Static Renal Scintigraphy with $^{99m}$Tc-DMSA for the Assessment of Renal Damage After Therapy for Acute Lymphoblastic Leukemia in Children

Introduction: Acute lymphoblastic leukemia (ALL) and its treatment may adversely affect kidney function.

The aim of the present study was to determine whether $^{99m}$Tc-DMSA static renal scintigraphy can be used to disclose kidney damage at the end of therapy for ALL in children.

Material and methods: The study group consisted of 48 ALL patients aged 6.6–22.9 years, with a mean time of continuous complete remission of 51 months. Static renal scintigraphy with $^{99m}$Tc-DMSA was performed in all patients.

Results: Minor scars in the renal cortex were diagnosed with scintigraphy in 6 (13%) patients. A significant correlation was found between renal scarring and a history of urinary tract infection.

Conclusions: No clinically significant kidney damage was found after completion of treatment of ALL. Static renal scintigraphy may be a valuable noninvasive method for visualization of renal cortex pathology.

Key words: acute lymphoblastic leukemia – chemotherapy – nephrotoxicity – renal scintigraphy – children – late effects.
Introduction

It has been reported that about 33% of cancers in children aged 0–14 years are leukemia-related. The most common form of leukemia is acute lymphoblastic leukemia (ALL), which has its peak incidence at 3–7 years of age. The main treatment option is intensive chemotherapy. Currently, the majority of ALL cases are curable, with 80% in complete remission after treatment [1, 2]. However, there remains the question of side effects caused by the treatment and the disease itself.

The kidney is one of the crucial organs that may be affected by both ALL and the chemotherapy agents used for treatment. The most common nephrotoxic cytostatic agents used for ALL treatment are methotrexate (MTX), cyclophosphamide and ifosfamide. Renal disorders after L-asparaginase, cytosine arabinoside, and less frequently, vincristine and rubidomycin, have also been reported [3, 4]. Biochemical tests assessing renal function combined with imaging techniques can be used for the screening of potential renal disorders.

A particularly useful, noninvasive and reliable method for the diagnosis of parenchymal damage is static renal scintigraphy (SRS) [5, 6, 7]. Dimercaptosuccinic acid (DMSA) labelled with technetium 99m ($^{99m}$Tc-DMSA) used for SRS binds to proximal tubular cells in the renal cortex. It is known that MTX may cause toxicity to renal tubules, either directly or indirectly by the mechanism of precipitation in the renal tubules. Therefore, decreased uptake of $^{99m}$Tc-DMSA might be a good indicator of renal tubular damage resulting from the use of cytostatic agents [8].

Because of the long life expectancy of ALL survivors together with the potential risk of renal damage as a result of the disease and its treatment, it is vital to perform investigations to measure if these children have any abnormalities in renal function several years after treatment.

Material and methods

The study protocol was approved by the Ethics Committee of the Pomeranian Medical University in Szczecin (project number: 22.03.2004 BN-001/69/04). Informed consent was obtained from the patients and/or parents before enrolment.

In total, 48 children – 29 boys (60%) and 19 girls (40%); mean age 13.2 years, range 6.6–22.9 years – were investigated for kidney disorder at an average of 4.3 years (51 months), (range 1 month–12.8 years) after the end of successful treatment for ALL (in eight children the observation time was < 1 year). The group of children was diagnosed and treated between 1989 and 2001. Acute lymphoblastic leukemia was diagnosed in these children at an average age of 5.7 years (range 1.4–18.4). At diagnosis renal function tests were performed: urinalysis, and serum creatinine, urea and electrolytes. Treatment was given according to recommended protocols for an average of 3.3 years (range 2.4–4.6) [9, 10]. Two protocols were applied (BFM 86 and BFM 90).

The patients, who were treated according to the BFM 86 protocol, received 1.0 g/m$^2$ MTX intravenously in 4 sessions every 14 days. During supportive therapy they received 0.02 g/m$^2$ MTX weekly over the period 30 months and up to ten 0.006–0.012 g MTX intrathecal injections, depending on their age, were given. The total MTX dose for the patient calculated by square meter was 6.654–6.71 g. An intravenous dose of cyclophosphamide at 1 g/m$^2$ was given over three sessions.

The patients, who were treated according to the BFM 90 protocol, received 5.0 g/m$^2$ MTX intravenously in 4 sessions every 14 days. During supportive therapy they received 0.02 g/m$^2$ weekly over the period 30 months and up to ten 0.006–0.012 g intrathecal injections, depending on their age, were given. The total MTX dose for the patient calculated by square meter was 22.65–22.71 g. An intravenous dose of cyclophosphamide at 1 g/m$^2$ was given over three sessions.

