Ph.D. theses

Acute and late nephrotoxicity in children with cancer

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2005

1. INTRODUCTION

As the outcome of childhood cancer improved substantially during the last 3 decades, the attitude of pediatric oncology has changed from “cure at any cost” to ”cure at least cost”. The quality of life may be due to the malignant process or may be secondary to a variety of treatment modalities, such as cytostatic treatment, irradiation, surgical or even supportive therapy. Side effects can affect all organs. Nephrotoxicity is one of the major side effects with respect of frequency and severity. Recent developments, including those presented in the Theses may contribute to early and accurate diagnosis, prevention and treatment of renal injury in children with cancer.

A number of cytostatic agents have been associated with clinically relevant nephrotoxicity, such as platinum compounds, alkylating agents, methotrexate (MTX) and anthracycline antibiotics. Among them, cisplatin (CPL) was reported to induce both long-lasting reduction in glomerular filtration rate (GFR) and renal magnesium wasting, in some instances associated with hypocalcaemia. The decrease in GFR and tubular dysfunction depends on the administration schedule of the drug and concomitant treatment with ifosfamide (IFO). Carboplatin (CARBO), a structural analogue of CPL has been proposed as less nephrotoxic.

MTX can induce acute renal failure, reduction in GFR and in tubular function. Since excretion of MTX is primary renal, acute renal failure results in decreased excretion leading to sustained high plasma levels, so that other toxic manifestations (myelosuppression, mucositis, nephrotoxicity) are more likely to develop. Accumulation of the drug in a “third fluid compartment” (pleural effusion, ascites, hygroma) also contribute to delayed excretion.

Alkylating agents, such as CP and IFO have been shown to induce tubular dysfunction including proteinuria, impaired amino acid transport, fluid, electrolyte and glucose loss, even partial or complete Fanconi syndrome and hypophosphatemic rickets in 10 to 40 % of

patients. In addition to the cumulative dose of IFO, concomitant therapy with platinum compounds, unilateral nephrectomy and young age have been established as risk factors.

Nephrotoxicity caused by anthracycline antibiotics, i.e. daunorubicine (DNR), doxorubicine (DOX), epirubicine (EPI), idarubicine (IDA) and mitoxantrone, has been attributed to their capacity of iron-mediated formation of reactive oxygen intermediates resulting in membrane lipid peroxidation and cell necrosis. As far as we know, the incidence and severity of nephrotoxicity caused by anthracyclin derivatives in humans has not been proven previously.

As a consequence of more aggressive therapeutic approaches in pediatric oncology, the use of more intensive supportive therapy with potentially nephrotoxic side effects is necessary. Anti-infective therapy, including aminoglycosides, amoxicillin, carbapenems, trimetroprim-sulfametoxazol and amfotericin B, may induce nephrotoxicity. Allopurinol treatment and immunglobuline substitution may also result in impaired renal function.

Recently, a genetically determined involvement of the renin-angiotensin system on the develpoment of renal function impairment has been recognized. Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II (AT2) and inactivates bradykinin. The insertional/deletional (I/D) polymorphism of the human ACE gene, characterized by the presence (I) or absence (D) of a 287 bp fragment in intron 16, has been shown to modulate ACE activity both in the circulation and in tissues. Subjects, homozygous for the deletional allele (DD) exhibit about two-times higher ACE activity than homozygotes for the insertional allele (II). AT2 and bradykinin determine vascular tone and smooth muscle proliferation. In addition, ACE expression may influence nitric oxide production, the synthesis of inflammatory cytokines and cardiovascular responses to them, as well as adrenomedullin secretion. An elevated activity of the renin-angiotensin system due to ACE I/D polymorphism has been connected with increased susceptibility and illness severity of cardiovascular and

renal pathology, adult respiratory distress syndrome and meningococcal meningitis in children. A possible impact of the I/D polymorphism of the ACE gene on renal injury elicited by nephrotoxic cytostatic agents has not yet been examined.

2. AIMS OF THE STUDY

1. To develop a sensitive and specific protocol for selective monitoring glomerular, proximal and distal tubular function in children with cancer.
2. To assess late glomerular and tubular damages in children and young adults after completing complex antineoplastic treatment.
3. To study the role of I/D polymophism of the human ACE gene in development of severe circulatory compromise in febrile neutropenic children with cancer and in nephrotoxic side effects.
4. To analyze prevention and treatment possibilities in connection with nephrotoxicity, with an emphasis on anthracyline induced proximal tubular toxicity and its prevention by dexrazoxane.

