancer. 2012 Jul 15. 59 (1): 126-32. doi: 10.1002/pbc.24017. Epub 2011 Dec 16. PMID: 22180128. PMCID: PMC3359936.

12. Greenberg J.H., Kakajiwala A., Parikh C.R., Furth S. Emerging biomarkers of chronic kidney disease in children. Pediatr Nephrol. 2018 Jun. 33(6): 925-933. doi: 10.1007/s00467-017-3701-9. Epub 2017 Jun 17. PMID: 28624980; PMCID: PMC5733707.

13. Bárdi E., Bobok I., Oláh A.V., Oláh E., Kappelmayer J., Kiss C. Cystatin C is a suitable marker of glomerular function in children with cancer. Pediatr Nephrol. 2004 Oct. 19 (10): 1145-7. doi: 10.1007/s00467-004-1548-3. Epub 2004 Jul 16. PMID: 15258844.

14. Гревцева Е.А. Маркеры острого повреждения почек у детей с лейкозами: дис. … канд. мед. наук: 14.01.08 Воронеж, 2017. – 142 с.

15. Zubowska M, Wyka K, Fendler W, Młynarski W, Zalewska-Szewczyk B. Interleukin 18 as a marker of chronic nephropathy in children after anticancer treatment. Dis Markers. 2013;35(6):811-8. doi: 10.1155/2013/369784. Epub 2013 Nov 27. PMID: 24379519. PMCID: PMC3860090.

16. Latoch E., Konończuk K., Taranta-Janusz K., Muszyńska-Rosłan K., Sawicka M., Wasilewska A., Krawczuk-Rybak M. Urinary Beta-2-Microglobulin and Late Nephrotoxicity in Childhood Cancer Survivors. J Clin Med. 2021 Nov 13. 10 (22): 5279. doi: 10.3390/jcm10225279. PMID: 34830560. PMCID: PMC8622945.

17. Latoch E, Konończuk K, Muszyńska-Rosłan K, Taranta-Janusz K, Wasilewska A, Szymczak E, Trochim J, Krawczuk-Rybak M. Urine NGAL and KIM-1-Tubular Injury Biomarkers in Long-Term Survivors of Childhood Solid Tumors: A Cross-Sectional Study. J Clin Med. 2021 Jan 21. 10 (3): 399. doi: 10.3390/jcm10030399. PMID: 33494327. PMCID: PMC7866176.

18. Krawczuk-Rybak M, Kuzmicz M, Kozlowska K, Wysocka J, Kitszel A, Luczynski W. Ocena czynności nerek po zakończeniu leczenia ostrej białaczki limfoblastycznej u dzieci [Renal function in children after treatment of acute lymphoblastic leukaemia (ALL)]. Med Wieku Rozwoj. 2001 Jul-Sep. 5 (3 Suppl 1): 43-54. Polish. PMID: 12004151.

19. Kaya Z, Gursel T, Bakkaloglu SA, Kocak U, Atasever T, Oktar SO. Evaluation of renal function in Turkish children receiving BFM-95 therapy for acute lymphoblastic leukemia. Pediatr Hematol Oncol. 2007 Jun. 24 (4): 257-67. doi: 10.1080/08880010701441286. PMID: 17613868.

БИОМАРКЕРЫ ПОВРЕЖДЕНИЯ ПОЧЕК У ДЕТЕЙ С ЛЕЙКОЗАМИ ПОСЛЕ ОКОНЧАНИЯ ПОЛИХИМИОТЕРАПИИ

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Аннотация. *Статья посвящена проблеме поражения почек у детей с лейкозом после противоопухолевой терапии. Установлено, что заболеваемость раком имеет устойчивую тенденцию роста во всем мире, в том числе и среди детского населения России. Сообщается, что значительная часть выживших после рака в детстве страдает серьезными поздними осложнениями, включая сердечную недостаточность, нейротоксичность, нефротоксичность, задержку роста, гормональные нарушения и вторичный рак. Поэтому современные исследования сосредоточены на проблемах ранней диагностики даже в «бессимптомном» периоде заболевания. Особое внимание уделено ранней диагностике патологии почек у детей, больных лейкозом, получающих противоопухолевое лечение. Целью исследования было изучение маркеров поражения почек после завершения полихимиотерапии и лучевой терапии. Полученные результаты свидетельствуют о том, что в первые два года после завершения противоопухолевой терапии у детей с острым лимфобластным лейкозом (ОЛЛ) повышен уровень молекулы мочевого повреждения почек-1 (КИМ-1). Подчеркнута необходимость дальнейших долгосрочных катамнестических исследований для оценки значимости мочевого KIM-1 и цистатина С в сыворотке крови и их связи с поражением почек после противоопухолевого лечения в детском возрасте.*

Ключевые слова: *лейкоз, дети, полихимиотерапия, нефротоксичность, биомаркеры, повреждение почек, ХБП.*