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ORIGINAL ARTICLE

Acute kidney injury during cisplatin therapy and associations with kidney outcomes 2 to 6 months post-cisplatin in children: a multi-centre, prospective observational study

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Abstract

Background Few studies describe acute kidney injury (AKI) burden during paediatric cisplatin therapy and post-cisplatin kidney outcomes. We determined risk factors for and rate of (1) AKI during cisplatin therapy, (2) chronic kidney disease (CKD) and hypertension 2–6 months post-cisplatin, and (3) whether AKI is associated with 2–6-month outcomes.

Methods This prospective cohort study enrolled children (aged < 18 years at cancer diagnosis) treated with cisplatin from twelve Canadian hospitals. AKI during cisplatin therapy (primary exposure) was defined based on Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria (≥ stage one). Severe electrolyte abnormalities (secondary exposure) included ≥ grade three hypophosphatemia, hypokalemia, or hypomagnesemia (National Cancer Institute Common Terminology Criteria for Adverse Events v4.0). CKD was albuminuria *or* decreased kidney function for age (KDIGO guidelines). Hypertension was defined based on the 2017 American Academy of Pediatrics guidelines.

Results Of 159 children (median [interquartile range [IQR]] age: 6 [2–12] years), 73/159 (46%) participants developed AKI and 55/159 (35%) experienced severe electrolyte abnormalities during cisplatin therapy. At median [IQR] 90 [76–110] days post-cisplatin, 53/119 (45%) had CKD and 18/128 (14%) developed hypertension. In multivariable analyses, AKI was not associated with 2–6-month CKD or hypertension. Severe electrolyte abnormalities during cisplatin were associated with having 2–6-month CKD *or* hypertension (adjusted odds ratio (AdjOR) [95% CI]: 2.65 [1.04–6.74]). Having both AKI *and* severe electrolyte abnormalities was associated with 2–6-month hypertension (AdjOR [95% CI]: 3.64 [1.05–12.62]).

Conclusions Severe electrolyte abnormalities were associated with kidney outcomes. Cisplatin dose optimization to reduce toxicity and clear post-cisplatin kidney follow-up guidelines are needed.

Keywords Paediatric nephrology · Cisplatin nephrotoxicity · Acute kidney injury · Chronic kidney disease · Hypertension · Epidemiology

Introduction

Childhood cancer survivors are at risk for acute and long-term health issues [1]. Cisplatin is commonly used to treat paediatric solid tumours and is associated with acute kidney injury (AKI), resulting in serum creatinine (SCr) rise and/or electrolyte wasting [2–7]. We previously found that AKI was common during individual cisplatin infusions [8]. However, the burden of AKI incurred *during the entire* cisplatin treatment and how best to define AKI in children receiving cisplatin remains unclear.

The prevalence of chronic kidney disease (CKD), hypertension (HTN), and electrolyte abnormalities one year or more following cancer treatment completion in children varies from 0–84%, depending upon outcome definitions used [9]. Few studies have used standardized definitions to describe post-cancer therapy CKD and HTN [9]. AKI is an

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important risk factor for long-term CKD and HTN development in adults [10, 11]. Emerging data in hospitalized children without cancer also support this relationship [12–14]. Little is known about AKI risk factors during paediatric cisplatin treatment or associations of AKI with CKD and HTN. Understanding the burden of kidney disease associated with cisplatin will enable refinement of nephroprotective strategies, provide rationale for minimizing nephrotoxicity of chemotherapeutic regimens and provide evidence upon which to base follow-up guidelines for long-term follow-up of CKD, HTN, and associated complications [15, 16].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend ascertainment of AKI resolution or progression to CKD by 3 months post-AKI [17]. Cisplatin treatment may last several months. Two to 6 months post-cancer therapy may be an important and clinically relevant time point to perform kidney health risk assessment and evaluate kidney health burden accrued during cancer therapy. Current paediatric post-cancer therapy follow-up guidelines are unclear about frequency and duration of kidney health follow-up [18].

We aimed to characterize the rate, severity of, and risk factors for AKI during cisplatin therapy, estimate the CKD and HTN burden at 2–6 months post-cisplatin, and determine if AKI is a risk factor for these outcomes. We hypothesized that AKI during paediatric cisplatin therapy is associated with CKD and HTN 2–6 months post-treatment completion.