3. MATERIALS AND METHODS

3.1.Patients

Renal tubular function was evaluated in 1381 serum and urine samples obtained from 207 children with cancer (92 on current chemotherapy and 115 long time survivors) who were treated according to standard protocols applied by the Hungarian Pediatric Oncology Group (HPOG) at the Hematology/Oncology Ward and Outpatient Clinic of the Department of Pediatrics, Medical and Health Science Center of the University of Debrecen (MHSCUD) between October 1, 1999 and December 31, 2003. The results of patients were compared to those of 144 children without any renal disease (negative controls) and 18 children with chronic renal insufficiency on current hemodialysis (positive controls). ACE I/D genotype was determined in 207 children with cancer.

3.2. Methods

Glomerular and tubular function of patients on chemotherapy were assessed immediately before and 24-48 hours after CPL, CARBO, CP, IFO, MTX, DNR, DOX, EPI and IDA treatment.

Serum and urinary creatinine concentrations were determined by the kinetic Jaffe method on Hitachi 717 analyzer. Creatinine clearance (C_{Cr}) was calculated using the standard formula: ($UxVx1.73m^2$)/(S_{Cr}xBSAx1440) (U_{cr} : urinary creatinine concentration [μmol/L], V: urine output [mL/min], estimated from the 24 h collection sample, BSA: body surface area [m^2]). Creatinine clearance based on the Counahan formula ($C_{Counahan}$) was calculated from S_{cr} and body length (l, [cm]), as: 38xl (cm)/S_{Cr} (μmol/L) and gives an estimate in ml/min/1.73 m^2.

Cystatin C concentration (cysC) was determined with particle enhanced immunoturbidimetric assay – in parallel with serum and urine creatinine- (Dako, Glostrup, Denmark) on Hitachi 717 analyzer according to manufacturer's recommendations.

Gross proteinuria was determined in a hygienic early morning urine sample by the dipstick and sulfosalicylic acid tests. The amount of urinary total protein, albumin, IgG, and $ß_2$ microglobulin in 24 hour collected urine samples of patients with gross proteinuria was determined on BN 100 Nefelometer (Dade Behring, Marburg, Germany). Quantitative analysis of proteinuria was determined by electrophoresis on Hydrasis analyser (Sebia, Lisses, France). Patients with persisting proteinuria were put on ACE inhibitor therapy and amount of proteinuria, parameters of glomerular and tubular function were checked regularly.

Urinary N-acetyl-β-D-glucosaminidase (NAG) enzyme activity was determined by the modification of the method of Horak et al. in early morning urine samples. NAG excretion was normalized to urinary creatinine levels (NAG_i) and expressed in μmol/min/mmol units.

Microalbuminuria (MA) was determined in a 24 hr collection sample by immunturbidimetric method (Cobas Integra 400, Roche, Basel, Switzerland).

Serum and urine osmolarity were determined on VAPRO osmometer.

Genomic PCR, according to standard methods, was performed to determine the I/D polymorphism of the ACE gene using 5'-CTGGAGACCACTCCCATCCTTTCT-3',,sense" and 5'-GATGTGGCCATCACATTCGTCAGAT-3' „antisense" oligonucleotide primers.

Descriptive statistics test of SAS for Windows was used to determine normal distribution within the groups of patients. The results are reported as mean±standard deviation (SD). CysC, NAG_i MA serum and urine osmolarity concentrations were compared by one-way ANOVA. Critical differences between groups were assessed by paired t-test and by Newman-Keuls post-hoc test. We used the χ^2 –test for analyzing whether allele frequencies in the investigated groups of patients fitted the Hardy Weinberg equation. Differences were regarded significant if $p<0.05$.

