

Clinical Study

Interleukin 18 as a Marker of Chronic Nephropathy in Children after Anticancer Treatment

**Małgorzata Zubowska, Krystyna Wyka, Wojciech Fendler,
Wojciech Młynarski, and Beata Zalewska-Szewczyk**

Department of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Lodz, 91-738 Łódź, Poland

Correspondence should be addressed to Małgorzata Zubowska; mzuba@poczta.onet.pl

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Novel markers of nephrotoxicity, including kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), and beta-2 microglobulin, were used in the detection of acute renal injury. The aim of the study was to establish the frequency of postchemotherapy chronic kidney dysfunction in children and to assess the efficacy of IL-18, KIM-1, and beta-2 microglobulin in the detection of chronic nephropathy. We examined eighty-five patients after chemotherapy (median age of twelve years). The median age at the point of diagnosis was 4.2 years, and the median follow-up time was 4.6 years. We performed classic laboratory tests assessing kidney function and compared the results with novel markers (KIM-1, beta-2 microglobulin, and IL-18). Features of subclinical renal injury were identified in forty-eight children (56.3% of the examined group). Nephropathy, especially tubulopathy, appeared more frequently in patients treated with ifosfamide, cisplatin, and/or carboplatin, following nephrectomy or abdominal radiotherapy ($P = 0.14$, $P = 0.11$, and $P = 0.08$, resp.). Concentrations of IL-18 and beta-2 microglobulin were comparable with classic signs of tubulopathy ($P = 0.0001$ and $P = 0.05$). Concentrations of IL-18 were also significantly higher in children treated with highly nephrotoxic drugs ($P = 0.0004$) following nephrectomy ($P = 0.0007$) and abdominal radiotherapy ($P = 0.01$). Concentrations of beta-2 microglobulin were higher after highly toxic chemotherapy ($P = 0.004$) and after radiotherapy ($P = 0.02$). ROC curves created utilizing IL-18 data allowed us to distinguish between children with nephropathy (value 28.8 pg/mL) and tubulopathy (37.1 pg/mL). Beta-2 microglobulin and IL-18 seem to be promising markers of chronic renal injury in children after chemotherapy.

1. Introduction

Significantly improved results of anticancer treatment in children have led to an increased number of survivors. However, available data show that up to 40% of these children suffer from serious late complications, including heart failure, neurotoxicity, nephrotoxicity, growth impairment, hormonal disorders, and secondary cancers [1]. Late complications not only seriously impair the patients' quality of life and cause higher rates of hospitalization, but in 15% of cases, they become the direct cause of the patient's death [2, 3]. Therefore current studies focus on the problems of early diagnosis in the asymptomatic period of the disease, which can result in an order of prophylactic or therapeutic procedures to prevent the progression of late complications.

The impairment of renal function after chemotherapy is a field of interest to many international study groups.

According to various authors, nephrotoxicity occurs in 30% to 70% of cured children [4–6]. The usage of especially toxic kidney drugs, such as cisplatin, carboplatin, and ifosfamide can cause renal failure, albuminuria, proteinuria, hypertension, Fanconi syndrome, tubulopathy, growth impairment and even hypophosphatemic rickets [7–10]. Syndromes can become aggravated over years following the cessation of chemotherapy, so diagnostic tools for their detection in the asymptomatic phase of complications are required [11–13]. Diagnostic methods traditionally used for renal function assessment include the analysis of cystatin, creatinine levels in serum, urinary loss of ions, proteins, and glucose. Glomerular dysfunction can be revealed by an analysis of one sample of serum and urine. The detection of tubulopathy is mainly conducted through a 24-hour period of urine collection, which can be inaccurate and uncomfortable for young patients as it requires the usage of catheters. Thus

some studies focused on more readily available markers of nephropathy, including kidney injury molecule (KIM-1), beta-2 microglobulin, interleukin 18 (IL-18), or urinary neutrophil gelatinase-associated lipocalin (NGAL). However, most published data describes ischemic, critically ill, or transplanted patients with acute renal injury in the course of treatment of basic diseases [14–19]. We have not found any studies focusing on renal function assessment with the usage of new markers in patients after chemotherapy. Therefore, we have identified a need to assess the usefulness of these markers for the detection of late chronic nephrotoxicity (especially tubulopathy) after chemotherapy in children. Tests should be accurate, specific, sensitive, widely available, and comparable to the classic, traditionally employed markers of chronic renal disease after chemotherapy.

The aim of the study is to establish the frequency of chronic tubular and glomerular kidney dysfunction in children treated with chemotherapy and to assess the usefulness of markers of renal injury (IL-18, KIM-1, and beta-2 microglobulin) in comparison with the results obtained from classic diagnostic methods.

2. Materials and Methods

The Ethical Committee of Medical University in Lodz has approved the study. Written informed consent was obtained from the parents of the participants.

