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Long-term Follow-up of Renal Disorders in Children with Acute Lymphoblastic Leukemia by Evaluating Urine NGAL

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Abstract:

Background and Aim: Recent developments in cancer treatment have provided a better survival rate for Acute Lymphoblastic Leukemia (ALL) patients. Survivors face different long-term complications after treatment, for instance, cardiac, neurologic, and kidney complications. The objective of this study was to evaluate late renal complications and function in ALL patients after treatment.

Methods: Forty-six children were included in this study. Treatment was based on the IC-BFM protocol including Cyclophosphamide, Cytarabine, Methotrexate, Daunorubicin, prednisolone, vincristine, and asparaginase. The mean age at the start of treatment was 53±23 years and the mean follow-up time was 48±11 months. Tubular damage evaluated by the urinary neutrophil gelatinase-associated lipocalin (NGAL) level and the renal function assessed by glomerular filtration rate (GFR).

Results: In this study, 56.7% of the patients were male. The NGAL level was abnormally high in 8.9% of the patients. The mean urine NGAL was 63±113 ng/mL. In addition, the mean GFR at the time of diagnosis and at the time of follow-up start was 102.8±25.6 mL/min/1.73 m^2 and 93.6±29.1 mL/min/1.73 m2, respectively. GFR was less than 60 mL/min/1.73 m^2 in 13.3% of the patients.

Conclusion: According to the urinary NGAL level, 8.9% of the patients developed tubular damage in this treatment protocol. In conclusion, the IC-BFM protocol is a safe protocol with little long-term damage.

Keywords: Survivorship; Late complications; Kidney diseases; ALL; Child.

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Introduction

Leukemia and lymphoma are the most prevalent childhood malignancies worldwide. ALL comprises 25% of childhood malignancies.

In 80% of ALL cases, B cells are the origin of malignant precursors (1). The etiology of this disease is not clear yet (2).

The outcome of pediatric cancer treatment has improved recently. This improvement changes the pediatric oncology perspective (3). In spite of advanced treatments, childhood cancer survivors (CCS) are impressively incised. This increase in the survival rate changes the treatment plan focus towards late post-treatment complications in patients who survive (4). Cancer chemotherapy and radiotherapy could affect different organs, including the kidneys. The kidneys are damaged during treatment for different reasons. For instance, radiotherapy, chemotherapy nephrotoxicity, and metabolic changes during chemotherapy can cause tubular and glomerular damage (5,6). Renal disorders in the treatment cycle may be acute or chronic. These kidney disorders can permanently affect the renal function and lead to mortality (7). Different chemotherapy agents can induce chronic renal toxicity. For instance, Cisplatin (CPL),

Carboplatin (CARBO), and Ifosfamide (IFO) can cause nephrotoxicity and affect the patient's GFR (8,9).

There are different biomarkers for kidney evaluation (10). neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, 24p3, and LCN2, is a member of the lipocalin family (11). NGAL is an iron transporter portion which is isolated from the epithelial cells of distal tubules and released from these cells in response to damages such as AKI (acute kidney injury). NGAL was isolated from neutrophils for the first time, but it also can be found in the kidneys, liver, and epithelial cells (12). Current studies use this marker in the urine for evaluation of chronic kidney disease in pediatric and adult patients (13,14). This marker is also used to evaluate kidney disorders in different conditions such as autosomal dominant polycystic kidney disease and SLE nephritis (15,16). Furthermore, β2-microglobulin is a 12-14 kD protein and part of the HLA class I molecule and its evaluation could be useful in the assessment of kidney function. It has been shown that increased β2-microglobulin levels in the serum and urine can reflect a reduction in the kidney function and renal damage (17).

However, limited studies have considered long-term renal evaluation in treated children with. In this study, we investigated 46 children with ALL after treatment for long-term renal disorders by evaluation of uNGAL and other renal markers. The objective of this study was to evaluate late kidney complications, renal function, and tubular damage in these patients after treatment.