Methods

Study design, setting and cohort

The Applying Biomarkers to Minimize Long-Term Effects of Childhood/Adolescent Cancer Treatment (ABLE) study was a prospective cohort study of children with cancer treated with cisplatin from April 2013 to December 2017 (enrolled between May 2013 and March 2017) at 12 Canadian paediatric oncology centres [19]. The last 2–6-month follow-up was completed in June 2018. Study methods have been published [8, 19]. Inclusion criteria were: age < 18 years at cancer diagnosis; planned cisplatin treatment [8]. Exclusion criteria were: history of kidney transplant; measured or estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 at baseline [8]. The inclusion criterion for this analysis was survival to cisplatin treatment end; exclusion criteria were having the outcome (CKD; HTN) at baseline (pre-cisplatin) or having insufficient 2–6-month CKD or HTN ascertainment data. All participating centres' research ethics boards approved the study. Informed consent (assent as appropriate) was obtained. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Study protocol

Online Resource 1 displays the protocol. Urine and blood were collected at two cisplatin cycles (Online Resource 1) [8]. A follow-up study visit was planned in oncology clinics 3 months ± 4 weeks (between 56–112 days) after cisplatin therapy completion (Online Resource 1) [19]. To minimize data loss, visits that occurred within 56–168 days (between 2–6 months) after cisplatin treatment end were included. At 2–6 months, blood and urine (spot sample) were collected; blood was spun at sites (1000 *g*; 21 °C; ten minutes). Serum and urine were stored at –80 °C and shipped bi-annually to Montreal (central site). Specimens were stored until measurement for creatinine (SCr, by isotope dilution mass spectroscopy-traceable method), potassium, magnesium, phosphorous and albumin; urine was thawed, processed and separated into aliquots (1000 *g;* 21 °C; ten minutes). Participants' height, weight and blood pressure (BP) were measured three times using standardized methods and expressed as percentiles [20–23]. BP was measured seated, using size-appropriate cuffs and an automated oscillometric device [19]. To minimize the white coat effect, which could overestimate BP values, the two lowest systolic BP and corresponding diastolic BP measures were averaged. For feasibility reasons and to reduce loss to follow-up, we measured BP during a single study visit and repeat BP assessments were not performed. Specimen collection and handling was tracked in real-time using an electronic data capture system [24].

Clinical data

Participant and cancer treatment data collected at baseline and during cisplatin treatment (from first cisplatin infusion up to ten days after last infusion) have been described (Online Resource 1) [8, 19]. Monthly routine SCr and electrolytes were recorded during cisplatin treatment. Data collected between cisplatin therapy end and the 2–6-month visit included cancer-specific data; kidney and non-kidney comorbidities; medications; most recent routine SCr and electrolytes (Online Resource 1). If BP, height or weight were unavailable at the 2–6-month visit, the most recent results were obtained from medical charts. If no height was available, it was extrapolated from height at cisplatin treatment end (using growth chart percentiles) [20, 21, 25]. Data were entered and managed by the Epidemiology Coordinating and Research Centre (Edmonton), with regular queries to study sites.

Primary AKI definition: SCr-AKI

SCr-AKI during cisplatin therapy was defined based on the KDIGO guidelines SCr criteria (using both protocol and routinely collected SCr values): ≥ stage one AKI (peak SCr during cisplatin therapy ≥ 50% or ≥ 26.5 µmol/L above baseline at any time) [17]. The baseline SCr was defined as the lowest SCr in the 3 months before cisplatin commencement. Severe SCr-AKI was ≥ stage two KDIGO-AKI (≥ peak SCr doubling from baseline) [17]. KDIGO urine output criteria were not considered since cisplatin-associated AKI is non-oliguric [17].

Secondary AKI definitions: electrolyte-AKI, composite-AKI

To recognize the unique clinical characteristics of cisplatin-injury [2, 3], a secondary AKI definition termed electrolyte-AKI (eAKI) was defined using electrolyte criteria adapted from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Online Resource 2) [26]. eAKI was ≥ grade one hypophosphatemia, hypokalemia or hypomagnesemia based upon the lowest electrolyte values during cisplatin treatment (Online Resource 2) [26]. Since eAKI with cisplatin is extremely common, we defined severe eAKI as ≥ grade three eAKI (Online Resource 2) [4, 8, 26]. Composite-AKI was the presence of SCr-AKI *and* severe eAKI.