2.1. Examined Group. We examined eighty-five patients (forty-five boys and forty girls) treated with chemotherapy at the Department of Pediatrics, Oncology, Hematology and Diabetology at the Medical University of Lodz. They were diagnosed from May, 1995 to January, 2009; however, only 14 patients were diagnosed in the 90s of the 20th century. Most of the patients (60) were diagnosed from January, 2002 to December, 2007. The basis for inclusion in the study was participation in complex assessment of late side effect of anticancer treatment performed in our department. Patients included in the study were at least two-year survivors. The median age of patients at the point of analysis was twelve years (quartiles: 6.9–15.7) and 4.2 years at the point of diagnosis of cancer (quartiles: 2.1–7.5). The median follow-up time after the cessation of chemotherapy was 4.6 years (quartiles: 3.0–7.2). The most common diagnoses were acute lymphoblastic leukemia (ALL), found in twenty-six patients, and nephroblastoma in nineteen patients. We also analyzed patients with neuroblastoma, brain tumours, soft tissue sarcomas, lymphomas, and germinal tumours, including hepatoblastoma (ten, seven, seven, ten, and six children, resp.). All patients had normal renal function before chemotherapy; they did not develop any signs of acute renal insufficiency during chemotherapy. In the cases of most patients, we analyzed all laboratory tests once, and in three cases laboratory results were obtained twice, with two-year intervals between analyses. However, in statistical analyses we considered only one set of the results obtained during the last followup. None of the patients complained of symptoms suggestive of renal insufficiency. They were not receiving oral supplements of magnesium, phosphorus, or potassium.

Moreover, patients were asked to stop any supplementation (including calcium) at least two weeks before the analysis.

2.2. Laboratory Methods and Analysis. All patients underwent blood pressure screening, kidney ultrasound, and general urinalysis, with assessments of urine specific gravity, pH, presence of glycosuria, and proteinuria. We also assessed loss of magnesium, calcium, and phosphorus ions (in mg/kg/d) and microalbuminuria (micrograms per minute) during a 24-hour collection of urine. Acid-base equilibrium, urea level in serum, and concentrations of magnesium, calcium, and phosphorus ions and creatinine were recorded. All the tests were performed according to standardized routine methods in a hospital laboratory with the Olympus 800 U apparatus. Methods used in the test include colorimetric (magnesium and phosphorus ions in serum and urine), complexometric (calcium ions in serum and urine), kinetic (urea and creatinine), and immunoturbidimetric (microalbuminuria) measurements. Based on the obtained results, we calculated glomerular filtration rate (GFR), standardized to 1.73 m^2 . Glomerular dysfunction was defined, according to classical tests, as $\text{GFR} < 75 \text{ mL/min/1.73 m}^2$, microalbuminuria $> 15 \text{ micrograms/min}$, or proteinuria ($> 0.15 \text{ g/24 h}$). Laboratory features of tubulopathy were determined by the presence of glycosuria, metabolic acidosis, and/or at least two out of three symptoms of increased loss of ions in the urine (calcium $> 5 \text{ mg/kg/d}$, phosphorus $> 20 \text{ mg/kg/d}$, and magnesium $> 2.5 \text{ mg/kg/d}$). Nephrotoxicity was defined as the presence of laboratory features of glomerular and/or tubular dysfunction. In the examined group, we also identified patients after nephrectomy as a risk group for nephropathy after chemotherapy.

Concomitantly the concentrations of interleukin-18, KIM-1, and beta-2 microglobulin in samples of urine from the 24-hour collection were established with the ELISA method. Tests were performed with kits produced by *Immundiagnostik AG, Germany* (beta-2 microglobulin), *BioSource, Belgium* (IL-18), and *USCN, China* (KIM-1). We regarded concentrations of beta-2 microglobulin $< 0.4 \text{ mg/mL}$, IL-18: $36.05\text{--}257.75 \text{ pg/mL}$ and KIM-1 $< 0.9 \text{ ng/mL}$ as results within normal limits according to the specifications provided by the kits' producers. According to manuals, normal values were established in the groups of blood donors (healthy adults). The sensitivity of the tests was 0.1 mg/mL for beta-2 microglobulin, 12.5 pg/mL for IL-18, and 27 pg/mL for KIM-1.

The results of classic and novel markers of nephrotoxicity were correlated with clinical data (type of cancer, sex, age at diagnosis and followup time to followup) and factors which could influence nephrotoxic development (including nephrotoxic chemotherapy, nephrectomy, radiotherapy of the abdomen). The modality of the chemotherapy was divided into two groups: highly toxic (ifosfamide, carboplatin, and cisplatin) and moderately toxic (cyclophosphamide) to kidneys.

2.3. Statistical Analysis. Categorical variables were presented as Ns and percentages. Continuous variables were presented as medians and interquartile ranges (25–75%). Due to the

nonnormal distribution of continuous variables, nonparametric analysis of variance (Kruskal-Wallis test) or the Mann-Whitney U test were used for between-group comparisons. The Spearman's correlation coefficient was used as a measure of correlation. Receiver operating characteristic curves (ROC) were drawn with 95% Confidence Intervals (95% CI) for areas under the curve (AUC) to establish the best cut-off values. A P value <0.05 was considered statistically significant.

3. Results

In examined group, thirty-three patients (38.8%) were treated only with cyclophosphamide, twenty-two patients (25.9%) with ifosfamide, seven patients (8.3%) with carboplatin and/or cisplatin, and twenty-three patients (27.1%) were not treated with potentially nephrotoxic drugs. Nephrectomy was performed in twenty-one patients (24.7% of examined group), mainly because of nephroblastoma (nineteen cases). Seven children (8.2% of the group) underwent radiotherapy of the abdominal cavity. In five cases we identified two or more risk factors for nephrotoxicity (nephrectomy and ifosfamide/cyclophosphamide treatment and/or radiotherapy of the abdominal cavity).