4. RESULTS

4.1. Acute glomerular injury

CysC of patients, negative and positive controls were 1.13 ± 0.54 mg/L, 0.95 ± 0.19 mg/L and 4.69 ± 2.19 mg/L, respectively. CysC of positive controls was significantly higher than cysC of either patients ($p< 0.001$) or negative controls ($p<0.001$). Linear regression analysis showed a significant correlation between cysC and S_{cr} ($r= 0.95$, $p< 0.001$). The correlations between 1/cysC and $C_{Counahan}$ was also significant however, weaker than between cysC and S_{cr} ($r=0.198$, $p= 0.002$).

Significant differences were found in pre- and post-treatment cysC in patients receiving CPL (1.14±0.48 vs. 1.37±0.32 mg/L, p=0.035), MTX (1.09±0.42 vs. 1.51±1.04 mg/L, p=0.023,), CP (1.06±0.41 vs. 1.18±0.36 mg/L, p=0.009) and IFO (1.11±0.43 vs. 1.31±0.33, p=0.002), in single application. Average post-treatment cysC levels were not as high as cysC levels seen in patients with chronic renal failure (4.69 ± 2.19 mg/L). We identified 7 patients, having received MTX (3), IFO (2), CP (1), and CPL (1), respectively with a cysC value

exceeding mean cysC levels of normal controls by 2 SD. Due to a massive pleural effusion, a 16-year-old osteosarcoma patient had toxic MTX levels lasting for 6 days and he required hemodialysis treatment in three occasions. Exceedingly high drug level (186,4 μmol/L at 36 hours post-treatment), accompanied by high serum creatinine levels were observed in a 14-yr-old girl with Burkitt lymphoma after the administration of 5g/m^2 MTX. Hyperhydration (4500 mL/m^2), diuretic treatment, aklalynization was applied and leukovorine was administered for 12 days in a cumulative dose of 27,060 mg. In parallel with the high MTX levels, she developed seizures. Cranial magnetic resonance imaging revealed a right sided subdural hygroma compressing the right ventricle. These two cases demonstrate the role of a third body fluid compartment in eliciting glomerular injury due to delayed MTX excretion. The other 5 patients improved spontaneously by the time of the application of the next chemotherapeutic course. There was no dose relationship found in cysC in connection with MTX treatment between the dose ranges of 0.5-5.0 g/m^2/24h and 12 g/m^2/6h. CysC was significantly elevated after cytostatic agents applied in various combinations on the same day (1.13±0.49 vs. 1.31±0.36 mg/L, p=0.007).

4.2. Acute tubular injury

Mean NAG_i was significantly elevated ($p<0.05$) after each CPL, CARBO, CP, IFO, DNR, IDA and EPI treatment. MA proved to be a less sensitive indicator of tubular damage than NAG_i but it was significantly elevated ($p<0.05$) after IFO and CP treatment.

Consecutive DNR courses were associated with an increasing post-treatment level of NAG excretion as expressed in per cent of the pretreatment NAGi (NAG%) of the individual patients. Linear regression analysis proved a significant ($p<0.05$) elevation. Mean post-treatment NAG% was three times as high after the fourth course as after the first course of DNR treatment.

The effect of dexrazoxane on DNR induced excretion of NAG was studied in 6 children with ALL treated outside of the frame of the HPOG study therefore, not receiving dexrazoxane prior to the application of DNR following strictly the rules of the original ALL BFM 95 protocol. NAG excretion of these patients was compared with that of 6 age- and sex-matched children with ALL who were treated within the frames of the HPOG study in the same period of time. These patients received dexrazoxane before DNR treatment. The mean NAG_i in the dexrazoxane treated group was significantly ($p<0.005$) lower (0.69±0.25 μmol/min/mmol) than in the group of patients not receiving dexrazoxane (1.79±1.45 μmol/min/mmol) in conjunction with DNR application. There was no significant effect of dexrazoxane treatment on DNR-induced MA (data not shown). No acute or late cardiotoxicity was noted in both groups of patients.

No significant differences between pre- and post-treatment serum and urine osmolarity values were found in association with cytostatic therapy suggesting that the investigated agents did not cause a severe distal tubular dysfunction.