Primary outcomes: CKD and HTN 2–6 months post-cisplatin

CKD was defined based on the KDIGO guidelines: low measured or estimated GFR (GFR categories G2–G5) *or* high urine albumin-to-creatinine ratio [uACR] for age (albuminuria categories A2–A3) [14, 27, 28]. Albuminuria for age was defined using age-based uACR thresholds (age < 2 years, uACR ≥ 7.5 mg/mmol; age ≥ 2 years, uACR ≥ 3 mg/mmol) [14, 28]. Low measured or estimated GFR for age was defined using age-based GFR thresholds (age ≤ 1 month, estimated GFR [eGFR] < 43 mL/min/1.73 m^2; age 1–4 months, eGFR < 47 mL/min/1.73 m^2; age 4–8 months, eGFR < 58 mL/min/1.73 m^2; age 8 months–1 year, eGFR < 65 mL/min/1.73 m^2; age 1–1.5 years, eGFR < 74 mL/min/1.73 m^2; age 1.5–2 years, eGFR < 76 mL/min/1.73 m^2, age > 2 years, eGFR < 90 mL/min/1.73 m^2) [14, 27, 28]. SCr at the 2–6-month visit was used to estimate GFR using a paediatric (Chronic Kidney Disease in Children SCr-equation) or the average of paediatric and adult GFR equations (CKD Epidemiology SCr-equation) as appropriate [29–31]; if unavailable, nuclear medicine GFR, 24-h creatinine clearance or routine SCr measured within the study window (56–168 days post-cisplatin) were used (in that order).

HTN was defined based on the 2017 paediatric/adult guidelines, using BP percentiles (≥ 95th percentile for age/sex/height if age < 13 years) and/or BP thresholds (≥ 130/80 mmHg) [23, 32]. Participants taking anti-hypertensive medications were classified as hypertensive.

Secondary outcomes

A composite outcome, CKD *or* HTN, was evaluated. We examined the presence of electrolyte supplementation (magnesium; potassium; phosphorous; bicarbonate) and electrolyte abnormalities (hypophosphatemia, hypokalemia, hypomagnesemia) at 2–6 months using NCI-CTCAE v4.0 (Online Resource 2) [26].

Statistical analysis

Analyses were performed using Stata (v.15.1, College Station, TX). We calculated the rate and severity of AKI by different definitions. We also calculated the rate of CKD, HTN, and CKD *or* HTN at 2–6 months post-cisplatin. Between-group variable comparisons were performed using distribution-appropriate univariable analyses (*t*-test; Mann–Whitney test; chi-square test; Fisher's exact test). Multivariable logistic regression was used to evaluate AKI risk factors and the association between AKI and 2–6-month CKD and HTN. For AKI prediction models, age was forced into models based on literature and clinical rationale [8, 33–35]. For 2–6-month CKD/HTN models, age and sex were forced into models. Purposeful selection and manual backward selection were used to select variables for multivariable models. Variables associated with AKI and the outcome ($P < 0.10$) in univariable analyses were considered for inclusion in multivariable models. Multicollinearity was evaluated using correlation (excluded if rho > 0.8) and variance inflation factor (excluded if > 10). Variables significant in multivariable analyses ($P < 0.05$) and with non-significant backward likelihood ratio test for removal were retained. Significant confounders were assessed and kept in models if other covariate estimates changed by ≥ 20%. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. $P < 0.05$ (two-tailed) was considered statistically significant.

For each outcome, only participants with non-missing values were included in the analyses. For composite outcomes (CKD; CKD *or* HTN), when one value was missing and the other was abnormal, the participant was classified as having the composite outcome. If one value was missing and the other was normal, the composite outcome was classified as *missing*. Sensitivity analyses were performed whereby (a) routine 24-h creatinine clearance results were

excluded to ascertain baseline measured or estimated GFR, (b) participants with missing outcome status were classified as *not* having the outcome, (c) only participants with outcome ascertainment within the strict 3-month window (56–112 days post-cisplatin) were included, (d) AKI associations with low eGFR for age were determined, and e) AKI rates in participants who were cisplatin naïve upon enrollment versus not, were calculated.