Features of subclinical renal injury were identified in forty-eight children (56.3% of the studied group). Glycosuria was observed in three children, microalbuminuria in twenty-six patients, magnesuria in nineteen, calciuria in seven, and phosphaturia in fifteen children, respectively. Decreased GFR was revealed in seventeen patients; however, only two of them had GFR lower than $50 \text{ mL/min/1.73 m}^2$, and in most cases GFR was $60\text{--}65 \text{ mL/min/1.73 m}^2$. An analysis of the influence of treatment modality on the frequency of renal complications was revealed to be nearly statistically significant ($P = 0.08$). Features of tubular dysfunction were observed more often in group of children treated with ifosfamide/carboplatin/cisplatin compared to the cyclophosphamide group ($P = 0.14$). GFR was also lower in groups of children treated with more nephrotoxic drugs compared to children treated without nephrotoxic drugs (24.2% versus 8.7%, $P = 0.13$). Nephrotoxicity appeared more often in children after nephrectomy (29.1% versus 19.4%), but the difference was not statistically significant ($P = 0.11$). Nephrotoxicity was found with higher frequency in children after radiotherapy of the abdomen ($P = 0.039$). Signs of tubulopathy and glomerulopathy were also identified more frequently in this group of patients, but differences were not statistically significant ($P = 0.08$ and 0.23 , resp.). No differences were observed in values of microalbuminuria between subgroups of patients differing in previous anticancer treatments.

Follow-up time was shorter in groups of children with nephropathy ($P = 0.07$) and significantly shorter in those with signs of tubulopathy ($P = 0.004$). No correlation between follow-up time and glomerulopathy was found ($P = 0.88$). Data is given in Table 1.

All of the patients in the studied group had normal results of measurements of blood pressure, kidney ultrasounds, and

general urinalyses with assessment of specific gravity and pH. We did not reveal any abnormalities in acid-base equilibrium and concentrations of ions in blood.

Assessments of beta-2 microglobulin, IL-18, and KIM-1 concentrations in urine showed significant differences between particular subgroups of patients. We found statistically significant connections between previously used treatments (without nephrotoxic drugs, with moderately nephrotoxic drugs, with highly nephrotoxic drugs, and nephrectomy) and concentrations of IL-18 ($P = 0.0004$) and beta-2 microglobulin ($P = 0.004$). Concentrations of IL-18 were lower in children treated with cyclophosphamide compared to children treated with ifosfamide/cisplatin/carboplatin ($P = 0.006$). Differences in KIM-1 concentrations in particular subgroups were nearly significant ($P = 0.11$). Patients after nephrectomy had significantly higher concentrations of IL-18 ($P = 0.0007$) and lower concentrations of KIM-1 than patients with both kidneys ($P = 0.03$). Data is shown in Figures 1(a) and 1(c).

Concentrations of IL-18 and beta-2 microglobulin were significantly higher in children who underwent radiotherapy of the abdominal cavity ($P = 0.01$ and $P = 0.019$, resp.). Concentrations of IL-18 and beta-2 microglobulin were significantly higher in children with traditional clinical features of tubulopathy, namely, glycosuria and/or excessive urinary loss of ions ($P = 0.0001$ and $P = 0.05$, resp.). No statistically significant differences were identified in concentrations of KIM-1, IL-18, or beta-2 microglobulin and signs of glomerular dysfunction. However, the concentration of IL-18 in children with any sign of nephrotoxicity (glomerular and/or tubular injury) was higher. Differences between concentrations of beta-2 microglobulin and IL-18 in relation to the presence of "classic" laboratory features of nephrotoxicity and nephrectomy or radiotherapy of the abdomen are presented in Table 2 and in Figures 1(b) and 1(d).

No correlations between concentrations of beta-2 microglobulin and IL-18 ($R = 0.15$, $P = 0.18$), IL-18 and KIM-1 ($R = -0.04$, $P = 0.68$), or beta-2 microglobulin and KIM-1 ($R = 0.09$, $P = 0.43$) were identified.

An ROC curve created utilizing IL-18 data allowed us to distinguish between children with and without laboratory features of nephropathy and tubulopathy; however, it was not useful in the identification of children with signs of glomerulopathy. The best diagnostic accuracy for nephropathy was achieved at 28.8 pg/mL cut-off threshold (area under curve—AUC 0.65, 95% CI 0.53–0.77). It allowed us to distinguish patients with and without tubular dysfunction with 51% sensitivity and 88% specificity. The best diagnostic accuracy for tubulopathy was achieved at 37.1 pg/mL cut-off threshold (area under curve—AUC 0.78, 95% CI 0.69–0.88). It allowed us to distinguish patients with and without tubular dysfunction with 66% sensitivity and 86% specificity. The possibility of excluding tubulopathy on the basis of low IL-18 concentration was 87%. ROC curves of IL-18 concentrations are shown in Figures 2(a) and 2(b).

ROC curves created utilizing beta-2 microglobulin and KIM-1 concentrations were not useful for diagnostic purposes (AUC = 0.61, 95% CI 0.46–0.75 and AUC = 0.54, 95% CI 0.40–0.68, resp.).