Additionally, patients were treated with cytosine arabinoside, prednisolone and 6-mercaptopurine, aminoglycoside antibiotics, amphotericin B, vancomycin and non-steroidal anti-inflammatory drugs.

At follow-up, a full history was collected of any kidney disorders during the treatment and observation periods. Special attention was paid to previous renal infections. All children had urinalysis, and serum creatinine, urea and electrolytes, 24-hour proteinuria and urinary albumin concentration measurements.

Static renal scintigraphy was performed in all the children; images were taken 90–120 minutes after injection of 100–200 MBq $^{99m}$Tc-DMSA in a supine position, in three projections (both oblique and posteroanterior projections), with 1 million counts per picture in a 128 × 129 pixels matrix. Defects in tracer accumulation, kidney shape, and split renal function were measured. Abnormal kidney function was set at < 45% for one kidney. Classification of renal scarring was based on the method of Smelie [11].

Statistical methods

Statistical analysis was carried out with Statistica 6.0 and Stata 5.0. All variables were analyzed with the Kolmogorov–Smirnov test to determine normal distribution within the groups. The results were reported as mean ± standard deviation (SD), median, minimum and maximum value. Results were given by probability and odds ratio (OR) with 95% confidence intervals (CI). P values less than 0.05 were considered to be statistically significant. 0.05 < p < 0.10 were considered to be the threshold of statistical importance.

Results

At the diagnosis of ALL only 2 (4.16%) children had elevated serum urea (44.7 mg/dL and 50.2 mg/dL) and serum creatinine (1.29 mg/dL and 2.28 mg/dL). No other pathologi-
nal findings concerning renal function were found before ALL treatment.

In all children serum creatinine (aver. 0.7 mg/dL, range 0.52–1.05, SD 0.1 mg/dL) and serum urea (aver. 27.5 mg/dL, range 14.2–43.1 mg/dL, SD 6.5 mg/dL) were normal after completing ALL treatment; 12 children (25%) had a well-documented history of urinary tract infection (UTI).

Static renal scintigraphy revealed cortical lesions suggestive of renal scarring in 6 (13%) children, of whom 1 had second-degree scarring, while the other 5 children had first-degree renal cortical defects (fig. 1); 5 children within this particular group had a history of UTI, which was a significant coexisting factor (p < 0.01). Split renal function < 45% was seen in nine children (19%); in eight (17%) of these, the function was 40–45%, and in the one remaining patient (4%), it was 37%. The biochemical kidney function tests were normal in these patients. Statistical analysis shows dependence on the history of UTI and the results of SRS (tab. 1 and 2).

Discussion

Renal damage may occur as a side effect of ALL itself or of the aggressive chemotherapy treatment and additional therapies used to treat the disease, such as nonsteroidal anti-inflammatory drugs, amphotericin B for systemic fungal infections, antibiotics and antivirus drugs, which are all a potential source of kidney impairment. Kidney function may be assessed by a number of biochemical tests and imaging techniques. Static renal scintigraphy with ⁹⁹ᵐTc-DMSA allows imaging of renal scars, and estimation of kidney shape and location. According to the National Institute for Health and Clinical Excellence (NICE) in the UK, ⁹⁹ᵐTc-DMSA scintigraphy is a reference standard in children with UTI [12]. Because MTX is eliminated mainly through renal clearance, it is of central interest as a potential agent of kidney parenchyma damage. It has been shown that MTX induces time-dependent renal tubular cell swelling and tubular death, thus ⁹⁹ᵐTc-DMSA SRS may be a useful tool for diagnosis [8].

Yetgin et al. evaluated patients with ALL (exclusively), using static (⁹⁹ᵐTc-DMSA) and dynamic (⁹⁹ᵐTc-mercapto-acetyltriglycine-3; ⁹⁹ᵐTc-MAG-3) scintigraphy, with a median duration of follow-up after treatment cessation of 35 months.