4.3. Late effects on renal glomerular and tubular function in childhood cancer survivors

Each patient, except for one with chronic renal failure, was in a good general health at the time of testing(s). Baseline blood and urine laboratory values were within the normal range except for 30 patients exhibiting gross proteinuria, i. e. exhibiting a positive dipstick test. To evaluate the effects of potentially nephrotoxic agents, three subgroups of patients were analyzed: leukemia/lymphoma survivors, Wilms tumor (WT) survivors and (other) solid tumor survivors. In WT patients abdominal ultrasound revealed a 10 % increase in the longest diameter of the remaining kidney vs. the size of kidneys of the leukemia/lymphoma patients, solid tumor survivors and age- and sex-matched controls. The kidneys of patients with proteinuria showed an increased echogenicity.

CysC concentrations, used to characterize glomerular function of patients were not significantly different from that of the controls. In parallel with cysC, serum creatinine concentrations and GFR values were within the normal range. Assessing the 3 subgroups of patients, cysC, serum creatinine concentrations and GFR values of leukemia/lymphoma patients and solid tumor survivors did not differ from the control group and were within the normal range. We found however, a significantly elevated cysC in WT patients, in particular in high risk (HR) patients, who were treated by IFO and CARBO. In this subgroup of patients, serum creatinine concentrations were mildly elevated (71±21 μmol/L), whereas GFR values (71±27 ml/min/1.73 m^2) were significantly lower ($p< 0.05$) than within the control group (132±79 ml/min/1.73 m^2). One patient with WT-aniridia has been put on chronic hemodialysis 7 years after heminephrectomy when he presented because of frequent vomiting at the Department of Internal Medicine of the County Hospital, Szolnok. Biopsy was not performed because of the end-stage nature of renal failure. History revealed frequent episodes of viral and bacterial respiratory tract inflammatory diseases since having lost to follow-up from our institute 3 years after diagnosis.

We identified 30 patients with gross proteinuria. Proteinuria disappeared completely in 20 cases spotaneously within 12 months after discovery. Persisting proteinuria was further analyzed with quantitation of the excreted protein in a 24 hr collection sample and by electrophoresis. Out of 10 patients, 5 glomerular and 5 mixed (glomerular and tubular) proteinuria were noted. Of these patients 4 had leukemia/lymphoma, 2 had solid tumors and 4 had WT. Each WT survivor had advanced disease, requiring treatment with IFO and CARBO containing protocols with additional irradiation. The glomerular proteinuria was selective in 1 case and non-selective in 9 cases, its extent varied between 214 to 907 mg/24h (mean: 455 mg/24h). In addition to gross glomerular proteinuria, these patients exhibited impaired tubular function, i.e. microalbuminuria (mean: 33 mg/L) and elevated NAG_i (mean: 1.13

μmol/min/mmol creatinine). As expected, the degree of proteinuria correlated significantly with the amount of microalbuminuria ($p<0.05$). We did not find significant correlations between other parameters of glomerular and tubular functions among patients with persisting proteinuria, i.e. between the degree of proteinuria, cysC and NAGi (data not shown). During an average follow-up of 36 months from its discovery, persisting proteinuria improved spontaneously in 7 cases and progressed in 3 cases. These patients, similar to all the other patients, had normal blood pressure values at the time of testing. However, patients with persisting proteinuria were put on ACE inhibitor therapy: two patients received enalapril (Renitec®, MSD, Whitehouse Station, NJ, USA, 2 X 2.5 mg/day) and one patient received captopril (Tensiomin®, EGIS Co., Budapest, Hungary, 2 X 12.5mg/day) because of her age (2 ½ years at the time of testing). After 12 months, proteinuria disappeared almost completely in the two patients on enalapril therapy and the third patient on captopril experienced a moderate improval.

Proximal tubular function was assessed by urinary NAG and MA. Pathologically elevated relative NAG_i, exceeding age-related reference values were noted in 24 (38 %) among leukemia/lymphoma, in 13 (54 %) among solid tumor, in 4 (20 %) among WT survivors. A similar distribution of pathological MA (>20 mg/L) was found within these groups: in 12 (16%) among leukemia/lymphoma, in 7 (25%) among solid tumor, and in 1 (5%) among WT survivors. Relative NAG_i and MA was significantly elevated only in solid tumor survivors. Former WT patients exhibiting either pathologic relative NAG_i or urinary MA levels received CARBO and IFO because of unfavorable disease. The mean ± SD relative NAG_i and urinary microalbumin levels were 178.2±10.5 % and 29.2±4.1 mg/L in HR WT patients, whereas 92.7 ±8.1 % and 11.0±5.8 mg/L in standard (SR) and intermediate risk groups (IR) of WT patients.