TABLE 1: Connections between time of followup and signs of nephropathy, and glomerulopathy, tubulopathy.

	Nephropathy			Glomerulopathy			Tubulopathy		
	Yes	No	<i>P</i>	Yes	No	<i>P</i>	Yes	No	<i>P</i>
Time to followup (median of years; quartiles)	4.03 (2.34–7.17)	5.17 (3.67–7.38)	0.0786	4.63 (2.59–8.12)	4.42 (3.25–6.08)	0.8889	3.43 (1.79–4.97)	5.13 (3.48–4.97)	0.0039

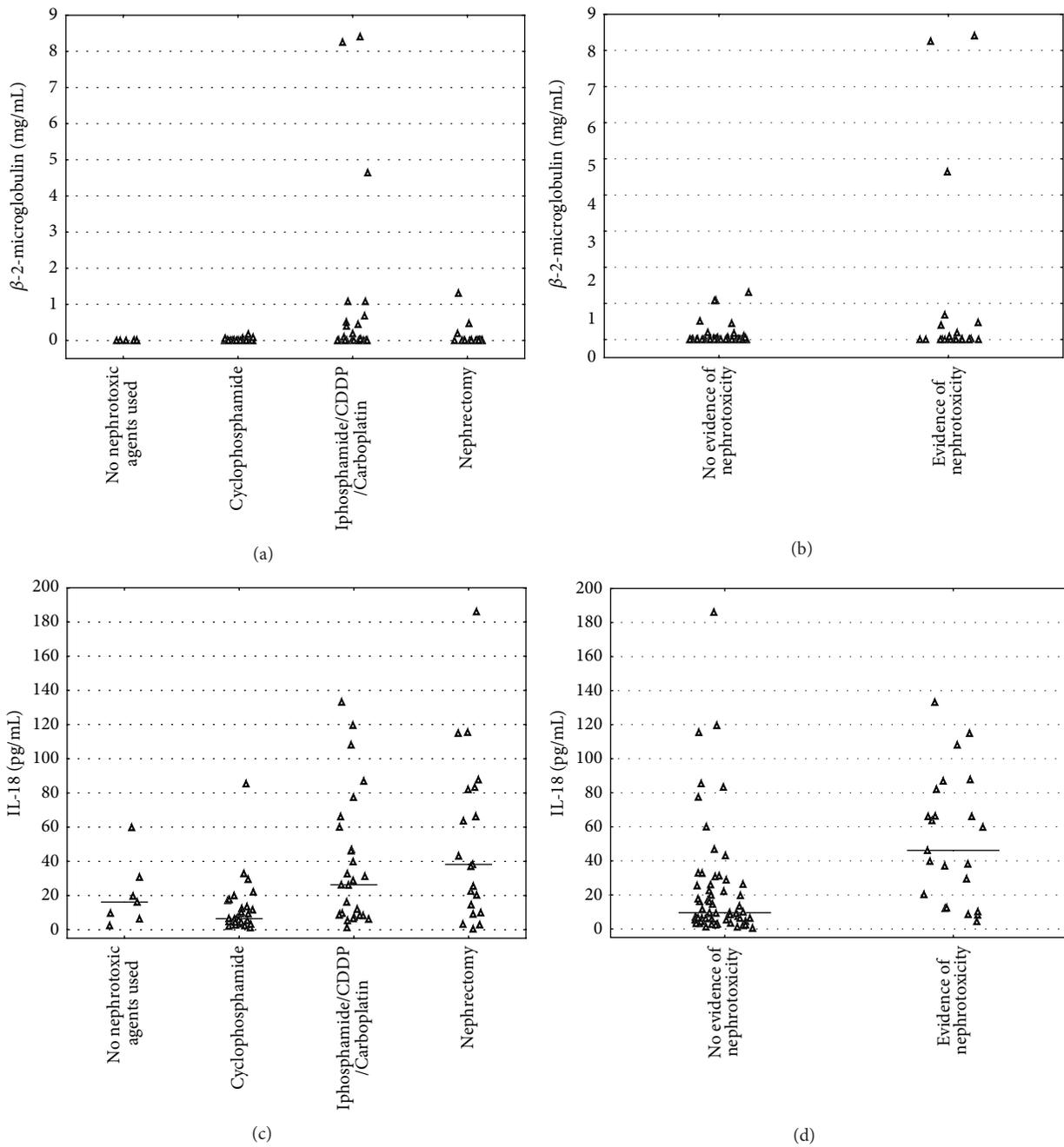


FIGURE 1: (a) Concentrations of beta-2 microglobulin depending on treatment modality. (b) Concentrations of beta-2 microglobulin depending on clinical evidence of nephrotoxicity. (c) Concentrations of IL-18 depending on treatment modality. (d) Concentrations of IL-18 depending on clinical evidence of nephrotoxicity.

TABLE 2: Concentrations of KIM-1, IL-18, and beta-2 microglobulin in patients after nephrectomy and radiotherapy of the abdominal cavity and of patients with/without signs of glomerulopathy and tubulopathy.