Methods

Patient selection

Forty-six children were included in this study conducted in Hazrat Ali Asghar Children's Hospital (affiliated with Iran University of Medical Science, Tehran, Iran). Moreover, patient treatment and follow-up were done in Hazrat Ali Asghar children Hospital, as well. ALL was confirmed in these patients by standard hematological features (18). Also, treatment was done based on the IC-BFM protocol, including cyclophosphamide, cytarabine, methotrexate, daunorubicin, prednisolone, vincristine, and asparaginase(19). The mean age of the patients at the start of treatment was 53±23 years and the mean follow-up time was 48±11 months. The data of the patients were collected by a questionnaire. The children included in this study were treated by the ICBFM2002 chemotherapy protocol. Moreover, relapsed patients, patients with bone marrow transplantation, and patients with kidney disorders at the time of the diagnosis were excluded.

Sample preparation

The renal function was assessed by urinary NGAL, GFR and tubular reabsorption of phosphorus (TRP) during the follow-up period. Furthermore, abdominal ultrasonography, urine analysis, serum electrolyte analysis, blood urea nitrogen (BUN), and hypertension were evaluated at the time of diagnosis and during the follow-up.

NGAL and GFR evaluation

Tubular damage was evaluated by the NGAL level. The urine samples were collected and stored at -80^{o}C until assay. The urine NGAL (uNGAL) was measured using a commercial ELISA kit (BIOPORTO, Denmark**)** based on the manufacturer's protocol. GFR was evaluated based on GFR estimation by Schwartz in this study (20). The urine and serum samples were collected and stored at -80^{o}C until the assay. The level of creatinine was measured by atomic absorption and spectrophotometry (Shimadzu, AA 7000, Japan).

Statistical analysis

The SPSS software version 22 was used for statistical analysis (IBM, SPSS Inc., Chicago, IL, USA). P-values less than 0.05 were considered significant. The statistical tests were selected according to the variables: T-test and chi-square test were used for quantitative and qualitative variables, respectively. This study was approved by Research and Ethic committee of Iran University of Medical Sciences.

Results

Twenty-six patients (56.7%) were male and 20 (43.4%) were female. The mean age of the participants was 53±23 months at the start of the treatment and the mean follow-up time was 48±11 months.

The urine NGAL was measured during the follow-up period. The mean urine NGAL was

63±113ng/mL. The urine NGAL was higher than the normal range in only 4 (8.9%) patients. The mean GFR was 102.8 ±25.6 mL/min/1.73 m^2 and 93.6 ±29.1 mL/min/1.73 m^2 at time of diagnosis and at the time of follow-up, respectively. Moreover, GFR was less than 60 mL/min/1.73 m^2 in 2.2% of the patients at the time of diagnosis and in 13.3% at the time of follow-up. The mean GFR in these two conditions was compared by pair T-test, indicating a statistically significant difference (P=0.036) (Table 1).

Table 1. Evaluation of the GFR levels in patients

GFR	Start of the treatment	Follow up
<60 mL/min/1.73m^2	1(2.2)	6(13.33)
60-90 mL/min/1.73 m^2	12(26.08)	13(28.88)
>90 mL/min/1.73m^2	33(71.72)	26(57.77)

Furthermore, the correlation of urine NGAL and age was 0.419 (P=0.004). A significant correlation was shown between uNGAL and TRP with a coefficient of 0.306 (P=0.041). There was no statistically significant correlation between urine NGAL and GFR in this study (P>0.05). The mean TRP in this study was 85.3±22.5 percent and it was abnormal in 30% of the patients. Table 2 presents the results of blood pressure and laboratory investigations. Urine analysis and abdominal sonography done at the time of diagnosis showed abnormal results in 9% and 7% of the patients, respectively. Urine analysis and abdominal sonography were abnormal in 7% and 3% of the patients at the start of the study, respectively (P>0.05).

Table 2. Paraclinical evaluations in the diagnosis time and time of the Start of the study

Test	Assessment time	Mean/ Abnormality	P-value
Systolic blood pressure	Diagnosis time	92.8±6.1 mm Hg	P>0.05
	Start of the study	93.26±5.5 mm Hg	
BUN	Diagnosis time	12.8±6.2 mg/dL	P=0.00
	Start of the study	27.4±4.5 mg/dL	
Serum Na^+	Diagnosis time	138.3±4.3 mEq/L	P>0.05
	Start of the study	138.2±3.6 mEq/L	
Serum K^+	Diagnosis time	4.3±0.5 mEq/L	P>0.05
	Start of the study	4.1±0.3 mEq/L	
Serum Ca^{2+}	Diagnosis time	9.2±0.6 mg/dL	P>0.05
	Start of the study	9.5±0.6 mg/dL	
Serum Potassium	Diagnosis time	4.78±0.9 mg/dL	P>0.05
	Start of the study	4.67±0.7 mg/dL	