4.4. ACE I/D polymorphism

The 207 patients did not differ significantly (p=0.20) from controls with respect to the frequencies of the D: n = 237 (57 %) vs. n = 87 (60 %), and I: n = 177 (43 %) vs. n = 57 (40 %) alleles, respectively. Neither did we find significant differences (p=0.34) with respect to the prevalences of the DD: n = 74 (36 %) vs. n = 52 (36 %), ID: n = 89 (43 %) vs. n = 71 (49 %) and II: n = 44 (21 %) vs. n = 21 (15%) genotypes, respectively, of the ACE gene. Allele distribution and prevalences of the three ACE genotypes were similar to those reported in healthy Caucasian individuals and followed the Hardy Weinberg equilibrium. Moreover, diagnostic subgroups of patients, including WT survivors, did not differ significantly from the controls with respect to D and I allele frequencies and ACE genotype prevalences.

4.4.1. Association of acute proximal tubular injury and ACE I/D polymorphism

The effect of the I/D polymorphism of the ACE gene on cytostatic drug-induced acute proximal tubular damage was investigated. In CP-treated patients a significantly higher ($p< 0.005$) NAG_i, whereas in DNR treated patients a significantly ($p<0.05$) higher MA was observed in association with the DD genotype of ACE polymorphism as compared with the ID and II genotypes.

4.4.2. ACE I/D polymorphism and late nephrotoxicity

ACE gene polymorphism of patients with proteinuria was investigated. The prevalence of the D allele, representing a risk factor in other forms of proteinuria, did not differ significantly from that of the control group. The distribution of genotypes, i.e. DD, ID and II were also similar to controls.

4.4.3. Association of ACE I/D polymorphism and severe circulatory compromise in febrile neutropenic children with cancer

Febrile neutropenic episodes occurred in 199 of the studied 207 patients. Fifty three patients (28 boys, 25 girls, age between 0.5-17 years, average 7.1 years) developed signs of circulatory compromise. Of these, 26 (13 boys, 13 girls, aged between 0.5-16.0 years, average: 6.3 years) were referred to the Intensive Care Unit (ICU) because of severe circulatory compromise. Each patient was febrile (axillary body temperature exceeding 38.0 ^{o}C) and neutropenic (absolute neutrophil count < 0.5 G/L or between 0.5 and 1.0 G/L and falling) at the time of referral. Tachycardia and hypotension resulted in a shock index exceeding 1.0. CRP and ESR were elevated. Hemoculture was positive in 12/26 cases. Fourteen patients had altered level of consciousness, 3 patients were oliguric, 1 patient developed jaundice. Empiric anti-infective therapy was started immediately and it was continued and modified if necessary during care in the ICU.

Each patient required administration of positive inotropic agents (dopamine with or without dobutamine). Ten patients received respiratory support (oxygen by mask or mechanical ventilation) for 1 to 4 days. Patients were treated for 1 to 18 days in the ICU. Twenty patients survived, 3 patients died due to irreversible shock while in remission from the underlying neoplasic disease.

Neither the I/D frequency nor the prevalence DD, ID and II genotypes of 27 patients developing mild-to-moderate circulatory compromise differed significantly from either the 207 patients or controls. However, the frequency of the D allele and the prevalence of the DD genotype were significantly ($p<0.05$) higher among patients with severe circulatory compromise (26) requiring treatment in the ICU than among the rest of the patients (181) and controls. Moreover, patients homozygous or heterozygous for the D allele (DD and ID genotypes) spent significantly ($p<0.05$) longer time (mean: 7 days) in the ICU than patients with the II genotype (mean: 4 days). All fatalities occurred among patents with the DD genotype.

5. DISCUSSION

Serum concentration of cystatine C, a low molecular weight protein (13.3 kDa) correlates better with GFR than creatinine-based methods, because its production rate is stable except for thyroid malfunction and corticosteroid medication, is freely filtered by the glomeruli and is completely reabsorbed and catabolized by proximal tubular cells. CysC is independent of height, weight, muscle mass and gender. GFR can be determined easily from a low amount of serum sample to be obtained from a single venipuncture connected to blood sampling for other diagnostic purposes by turbidimetric or nephelometric method. There is no need of urine collection. In our study we proved that cysC assay may become a useful method to monitor glomerular function of children with cancer. The cysC assay was used to analyze acute and late effects of potential nephrotoxic cytostatic agents on glomerular function of children with cancer.