(a)									
	Nephrectomy			Glomerulopathy			Tubulopathy		
	Yes	No	<i>P</i>	Yes	No	<i>P</i>	Yes	No	<i>P</i>
KIM-1 (ng/mL)	0.46 (0.36–0.66)	0.76 (0.40–1.20)	0.0321	0.51 (0.39–1.07)	0.66 (0.39–1.05)	0.8995	0.57 (0.36–1.03)	0.66 (0.39–1.07)	0.5720
IL-18 (pg/mL)	38.20 (14.62–82.08)	9.91 (6.04–30.09)	0.0064	8.41 (4.43–17.71)	17.93 (6.79–41.47)	0.1323	46.15 (12.37–82.08)	9.55 (5.39–26.06)	0.0001
B2m (mg/mL)	0.00 (0.00–0.00)	0.00 (0.00–0.05)	0.5337	0.00 (0.00–0.00)	0.00 (0.00–0.06)	0.6513	0.00 (0.00–0.40)	0.00 (0.00–0.00)	0.0500

(b)			
	Radiotherapy of abdominal cavity		<i>P</i>
	Yes	No	
KIM-1 (ng/mL)	0.48 (0.43–0.84)	0.66 (0.39–1.07)	0.761321
IL-18 (pg/mL)	37.09 (20.31–115.52)	11.81 (6.20–38.20)	0.0010290
B2m (mg/mL)	0.45 (0.00–1.31)	0.00 (0.00–0.00)	0.019508

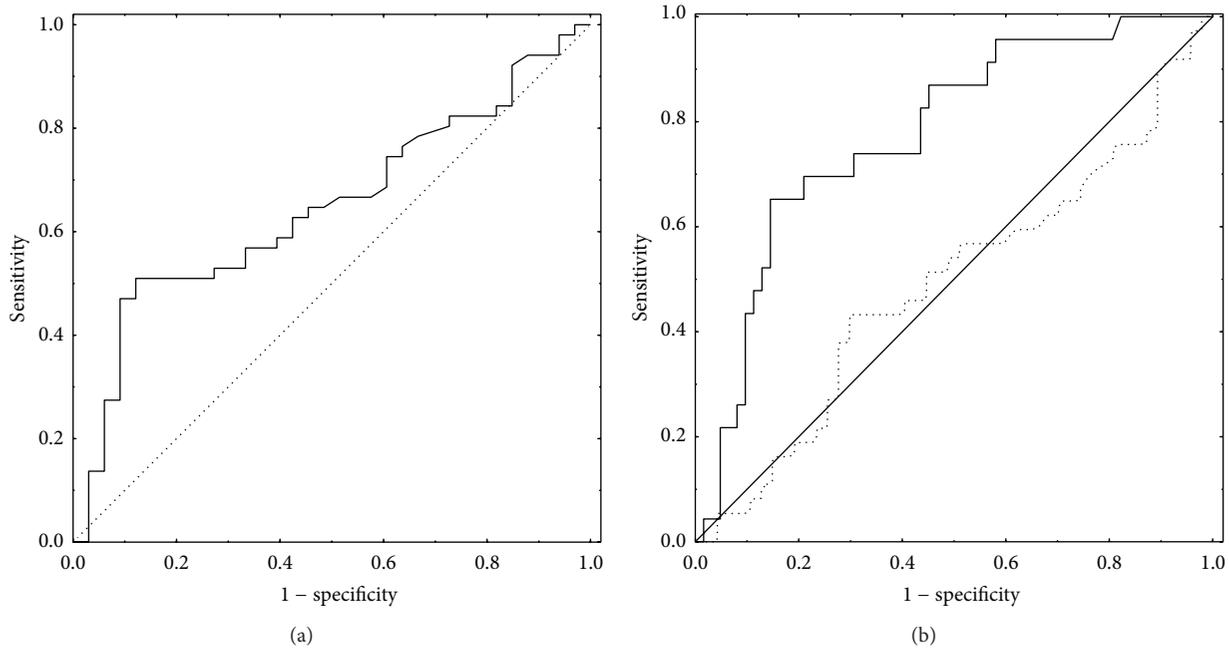


FIGURE 2: (a) Receiver operating characteristic (ROC) curve of IL-18 for the detection of nephropathy. The best cut-off threshold of >28.8 pg/mL allowed for a sensitivity of 51% and specificity of 88%. Area under the curve equaled (0.65; 95% Confidence Interval 0.53–0.77). (b) ROC curves for tubulopathy (solid line) and glomerulopathy (dashed line). The optimal cut-off value for diagnosing tubulopathy using IL-18 equaled 37.1 pg/mL which showed sensitivity of 66% and specificity of 86%; AUC equaled 0.78 (95% CI 0.69–0.88).

The study did not reveal any connections between nephrotoxicity (established according to classic and novel markers) and the sex, age, or type of cancer of the patients.

4. Discussion

Signs and symptoms of nephrotoxicity can appear during chemotherapy (i.e., acute renal injury in the course of tumor

lysis syndrome or nephrotoxicity after methotrexate) [20, 21] or can develop years after the cessation of treatment. In such cases, the impairment of renal function is chronic and its frequency can increase with time. Published data shows that 25% to 95% of children treated with chemotherapy can be affected [22, 23]. Some drugs like ifosfamide, carboplatin, and cisplatin are extremely toxic to kidneys [4–13].