Results

Study cohort and AKI during cisplatin therapy

All 159 participants had AKI data available (Fig. 1). All participants had a baseline SCr measurement available. Median [interquartile range (IQR)] time to measurement of baseline SCr prior to cisplatin commencement was 1 [0–7] day(s). At baseline, eight participants had a low GFR for age and eight others had a history of HTN (Fig. 1). Participants received 60–200 mg/m^2 of cisplatin per cycle and were treated with 1–8 cisplatin cycles (Online Resource 3 describes cisplatin protocols). The most common nephrotoxic treatments included carboplatin (43%), stem cell transplant (SCT) (45%), and radiation (50%) (other nephrotoxic treatments are described in Online Resource 4). Sixty of 71 (85%) patients with SCT also received carboplatin. For the 159 participants, median [IQR] age at cisplatin commencement was 6 [2–12] years; 80 (50%) were male; 118 (74%) were Caucasian; the main cancer diagnoses were central nervous system (CNS) tumours (36%) and neuroblastoma (27%) (Table 1). Median [IQR] total cumulative cisplatin dose received was 378 [272–444] mg/m^2 (Table 1). During cisplatin treatment, no participant received dialysis; one died from tumour progression. Table 2 shows that 46% of participants developed SCr-AKI; 94% had eAKI (35% severe eAKI); 19% had composite-AKI during cisplatin therapy. Most AKI was mild (most commonly stage/grade 1; Fig. 2). Twenty (13%) participants had stage two SCr-AKI or worse (Fig. 2). Hypophosphatemia was the most common electrolyte abnormality; severe hypokalemia was the main severe eAKI contributor (Fig. 2).

Characteristics associated with AKI during cisplatin therapy

A greater proportion of participants with *vs.* without SCr-AKI were less than 3 years old at cisplatin start (42% *vs.* 26%; Table 1). Participants with *vs.* without SCr-AKI had a higher baseline GFR (mean (standard deviation (SD)): 147 (48) *vs.* 133 (31) mL/min/1.73 m^2, respectively), more commonly had CNS tumours (45% *vs.* 29%, respectively) and less commonly had osteosarcoma (11% *vs.* 29%, respectively; Table 1). In multivariable analyses of pre-cisplatin risk factors, CNS tumours were associated with SCr-AKI (Adjusted OR (AdjOR) [95% CI]: 3.43 [1.29–9.16], relative to osteosarcoma; Table 3). Neuroblastoma was associated with severe eAKI (AdjOR [95% CI]: 0.12 [0.04–0.38], decreased odds relative to osteosarcoma); age less than 3 years was associated with composite-AKI (AdjOR [95% CI]: 2.84 [1.26–6.40]; Table 3). Treatment protocols of participants with *vs.* without SCr-AKI more commonly included aldesleukin, autologous SCT, vincristine, isotretinoin, and filgrastim (Online Resource 4).

CKD and HTN 2–6 months post-cisplatin

After exclusions, 149 participants had data available at the 2–6-month post-cisplatin follow-up; 137 had 2–6-month post-cisplatin therapy uACR or GFR data; 128 had BP data (Fig. 1). For the CKD outcome, only 4 participants had GFR expressed using a nuclear medicine measured GFR (none measured by creatinine clearance) due to missing SCr. Robust quality assurance checks resulted in low amounts of missing specimens and data (Online Resource 5; Online Resource 6). Height at the 2–6-month visit was not available in two patients and was extrapolated from height at cisplatin therapy end. For the HTN outcome, 75 (59%) participants had 3 BP measurements, 3 (2.3%) had 2 BP measurements, and 50 (39%) had one BP measurement. Follow-up visits occurred a median [IQR] of 90 [76–110] days post-cisplatin therapy end; two participants relapsed; none required dialysis; one had a nephrectomy. Except for cancer diagnosis, baseline and cisplatin characteristics were similar between participants who did *vs.* did not complete 2–6-month visits (Online Resource 7). eGFR was significantly lower at 2–6 months compared to baseline (median [IQR]: 137 [110–164] *vs.* 147 [124–176] mL/min/1.73 m^2, respectively; $P < 0.001$; Online Resource 8). At 2–6 months, 11/135 (8%) had a low measured or estimated GFR for age; 43/118 (36%) had albuminuria; 53/119 (45%) had CKD; 18/128 (14%) had HTN (Table 4). Individual kidney and BP characteristics at 2–6 months were similar between participants with *vs.* without SCr-AKI (Table 4). At 2–6 months, 47/149 (32%) participants were taking electrolyte supplements (most commonly magnesium); 20% (29/143) had hypokalemia, hypomagnesemia, or hypophosphatemia (Table 4). Eighty-five of 120 (71%) participants either had CKD, HTN, or electrolyte abnormalities or were taking electrolyte supplements at 2–6 months. Participants with estimated or measured GFR ≥ *vs.* < 150 ml/min/1.73 m^2 at 2–6 months had higher uACR (median [IQR]: 3.7 [1.6–6.2 mg/mmol, $n = 45$] *vs.* 2.3 [1.2–4.4] mg/mmol, $n = 71$; $P < 0.05$).