Investigating NAG excretion and MA confirmed the known proximal tubular toxicity of platinum compounds and alkylating agents. As far as we know, an acute tubulopathy caused by anthracycline derivatives has not been proven previously in humans. In this study, three of the studied anthracycline antibiotics, i.e. DNR, EPI and IDA induced a similar tubulotoxicity as platinum derivatives and alkylating agents, being DNR the most toxic one. The progressive nature of DNR-induced tubulopathy is similar to that of CPL, CARBO, CP and IFO.

Dexrazoxane is used for preventing cardiotoxicity in patients receiving anthracycline treatment. Recent experimental evidences demonstrated that anthracycline-induced nephrotoxicity can also be prevented by the use of dexrazoxane in rats, but no related human data were found in the literature. Comparing post-treatment NAG_i in DNR-treated ALL patients, not having received dexrazoxane prior to the use of DNR, with the proximal tubular function of ALL patients who received dexrazoxane demonstrated that dexrazoxane can diminish renal tubular damage in humans.

Enzyme activity determined by the I/D polymorphism of the ACE gene was shown to play a pathogenetic role in the development and severity of certain renal disorders. The significant impact of the I/D polymorphism of the ACE gene on DNR-and CP-induced tubular damages suggested, for the first time, a genetic influence in the manifestation and severity of nephrotoxicity elicited by cytostatic agents.

The presence of the D allele increases ACE activity both in circulation and tissues. Consequently elevated production of proinflammatory cytokines and nitric oxyde (NO) downregulate type 1 and 2 receptors for AT2 and increase vascular permeability. We have demonstrated that the frequency of the D allele significantly exceeded that of the I allele in febrile neutropenic children with cancer developing severe cardiovascular compromise. Patients with the DD genotype required significantly longer intensive care than patients with the ID and II genotypes.

6. ORIGINAL OBSERVATIONS

1. A comprehensive survey of acute and late nephrotoxic side effects in children with cancer was performed for the first time in Hungary.
2. Cystatin C assay was proven for the first time as a suitable method for monitoring glomerular function of children with cancer.
3. The role of a third body fluid compartment in methotrexate-induced acute glomerular toxicity was first reported in Hungary.
4. Late glomerular toxicity can only be observed in Wilms tumor patients undergoing heminephrectomy. Carboplatin and ifosfamide contributed to renal damage in high risk Wilms tumor patients. Acute and late glomerular and tubular toxicity of known nephrotoxic cytostatic drugs, such as. cisplatin, carboplatin, cyclophosphamide, ifosfamide and methorexate was confirmed.

5. Acute proximal tubular injury elicited by 3 anthracycline antibiotics i.e. daunorubicine, idarubicine and epirubicine was proven for the first time in humans.
6. The protective role of dexrazoxane in reducing tubular injury caused by danorubicine was proven for the first time.
7. Late tubular injury was found only in a small proportion of long term cancer survivors. The incidence and severity of toxicity differs in different patient groups treated by different protocols.
8. Successful application of ACE blockers in the treatment of children with proteinuria induced by cytostatic therapy was first reported in Hungary.
9. An influence of ACE I/D polymorphism on cyclophosphamide- and daunorubicine-induced acute tubular injury was noticed for the first time.
10. An association between the presence of the D allele of the ACE gene and the development of severe circulatory compromise in febrile neutropenic children with cancer was reported for the first time.
11. An easy-to-perform and accurate protocol was suggested to monitor renal function in children with cancer.