In this study, the laboratory signs of subclinical nephrotoxicity were revealed in 56.3% of treated patients. That observation confirms results obtained by other authors who identified signs of nephrotoxicity in 50–70% of examined patients. It is also comparable with results of our own previously published studies [24]. In this study, GFR was decreased in seventeen out of eighty-five patients (20%), but GFR was only significantly low in five children (<60 mL/min/1.73 m²). Skinner et al. observed GFR lower than 60 mL/min/1.73 m² in 13% of patients ten years after the cessation of chemotherapy with ifosfamide, independent of the cumulative dose of the drug and age of the patients [11]. Other authors described decreased GFR in 11–22% of children, proximal tubular injury in 4–24% of patients, and glycosuria in 36% [12, 25]. Excluding ifosfamide, other highly nephrotoxic drugs include cisplatin and carboplatin. A severe decrease of GFR after treatment with cisplatin was observed in 11–22% of children, 7–12% of patients requiring supplementation of magnesium due to excessive urinary loss of these ions [10, 14]. In our study, the excessive urinary loss of magnesium or phosphorus ions was subclinical; we did not identify any patients with hypomagnesaemia or hypophosphatemia, and none of them required supplementation. Glucosuria was identified in three patients: all of them had other signs of tubulopathy (i.e., excessive urinary loss of magnesium or phosphorus ions). Some authors paid attention to risk factors development of nephrotoxicity, including younger age at the point of diagnosis, cumulative dose of ifosfamide, and longer period of observation [12, 25]. In our study we did not find any connection between the age of children at the commencement of chemotherapy and the frequency of chronic renal complications; however, there is some data suggesting that children under five years of age are more vulnerable [26]. We did not analyze the influence of the cumulative dose of cytostatic drugs on nephrotoxicity frequency. A short observation time (with a median time of 4.6 years) can explain lower percentages of complications in our group. However, the follow-up time in our study was shorter (median time 3.43 years) in the group of children with identified tubulopathy. This suggests that longer follow-up times do not affect the frequency of tubulopathy, though other data described this process as irreversible and more frequent with time [7, 8, 11, 12]. Further observation of our group is required to reveal higher frequencies of nephrotoxicity during longer follow-up periods.

However, most of the patients with subclinical signs of nephrotoxicity were treated with ifosfamide and/or cisplatin, so it should be underlined that in our study laboratory signs of subclinical renal impairment were also observed in 13% of children treated only with cyclophosphamide. To date this anticancer drug is regarded by most investigators as less nephrotoxic. Our observation requires confirmation in larger groups of patients treated only with cyclophosphamide, and we must also exclude the negative influence of other nephrotoxic drugs (i.e., aminoglycoside antibiotics).

In our study, earlier observations that concomitant usage of nephrotoxic drugs increases the risk of renal injury development were confirmed [4, 27]. In patients treated with

ifosfamide and cisplatin/carboplatin, signs of nephrotoxicity appeared in 33% of cases, and nephrectomy increased the frequency of renal impairment by up to 43%. Radiotherapy of the abdominal cavity was also an important factor, significantly increasing the frequency of tubulopathy.

Studies which analyzed the modification of the ifosfamide metabolism or the usage of novel substances such as the liposomal form of cisplatin or cilastatin are in their early stages [11, 28, 29]. Thus far the only way to decrease the risk of nephrotoxicity progression is to find simple but accurate diagnostic tools to identify patients at risk. Many investigators have analyzed urinary concentrations of beta-2 microglobulin, KIM-1, and IL-18 to find early markers of renal injury. Beta-2 microglobulin is reabsorbed in proximal renal tubules so its higher concentration in urine can be the marker of impairment of their function. Higher expression of KIM-1 is observed in cases of toxic or hypoxemic kidney injury; in such cases it may be detected in urine. Interleukin-18 is a proinflammatory cytokine produced by proximal renal tubules in the event of their injury [16, 17, 29–33]. All these markers were used to identify patients with acute renal injury [14, 34]. However, studies assessing their value as the markers of chronic glomerular/tubular disorders after chemotherapy have not yet been published. Interleukin-18 is an especially promising marker already used to assess renal function after transplantations in metabolic diseases or heart diseases [15, 17, 35, 36]. An increase in the urinary concentration of IL-18 followed the expression of classic laboratory features of renal insufficiency. IL-18 was also a strong prognostic indicator of mortality in children treated in intensive care units [14]. Edelstein pointed out that IL-18 can also be a very useful predictive marker of renal insufficiency [37].

In our study, we found statistically significant differences in IL-18 and beta-2 microglobulin urinary concentrations, confirming results obtained from classic laboratory tests. They were statistically significantly higher in children with signs of tubulopathy identified in classic laboratory tests. Urinary concentration of IL-18 above 37 pg/mL (ROC curve) allowed us to identify patients with subclinical nephropathy. The concentration of IL-18 was significantly higher in children treated with ifosfamide/cisplatin and after nephrectomy.

Its connection with treatment modality confirms earlier observations that chemotherapy with ifosfamide/cisplatin is more nephrotoxic, especially in relation to renal tubules.