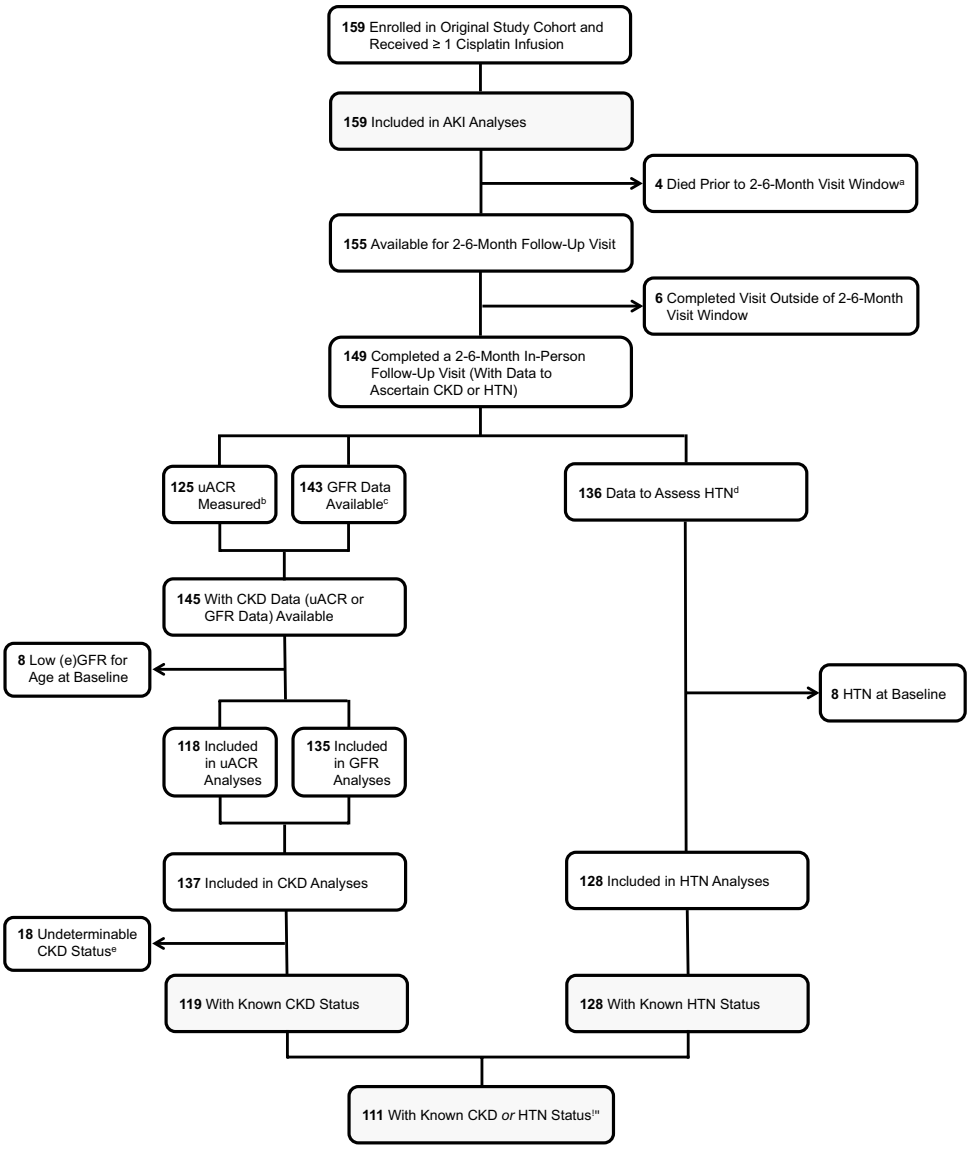

Fig. 1 Flow Diagram of study cohort from cisplatin treatment to 2–6-month follow-up study visit (between 56 and 168 days post-cisplatin). The study flow diagram outlines the number of patients enrolled and with available data for analyses. [a]The 4 deaths before the 2–6-month visit window were due to disease progression ($n=3$) and viral infection ($n=1$). [b]Reasons for no uACR measurement for 24 participants: missed urine collection ($n=7$), child/family refused ($n=1$), insufficient quantity ($n=2$), sample misplaced ($n=1$), urine ACR outside of visit window ($n=7$), deceased/withdrew ($n=6$). [c]Reasons for no GFR data for 6 participants: blood collected outside of visit window ($n=2$), child/family refused ($n=1$), deceased/withdrew ($n=3$). [d]Reasons for no HTN data for 13 participants: BP data is outside of visit window ($n=12$), no BP measurement ($n=1$). [e]For the 18 with an undetermined CKD status, 2 did not have albuminuria but did not have GFR data and 16 did not have a low estimated or measured GFR for age but did not have uACR data. [f]For the 38 with an undetermined CKD *or* HTN status, 16 had CKD or HTN at baseline, 4 did not have CKD but did not have HTN data and 13 did not have HTN but did not have CKD data and 5 did not have either a CKD or HTN status ($n=1$ did not have albuminuria and had no GFR data; $n=4$ did not have a low estimated or measured GFR and had no albuminuria data). Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HTN, hypertension; uACR, urine albumin-to-creatinine ratio; GFR, glomerular filtration rate