![Fig. 1. Scar in left kidney seen with ⁹⁹ᵐTc-DMSA scintigraphy](image)

**Table 1. The impact of urinary tract infection in anamnesis on the results of static renal scintigraphy**

<table>
<thead>
<tr>
<th>Parameter / Parametr</th>
<th>History of urinary tract infection</th>
<th>100%</th>
<th>χ² Yates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Przebyte zakażenie w drogach moczowych</td>
<td>total łącznie</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no / nie</td>
<td>yes / tak</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 36)</td>
<td>(n = 12)</td>
<td></td>
</tr>
<tr>
<td>Scars in kidney cortex</td>
<td>yes / tak</td>
<td>1</td>
<td>2.9%</td>
</tr>
<tr>
<td>Blizny w korze nerki</td>
<td></td>
<td>5</td>
<td>41.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>p = 0.0025</td>
</tr>
<tr>
<td>Split renal function</td>
<td>decreased</td>
<td>5</td>
<td>14.3%</td>
</tr>
<tr>
<td>Rozdzielcza czynność obu nerek</td>
<td></td>
<td>4</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>p = 0.2857</td>
</tr>
</tbody>
</table>

**Table 2. The impact of urinary tract infection in anamnesis on the relative risk of renal scars and decreased split renal function**

<table>
<thead>
<tr>
<th>Risk factor – history of urinary tract infection</th>
<th>Czynnik ryzyka – przebyte zakażenie w drogach moczowych</th>
<th>OR*</th>
<th>95% CI</th>
<th>interval / przedział</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scars in kidney cortex / Blizny w nerках</td>
<td></td>
<td>17.85</td>
<td>1.58</td>
<td>201.92</td>
<td>0.020</td>
</tr>
<tr>
<td>Split renal function decreased / Zmniejszenie</td>
<td></td>
<td>2.43</td>
<td>0.47</td>
<td>12.68</td>
<td>0.292</td>
</tr>
<tr>
<td>względnej ilości czynnego miąższa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR – odds ratio after adjustment for gender and age / iloraz szans liczono przy kontrolowaniu płci i wieku; p – level of significance < 0.05 / p < 0.05 uznano za istotne statystycznie
They analyzed late nephrotoxicity among 115 children with various cancers, including ALL, by means of dynamic and static scintigraphy. They found abnormalities in 5 cases, of which showed unilateral reduction of DMSA uptake as a result of tumor invasion [6].

In a paper published in 2008, Kurt et al. showed that renal toxicity after MTX administration is generally acute but reversible [13]. These authors suggested periodic monitoring of patients with laboratory abnormalities. Bárdi et al. confirmed a slight influence of MTX on kidney status at least 48 months after chemotherapy treatment [14]. They analyzed late nephrotoxicity among 115 children treated for various malignancies (including 60 cases of leukemia), but did not use any nuclear imaging methods. Using laboratory investigations, Kakihara et al. assessed late nephrotoxicity in a heterogenous group of 30 patients, half of whom had leukemia, 2 months after treatment cessation. Clearance of para-aminohippurate was decreased and the creatinine level increased [15]. Owing to the short follow-up time, a comparison with our data was not possible. Gronroos and coworkers showed that MTX induces cell swelling and necrosis in renal tubular cell in an in vitro model [8].

In our study, we found mild degree renal scarring in 6 (13%) children (only one child had second-degree scarring) and reduced split renal function of <45% in nine children. In all these children, biochemical kidney function tests were within normal limits. Apart from ALL, 5 of these children had a history of UTI. It is possible that children with a history of UTI are particularly subjected to renal side effects of anticancer drugs. It is difficult to determine whether the scars are the result of ALL, chemotherapy treatment, UTI or other factors, and which of these is most responsible for renal scar formation. It is likely that a combination of factors is responsible, but UTI is a well-documented cause of renal scarring [16, 17, 18]. It may be helpful to perform SRS before and after treatment, and during follow-up in such patients. The drawback of the work was the lack of SRS before commencing this study. The clinical implication is that leukemia survivors should be subjected to a detailed follow-up protocol and the renal function should be analyzed. Despite our optimistic study results, the data from existing literature is equivocal.

The need for long-term monitoring of patients for late side effects of chemotherapy was emphasised by the Organisation of European Cancer Institutes during a workshop in October 2008. Arriagada and coworkers suggested a 20-year follow-up, as children can be more sensitive than adults to the iatrogenic effects of chemotherapy. The life expectancy of treated children is longer than that of adults, therefore there is a greater chance of developing complications [19]. In the past few years, there have been a number of publications in the area of pharmacogenomics, a new branch of science, which may provide new data on the optimisation of chemotherapy to allow drug-matching, dose-matching and establishment of the optimum duration of administration. Thus, effective prediction of treatment effects and avoidance of side effects by individualised chemotherapy protocols may become a reality [20].

**Conclusion**

There are no clinically significant kidney impairments seen in children after ALL treatment in long-term follow-up. Static renal scintigraphy can be a valuable, noninvasive method for visualization of kidney cortex abnormalities.

**References**