Our data suggests the confirmation of the hypothesis that beta-2 microglobulin and especially IL-18 can be used as the early markers of chronic proximal tubular injury in children after chemotherapy. Further study should be performed in larger and more homogenous groups of patients (i.e., those treated with similar protocols and doses of the most nephrotoxic drugs). Longer periods of observation can increase the number of patients with clinically relevant or subclinical signs of nephropathy, because some earlier studies have shown that frequency of nephrotoxicity after chemotherapy increases with longer time of followup. It is also worthwhile to repeat the analysis in certain patients to confirm the hypothesis that an increasing concentration of IL-18 is a predictive factor of tubulopathy development in its

subclinical early stage. Further comparative analysis of IL-18 concentrations in morning samples of urine and 24-hour urine collections should also be performed. Comparative concentrations of IL-18 in both urine samples could allow us to avoid 24-hour urine collections, which are troublesome for patients (especially young children). We should also check-up if the normal values of IL-18 and beta-2-microglobulin established in healthy adults (and provided in manuals to the kits) are comparable to the results obtained in population of healthy children.

5. Conclusions

The chronic impairment of renal (glomerular and/or tubular) function after chemotherapy in children affected 56% of the examined patients. All of our patients had subclinical disorders, but knowing that such an injury can be progressive, we tried to find early markers of the disease to identify patients at higher risk of renal disease. Beta-2 microglobulin and IL-18 seem to be reliable and accurate markers of chronic nephropathy, especially tubulopathy in children with previous anticancer treatment.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

- [1] M. M. Geenen, M. C. Cardous-Ubbink, L. C. M. Kremer et al., "Medical assessment of adverse health outcomes in long-term survivors of childhood cancer," *Journal of the American Medical Association*, vol. 297, no. 24, pp. 2705–2715, 2007.
- [2] D. A. Mulrooney, D. C. Dover, S. Li 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*, vol. 112, no. 9, pp. 2071–2079, 2008.
- [3] B. A. Kurt, V. G. Nolan, K. K. Ness et al., "Hospitalization rates among survivors of childhood cancer in the childhood cancer survivor study cohort," *Pediatric Blood & Cancer*, vol. 59, no. 1, pp. 126–132, 2012.
- [4] B. S. Lee, J. H. Lee, H. G. Kang et al., "Ifosfamide nephrotoxicity in pediatric cancer patients," *Pediatric Nephrology*, vol. 16, no. 10, pp. 796–799, 2001.
- [5] R. Rossi, J. Pleyer, P. Schäfers et al., "Development of ifosfamide-induced nephrotoxicity: prospective follow-up in 75 patients," *Medical and Pediatric Oncology*, vol. 32, no. 3, pp. 177–182, 1999.
- [6] R. Skinner, I. M. Sharkey, A. D. J. Pearson, and A. W. Craft, "Ifosfamide, mesna, and nephrotoxicity in children," *Journal of Clinical Oncology*, vol. 11, no. 1, pp. 173–190, 1993.
- [7] R. Skinner, S. J. Cotterill, and M. C. G. Stevens, "Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study," *British Journal of Cancer*, vol. 82, no. 10, pp. 1636–1645, 2000.
- [8] R. Skinner, A. D. J. Pearson, M. W. English et al., "Risk factors for ifosfamide nephrotoxicity in children," *The Lancet*, vol. 348, no. 9027, pp. 578–580, 1996.
- [9] R. Skinner, A. D. J. Pearson, L. Price, K. Cunningham, and A. W. Craft, "Hypophosphataemic rickets after ifosfamide treatment in children," *British Medical Journal*, vol. 298, no. 6687, pp. 1560–1561, 1989.
- [10] S. L. Knijnenburg, M. W. Jaspers, H. J. van der Pal et al., "Renal dysfunction and elevated blood pressure in long-term childhood cancer survivors," *Clinical Journal of the American Society of Nephrology*, vol. 7, no. 9, pp. 1416–1427, 2012.
- [11] R. Skinner, A. Parry, L. Price, M. Cole, A. W. Craft, and A. D. J. Pearson, "Glomerular toxicity persists 10 years after ifosfamide treatment in childhood and is not predictable by age or dose," *Pediatric Blood and Cancer*, vol. 54, no. 7, pp. 983–989, 2010.
- [12] O. Oberlin, O. Fawaz, A. Rey et al., "Long-term evaluation of ifosfamide-related nephrotoxicity in children," *Journal of Clinical Oncology*, vol. 27, no. 32, pp. 5350–5355, 2009.
- [13] R. Skinner, A. Parry, L. Price, M. Cole, A. W. Craft, and A. D. J. Pearson, "Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors," *European Journal of Cancer*, vol. 45, no. 18, pp. 3213–3219, 2009.
- [14] K. K. Washburn, M. Zappitelli, A. A. Arikian et al., "Urinary interleukin-18 is an acute kidney injury biomarker in critically ill children," *Nephrology Dialysis Transplantation*, vol. 23, no. 2, pp. 566–572, 2008.
- [15] M. H. Rosner, "Urinary biomarkers for the detection of renal injury," *Advances in Clinical Chemistry*, vol. 49, pp. 73–97, 2009.
- [16] E. Ho, A. Fard, and A. Maisel, "Evolving use of biomarkers for kidney injury in acute care settings," *Current Opinion in Critical Care*, vol. 16, no. 5, pp. 399–407, 2010.
- [17] X. L. Liang, S. X. Liu, Y. H. Chen et al., "Combination of urinary kidney injury molecule-1 and interleukin-18 as early biomarker for the diagnosis and progressive assessment of acute kidney injury following cardiopulmonary bypass surgery: a prospective nested casecontrol study," *Biomarkers*, vol. 15, no. 4, pp. 332–339, 2010.
- [18] J. L. Koyner, V. S. Vaidya, M. R. Bennet et al., "Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury," *Clinical Journal of the American Society of Nephrology*, vol. 5, no. 12, pp. 2154–2165, 2010.
- [19] C. R. Parikh, J. C. Lu, S. G. Coca, and P. Devarajan, "Tubular proteinuria in acute kidney injury: a critical evaluation of current status and future promise," *Annals of Clinical Biochemistry*, vol. 47, no. 4, pp. 301–312, 2010.
- [20] B. C. Widemann, F. M. Balis, A. Kim et al., "Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome," *Journal of Clinical Oncology*, vol. 28, no. 25, pp. 3979–3986, 2010.
- [21] M. Darmon, I. Guichard, F. Vincent, B. Schlemmer, and L. Azoulay, "Prognostic significance of acute renal injury in acute tumor lysis syndrome," *Leukemia and Lymphoma*, vol. 51, no. 2, pp. 221–227, 2010.
- [22] K. A. Janeway and H. E. Grier, "Sequelae of osteosarcoma medical therapy: a review of rare acute toxicities and late effects," *The Lancet Oncology*, vol. 11, no. 7, pp. 670–678, 2010.