Characteristics associated with 2–6-month outcomes

A higher proportion of participants with *vs.* without CKD and with *vs.* without HTN were aged less than 3 years at cisplatin commencement, had SCT (and carboplatin) in their treatment protocol, and had infections during cisplatin therapy (Table 5; Online Resource 9). A higher proportion of participants with *vs.* without 2–6-month HTN were males, were admitted to the intensive care unit during cisplatin therapy, and received loop diuretics before cisplatin commencement (Table 5; Online Resource 9 details

Table 1 Characteristics of study participants by SCr-AKI during cisplatin therapy status

Characteristic	All ($n=159$)	SCr-AKI during cisplatin therapy ($n=73$)	No SCr-AKI during cisplatin therapy ($n=86$)
Baseline (prior to 1st cisplatin infusion)			
Age at cisplatin treatment start, median (IQR), years	6 (2–12)	4 (2–10)	7 (3–12)
Age at cisplatin treatment start < 3 years, No. (%)	53 (33%)	31 (42%)	22 (26%)*
Male, No. (%)	80 (50%)	39 (53%)	41 (48%)
Race			
Aboriginal, No. (%)	8 (5%)	3 (4%)	5 (6%)
American Indian/Alaskan, No. (%)	1 (0.6%)	0 (0.0%)	1 (1%)
Caucasian/White, No. (%)	118 (74%)	56 (77%)	62 (72%)
Black/African American, No. (%)	5 (3%)	1 (1%)	4 (5%)
Asian, No. (%)	15 (9%)	7 (10%)	8 (9%)
Mixed race, No. (%)	10 (6%)	5 (7%)	5 (6%)
Hispanic, No. (%)	2 (1%)	1 (1%)	1 (1%)
Cancer diagnosis			*
Osteosarcoma, No. (%)	33 (21%)	8 (11%)	25 (29%)**
Germ cell tumour, No. (%)	14 (9%)	5 (7%)	9 (11%)
Neuroblastoma, No. (%)	43 (27%)	21 (29%)	22 (26%)
CNS tumour, No. (%)[a]	58 (36%)	33 (45%)	25 (29%)*
Hepatoblastoma, No. (%)	9 (6%)	5 (7%)	4 (5%)
Other, No. (%)[b]	2 (1%)	1 (1%)	1 (1%)
Baseline measured or estimated GFR, mean (SD), mL/min/1.73 m^2 [c]	139 (40)	147 (48)	133 (31)*
Low baseline measured or estimated GFR for age, No. (%)	8 (5%)	5 (7%)	3 (4%)
Kidney medical history, No. (%)[d]	13 (8%)	6 (8%)	7 (8%)
Nephrotoxic drug (in 2 weeks prior to 1st cisplatin), No. (%)[e]	27 (17%)	12 (16%)	15 (17%)
Acyclovir, No. (%)	2 (1%)	2 (3%)	0 (0.0%)
Aminoglycosides, No. (%)[f]	7 (4%)	3 (4%)	4 (5%)
Amphotericin, No. (%)	1 (0.6%)	0 (0.0%)	1 (1%)
ACE inhibitor, No. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ganciclovir/valganciclovir, No. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ifosfamide, No. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Methotrexate, No. (%)	11 (7%)	3 (4%)	8 (9%)
Vancomycin, No. (%)	8 (5%)	4 (6%)	4 (5%)
Loop diuretics (in 2 weeks prior to 1st cisplatin), No. (%)[g]	5 (3%)	4 (6%)	1 (1%)
NSAIDS or ASA (in 2 weeks prior to 1st cisplatin), No. (%)[h]	18 (11%)	11 (15%)	7 (8%)
During cisplatin/cancer treatment (between first and last cisplatin infusion)			
Cancer involves one or both kidneys, No. (%)	11 (7%)	5 (7%)	6 (7%)
Flank (left or right), whole abdomen, or total body radiation given or planned, No. (%)	22 (14%)	12 (16%)	10 (12%)
Total cumulative cisplatin dose, median (IQR), mg/m^2	378 (272–444)	359 (260–413)	389 (283–466)
Radiation in chemotherapy protocol, No. (%)[i]	80 (50%)	40 (55%)	40 (47%)
Infection, No. (%)[j]	58 (37%)	29 (40%)	29 (34%)
Sepsis, No. (%)	6 (4%)	2 (3%)	4 (5%)
Kidney infection or UTI, No. (%)[k]	10 (6%)	5 (7%)	5 (6%)
PICU admission, No. (%)	14 (9%)	8 (11%)	6 (7%)
Between last cisplatin infusion and 2–6-month visit			
Relapse, No. (%)	3 (2%)	1 (1%)	2 (2%)
Veno-occlusive disease, No. (%)	6 (4%)	4 (6%)	2 (2%)
Nephrectomy, No. (%)	1 (0.6%)	1 (1%)	0 (0.0%)
Radiation to abdomen, No. (%)	6 (4%)	3 (4%)	3 (4%)