7. LIST OF PUBLICATIONS

7.1. Full articles in peer-reviewed journals (representing the basis of the Theses)

1. Bárdi E, Bobok I, Oláh VA, Oláh É, Kappelmayer J, Kiss C: Cystatin C is a suitable marker of glomerular function in children with cancer Pediatr Nephrol 2004;10:1145-47 IF: 1.219*
2. Bárdi E, Oláh VA, Bartyik K, Endreffy E, Jenei C, Kappelmayer J, Kiss C: Late effects on renal glomerular and tubular function of childhood cancer survivors Pediatr Blood Cancer 2004;43:668-673 IF:1.737**
3. Bárdi E, Bobok I, Kiss C: Daganatos gyermekek vesekárosodása. A megelőzés és a kezelés lehetőségei. – összefoglaló klinikai tanulmány. Hypertonia és Nephrologia 2004; 8:162-170
4. Bárdi E, Jenei C, Kiss C: Angiotensin converting enzyme polymorphism is associated with septic shock in cancer children. Pediatric Blood and Cancer (published online) IF:1.737
5. Bárdi E, Szegedi I, Kiss C: Harmadik folyadéktér szerepe a methotrexát toxicitás kialakulásában, esetbemutatások kapcsán. Gyermekgyógyászat (in press)
6. Bárdi E, Bobok I, Oláh VA, Oláh É, Kappelmayer J, Kiss C: Anthracyclin antibiotics induce acute tubular toxicity in children with cancer. (submitted)

*The author was awarded by the Petényi price 2nd degree by the Hungarian Pediatric Association on the basis of the article, (Appendix 1.).
The article was between the top ten most read nephrology-related articles of the week on the Website of Doctrors Guide on 28 July, 2004, (Appendix 2.).
** The summary of the article was published in the "Hungarian Science in the World"column of Lege Artis Medicinae: Bardi E et al.: A gyermekkori rákos betegséget túlélők késői renális glomeruláris és tubuláris funkciója. LAM (in press), (Appendix 3.).

7.2. Further articles in peer-reviewed journals (not strictly related to the Theses)

1. Bárdi E, Tóth J, Szokoly V: Keresztezett dystopias multicystás vese. Gyermekgyógyászat 1998; 49:378-384
2. Bárdi E, Kőrösi T, Aranyosi J, Maródi L: Habitualis abortus kivédése IVIG-el. Transfusio 2000; 33:35-41
3. Müller J, Koós R, Garami M, Hauser P, Borgulya G, Schuler D, Benyó G, Magyarosy E, Galántai I, Milei K, Török K, Bárdi E, Hunyadi K, Gábor K, Masáth P, Bodnár L, a Magyar

Gyermekonkológiai Hálózat* és Kovács G: Gyermekkori Langerhans sejtes histiocytosissal szerzett magyarországi tapasztalataink. Magyar Onkológia2004;48:289-295

4. Sohajda Z, Damjanovich J, Bárdi E, Kiss C, Berta A: Combined chemotherapy and local treatment in the management of bilateral retinoblastomas in Hungary. (submitted)

Cumulative impact factor: 4.693

7.3. Citable abstract in peer-reviewed jornal

Bárdi E, Szegedi I, Udvardi E, Kiss C, Rényi I: Preliminary experiences with recombinant urate oxidase (Fasturtec®) for prevention of hyperuricemia in children with leukemia or lymphoma. Nephrol. Dial. Transplant. 18: 272-272, 2003 IF: 2.607

7.4. Lectures and poster presentations in national and international conferences

1. Bárdi E, Tóth J, Szokoly V: Keresztezett dystopias multicystás vese. Magyar Gyermekgyógyász Társaság (MGYT) Nagygyűlése, Szeged,1998
2. Bárdi E, Kőrösi T, Aranyosi J, Maródi L: Habitualis abortus kivédése IVIG-el. Debrecen, Magyar Szülész és Nőgyógyász Ultrahangos Társaság Ülése, 1999
3. Bárdi E, Bobok I, Oláh VA, Kappelmayer J, Kiss C: Cystatin C meghatározás gyermekkorban. MGYT Nagygyűlése, Debrecen, 2000
4. Bárdi E, Bobok I, Kiss C: ACE gén polimorphismus vizsgálat eredményei tumoros és leukémiás gyermekekben. MGYT Gyereknephrológiai Szekció Ülés, Budapest, 2001
5. Bárdi E, Bobok I, Kiss C: A malignus betegségben szenvedő gyermekek ACE gén polimorphismus vizsgálata. MGYT Nagygyűlése, Pécs, 2001
6. Bárdi E, Bobok I, Oláh VA, Oláh É, Kappelmayer J, Kiss C: A citosztatikus kezelés akut és késői mellékhatásai. MGYT Gyereknephrológiai Szekció Ülés, Seregélyes, 2002