- [23] M. S. Ashraf, J. Brady, F. Breatnach, P. F. Deasy, and A. O'Meara, "Ifosfamide nephrotoxicity in paediatric cancer patients," *European Journal of Pediatrics*, vol. 153, no. 2, pp. 90–94, 1994.
- [24] E. Zielińska, M. Zubowska, and K. Misiura, "Role of GSTM1, GSTP1, and GSTT1 gene polymorphism in ifosfamide metabolism affecting neurotoxicity and nephrotoxicity in children," *Journal of Pediatric Hematology/Oncology*, vol. 27, no. 11, pp. 582–589, 2005.
- [25] W. Stöhr, M. Paulides, S. Bielack et al., "Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: a report from the late effects surveillance system," *Pediatric Blood and Cancer*, vol. 48, no. 4, pp. 447–452, 2007.
- [26] R. Skinner, "Chronic ifosfamide nephrotoxicity in children," *Medical and Pediatric Oncology*, vol. 41, no. 3, pp. 190–197, 2003.
- [27] N. M. Marina, C. A. Poquette, A. M. Cain, D. Jones, C. B. Pratt, and W. H. Meyer, "Comparative renal tubular toxicity of chemotherapy regimens including ifosfamide in patients with newly diagnosed sarcomas," *Journal of Pediatric Hematology/Oncology*, vol. 22, no. 2, pp. 112–118, 2000.
- [28] K. Arjmandi-Rafsanjani, N. Hooman, and P. Vosoug, "Renal function in late survivors of Iranian children with cancer: single centre experience," *Indian Journal of Cancer*, vol. 45, no. 4, pp. 154–157, 2008.
- [29] S. Camano, A. Lazaro, E. Moreno-Gordaliza et al., "Cilastatin attenuates cisplatin-induced proximal tubular cell damage," *Journal of Pharmacology and Experimental Therapeutics*, vol. 334, no. 2, pp. 419–429, 2010.
- [30] E. Moore, R. Bellomo, and A. Nichol, "Biomarkers of acute kidney injury in anesthesia, intensive care and major surgery: from the bench to clinical research to clinical practice," *Minerva Anestesiologica*, vol. 76, no. 6, pp. 425–440, 2010.
- [31] M. Che, B. Xie, S. Xue et al., "Clinical usefulness of novel biomarkers for the detection of acute kidney injury following elective cardiac surgery," *Nephron Clinical Practice*, vol. 115, no. 1, pp. c66–c72, 2010.
- [32] R. Oberbauer, "Biomarkers—a potential route for improved diagnosis and management of ongoing renal damage," *Transplantation Proceedings*, vol. 40, no. 10, pp. S44–S47, 2008.
- [33] P. Devarajan, "The future of pediatric acute kidney injury management-biomarkers," *Seminars in Nephrology*, vol. 28, no. 5, pp. 493–498, 2008.
- [34] R. J. Trof, F. Di Maggio, J. Leemreis, and A. B. J. Groeneveld, "Biomarkers of acute renal injury and renal failure," *Shock*, vol. 26, no. 3, pp. 245–253, 2006.
- [35] E. D. Siew, T. A. Ikizler, T. Gebretsadik et al., "Elevated urinary IL-18 levels at the time of ICU admission predict adverse clinical outcomes," *Clinical Journal of the American Society of Nephrology*, vol. 5, no. 8, pp. 1497–1505, 2010.
- [36] H. Wu, M. L. Craft, P. Wang et al., "IL-18 contributes to renal damage after ischemia-reperfusion," *Journal of the American Society of Nephrology*, vol. 19, no. 12, pp. 2331–2341, 2008.
- [37] C. L. Edelstein, "Biomarkers of acute kidney injury," *Advances in Chronic Kidney Disease*, vol. 15, no. 3, pp. 222–234, 2008.



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