Discussion

Advances in the treatment of ALL and improvement of the cancer survival rate have, increased these patients' life expectancy, which could expose patients to long-term complications of treatment (21). One of these complications includes kidney disorders (2). According to the results of the current study, the mean urine NGAL and GFR levels were 63±113 ng/mL and 93.6 ±29.1 mL/min/1.73 m^2 at the time of the follow-up respectively. The study found that increased urine NGAL and decreased levels of GFR (less than 60 mL/min/1.73 m^2) were seen in 8.9% and 13.33% respectively.

Bonnesen et al investigated long-term renal complications in children surviving cancer. In this study, 211156 patients were followed for one year after the treatment. The study results showed that 1645 subjects experienced renal disorders (22). In addition, Yetgin et al investigated renal dysfunction in ALL patients for 35 months after treatment and found that GFR was abnormal in 19% of the cases. The median GFR in the study by Yetgin et al was 115 mL/min/1.73 m^2 (range=42-170). The results also showed that TRP and β2-microglobulin were abnormal in 16.4% and 6% of the patients respectively, and abdominal ultrasonography results were abnormal in patients with a hemoglobin level <10g/dL(23). Bardiet et al investigated long-term kidney disorders in a variety of cancers. They found that the mean GRF was

102±35mL/min/1.73 m^2 in ALL patients in the follow-up period (10).

In our study, the mean GFR was 93.6±29.1 mL/min/1.73 m^2 in patients at time of follow-up and an abnormal GFR was observed in 13.3% of the patients. TRP was also abnormal in 30% of the patients. Abdominal ultrasonography did not show abnormal results in our patients. Differences in the sample size, treatment regimen, the mean age of the patients, and their follow-up period could explain these differences in results. GFR assessment is an important element in the diagnosis of kidney disorders. There is a variety of approaches to GFR assessment. The most common method for GFR assessment is to evaluate the level of creatinine in serum and urine. There are different controversial factors in the assessment of GFR based on creatinine (24). The differences in the GFR assessment methods could be another reason for differences in the results of these studies.

Different studies have suggested the urine NGAL level as a useful biomarker in AKI (25,26). Moreover, some researchers use this biomarker in CKD (chronic kidney disease) (27). Several studies have used NGAL in different renal conditions. For instance, Wu et al compared NGAL with other biomarkers and found that it was a good biomarker for drug induced CKD (28).

In 2010, Viau et al reported that increased levels of NGAL could be a helpful biomarker for diagnosis and progression of chronic renal disorders (29). Nishida et al. investigated the urinary NGAL levels in children with renal disorders. Their results showed that the mean NGAL level was 340±140ng/mL and 662±148ng/mL in chronic renal disorders and tubular disorders, respectively (14). Furthermore, Rahimzadeh et al studied the urine and serum NGAL levels in kidney transplant children. They could not find any statistically association between NGAL levels and graft function but they found that urine NGAL levels could be used to predict ischemia. This study also showed that the NGAL levels were higher (174 ng/mL) in patients who did not have good creatinine clearance results (30). No study evaluated NGAL in the follow-up period of ALL survivors, indicating the novelty of the present study. According to the results of this study, the mean NGAL was 63±113ng/mL in the ALL patients after treatment.

There was a marked difference in the mean range of NGAL between our patients and other studies, indicating lower levels of chronic renal damage in our study.

Moreover, part of the difference in the mean NGAL between this study and other studies could be due to differences in the patients' disorders and the sample size of these studies. A major limitation of our study was its small sample size. However, there is a need for further research into urinary NGAL as a useful biomarker and its advantages and disadvantage in renal and tubular disorders.

Conclusion

The GFR level showed a statistically significant difference between the time of ALL diagnosis and the start of this study, indicating the importance of long-term follow-up of ALL survivors for kidney disorders. The urinary NGAL and GFR levels showed that 8.9% and 13.3% of the patients had tubular damage following the administration of the IC-BFM 2002 treatment protocol. The study found that IC-BFM is a safe protocol with little long-term damage. Further studies in larger sample sizes using more kidney markers are needed to confirm the results.

Conflict of Interest

Authors declared no conflict of interest to declare.

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