Table 1 (continued)

Characteristic	All ($n=159$)	SCr-AKI during cisplatin therapy ($n=73$)	No SCr-AKI during cisplatin therapy ($n=86$)
Aminoglycosides, No. (%)[f]	20 (13%)	8 (11%)	12 (14%)
Nephrotoxic drug (in 1 month prior to 2–6-month visit), No. (%)[l]	60 (38%)	27 (37%)	33 (38%)
Other aminoglycosides (in 1 month prior), No. (%)[m]	2 (1%)	0 (0.0%)	2 (2%)
Acyclovir (in 1 month prior), No. (%)	19 (12%)	14 (19%)	5 (6%)*
Amphotericin (in 1 month prior), No. (%)	3 (2%)	3 (4%)	0 (0.0%)
ACE Inhibitor (in 1 month prior), No. (%)	1 (0.6%)	1 (1%)	0 (0.0%)
Ganciclovir/valganciclovir (in 1 month prior), No. (%)	1 (0.6%)	1 (1%)	0 (0.0%)
Ifosfamide (in 1 month prior), No. (%)	3 (2%)	1 (1%)	2 (2%)
Methotrexate (in 1 month prior), No. (%)	21 (13%)	5 (7%)	16 (19%)*
Vancomycin (in 1 month prior), No. (%)	25 (16%)	13 (18%)	12 (14%)
Loop diuretics (in 1 month prior to 2–6-month visit), No. (%)[g]	13 (8%)	5 (7%)	8 (9%)
NSAIDS or ASA (in 1 month prior to 2–6-month visit), No. (%)[h]	8 (5%)	2 (3%)	6 (7%)
Time between cisplatin treatment end and 2–6-month visit, median (IQR), days	89 (72–110)	85 (64–105)	89.5 (76–112)
BMI percentile at 2–6-month visit, median (IQR)	36 (10–67)	37 (13–60)	35 (10–68)

[a]CNS Tumours: astrocytoma, choroid plexus tumour, ependymoma, medulloblastoma, primitive neuroectodermal tumour, atypical teratoid/rhabdoid tumour

[b]Other cancer: lymphoma and nasopharyngeal carcinoma

[c]Baseline measured or estimated GFR was assessed using measured GFR if available or 24-h creatinine clearance if unavailable; if both were unavailable GFR was estimated (using the lowest 3-month pre-cisplatin SCr level). Composition of baseline measured or estimated GFR: routine care nuclear medicine measured GFR ($n=98$); routine care 24-h creatinine clearance measured GFR ($n=9$); GFR estimated using the study measured SCr or a routine care SCr value ($n=52$)

[d]Kidney medical history (based on medical chart review): hypertension, treatment with antihypertensives, family history of kidney disease, chronic kidney disease, dialysis, congenital kidney anomaly, kidney stones, vesicoureteral reflux, urinary tract infection, serum electrolyte abnormality requiring treatment or AKI

[e]Nephrotoxic drugs include acyclovir, amphotericin, aminoglycosides (gentamycin, tobramycin, amikacin), vancomycin, ACE inhibitor, ganciclovir/valganciclovir, ifosfamide, or methotrexate

[f]Gentamycin; tobramycin; amikacin

[g]Furosemide, ethacrinic acid, bumetanide

[h]Ibuprofen, naproxen, cox-inhibitors, diclofenac, ketorolac, or any form of aspirin

[i]Radiation information was extrapolated from each participant's chemotherapy protocol

[j]Only infections with a positive culture and documentation were tabulated

[k]Kidney infection or UTI includes any infection with a specimen originating from the kidneys or UTI