7. Bárdi E, Bobok I, Oláh VA, Oláh É, Kappelmayer J, Kiss C: A citosztatikus kezelés késői mellékhatásai. MGYT Gyerekhemato-Onkológiai Szekció XXXI. Ülése, Debrecen, 2002
8. Bárdi E, Bobok I, Oláh VA, Oláh É, Kappelmayer J, Kiss C: Evaluation of kidney function of long-term childhood cancer survivors. 7th International Conference on the Long Term Complications of Treatment of Children & Adolescents for Cancer, Niagara-on-the Lake, Ontario, Canada, 2002
9. Bárdi E, Szegedi I, Udvardi E, Kiss C, Rényi I: Preliminary experiences with recombinant urate oxidase (Fasturtec®) for prevention of hyperuricemia in children with leukemia or lymphoma. World Congress of Nephrology, Berlin, Németország, 2003
10. Bárdi E, Bobok I, Oláh VA, Kappelmayer J, Kiss C: Evaluation of kidney function of long-term childhood cancer survivors. Europediatrics, Prága, Csehország, 2003
11. Bárdi E, Bobok I, Oláh VA, Kappelmayer J, Kiss C: Megelőzheti-e a dexrazoxane az antracyclinek nephrotoxicitását? Fiatal Gyermekorvosok Országos Találkozója, Szeged, 2004
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8. ACKNOWLEDGEMENT

Supporting grants and foundations: Scientific Health Council (ETT) grant of the Ministry of Health No 225, the “For the Leukemic Children” and the “Hope for the Leukemic Children” Foundations.

The project was planned with the help of the thesis supervisor, Prof. Csongor Kiss, M.D., Ph.D., D.Sc. and Ildikó Bobok, M.D. Samples were obtained and collected systematically with the help of nurses in the Hematology/Oncology Ward and Outpatient Clinic of the Department of Pediatrics, Medical and Health Science Center, University of Debrecen (MHSCUD) and with a special help of Mrs. Magdolna Gellért Bartha in the Experimental Hematology Lab of the Department of Pediatrics, MHSCUD. Patients were investigated and the documentation was recorded with the help of the doctors attending the Hematology/Oncology Ward and Outpatient Clinic. Immunoturbidimetric assay of cystatin C was done with the help of Mrs Irén Tóth Rábai, Department of Clinical Biochemistry and Molecular Pathology (CBMP), MHSCUD. The method was installed with the help of János Kappelmayer, M.D., Ph.D., Department of CBMP, MHSCUD. ACE polymorphism was assessed with the help of Csaba Jenei, M.D., H-Med Diagnostic and Research Laboratory, Budapest. Twenty one WT patients were cared by Katalin. Bartyik, M.D., their ACE genotype was determined by Emőke Endreffy, Ph.D. at the Department of Pediatrics, Szeged University of Sciences. Serum and urinary creatinine concentrations and microalbuminuria was measured in the Laboratories of the Department of CBMP, MHSCUD (Chair: Prof. László Muszbek, M.D., Ph.D., D.Sc., from 2004 János Kappelmayer, M.D., Ph.D.) as routine investigations. NAG activity was determined in the Routine Laboratory of the Department of Pediatrics, from 2004 Department of CBMP, MHSCUD by Anna V. Oláh, Ph.D. Abdominal ultrasound images were taken and evaluated by Judit Tóth, M.D., Department of Pediatrics, MHSCUD.

Proper conditions for performing my research program were provided by the thesis supervisor, Prof. Csongor Kiss, M.D., Ph.D., D.Sc. and by the Chairperson and Director of the Department of Pediatrics, MHSCUD, Prof. Éva Oláh, M.D., Ph.D., D.Sc.

Statistical analyses were performed with the help of Zsolt Karányi, Ist Department of Medicine, MHSCUD. Manuscripts were critically read by Giulio J. D'Angio, M.D., Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA, by Prof. István Édes M.D., Ph.D., D.Sc., Institute of Cardiology, MHSCUD and by József Balla, M.D., Ph.D., D.Sc, Ist Department of Medicine, Division Nephrology, MHSCUD.

My family background, the love and patience of my children provided an invaluable contribution to completion of my Theses.