[l]Nephrotoxic drugs include: acyclovir, amphotericin, aminoglycosides (other than gentamycin, tobramycin and amikacin), vancomycin, angiotensin-converting enzyme inhibitor, ganciclovir/valganciclovir, ifosfamide, or methotrexate

[m]Aminoglycosides other than gentamycin; tobramycin; amikacin

*Stands for significant difference between AKI and non-AKI groups: *$P<0.05$; **$P<0.01$; ***$P<0.001$

Abbreviations: *SCr*, serum creatinine; *AKI*, acute kidney injury; *IQR*, interquartile range; *CNS*, central nervous system; *GFR*, glomerular filtration rate; *ACE*, angiotensin converting enzyme; *NSAIDS*, nonsteroidal anti-inflammatory drugs; *ASA*, acetylsalicylic acid; *UTI*, urinary tract infection; *PICU*, paediatric intensive care unit; *BMI*, body mass index

drugs received before, during, and post-cisplatin therapy). A higher proportion of participants with *vs.* without CKD received nephrotoxins in the month preceding the 2–6-month visit (Table 5). In general, characteristics of participants with *vs.* without CKD *or* HTN at 2–6 months followed similar patterns; however, osteosarcoma was less common in participants with *vs.* without 2–6-month CKD *or* HTN (Online Resource 10).

Associations between AKI and 2–6-month outcomes

In univariable (Table 2) and multivariable (Table 6) analyses, SCr-AKI was not associated with 2–6-month outcomes. However, severe eAKI was associated with 2–6-month CKD *or* HTN (AdjOR [95% CI] 2.65 [1.04–6.74]); composite-AKI during cisplatin therapy was associated with 2–6-month HTN (AdjOR [95% CI] 3.64 [1.05–12.62]; Table 6).

Table 2 AKI rates and types during cisplatin therapy and univariable associations with 2–6-month outcomes

	All ($n=159$)	CKD Outcome ($n=119$)		HTN Outcome ($n=128$)		CKD *or* HTN Outcome ($n=111$)	
	No. (%)	CKD ($n=53$)	No CKD ($n=66$)	HTN ($n=18$)	No HTN ($n=110$)	CKD *or* HTN ($n=57$)	No CKD *or* HTN ($n=54$)
		OR (95% CI)[a]		OR (95% CI)[a]		OR (95% CI)[a]	
SCr-AKI during cisplatin therapy							
SCr-AKI	73 (46%)	23/53 (43%)	28/66 (42%)	10/18 (56%)	45/110 (41%)	26/57 (46%)	22/54 (41%)
		1.04 [0.50–2.16]		1.80 [0.66–4.93]		1.22 [0.57–2.59]	
Severe SCr-AKI (≥ Stage 2 SCr-AKI)	20 (13%)	8/53 (15%)	8/66 (12%)	4/18 (22%)	13/110 (12%)	8/57 (14%)	7/54 (13%)
		1.29 [0.45–3.70]		2.13 [0.61–7.46]		1.10 [0.37–3.26]	
eAKI during cisplatin therapy							
eAKI[c]	149 (94%)	51/53 (96%)	61/66 (92%)	18/18 (100%)	106/110 (96%)	55/57 (97%)	52/54 (96%)
		2.09 [0.39–11.23]		1 (omitted)[b]		1.06 [0.14–7.79]	
Severe eAKI (≥ grade 3 eAKI)	55 (35%)	23/53 (43%)	20/66 (30%)	10/18 (56%)	36/110 (33%)	25/57 (44%)	16/54 (30%)
		1.76 [0.83–3.75]		2.57 [0.93–7.06]		1.86 [0.85–4.06]	
Composite-AKI during cisplatin therapy							
Composite-AKI[d]	30 (19%)	12/53 (23%)	9/66 (14%)	8/18 (44%)**	16/110 (15%)	14/57 (25%)	6/54 (11%)
		1.79 [0.68–4.71]		***2.68 [1.02–7.04]***		2.60 [0.92–7.38]	

Significant odds ratios are italicized and bolded

[a]Odds ratios represent the univariable (crude) association of AKI with each outcome

[b]Variable omitted because it predicted failure perfectly

[c] ≥ Grade 1 hypophosphatemia, hypokalemia, or hypomagnesemia as per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0[26]

[d]SCr-AKI *and* severe eAKI

[*]Stands for significant difference between Outcome versus No Outcome groups by Fisher's exact test or chi-square test as appropriate: *$P<0.05$; **$P<0.01$; ***$P<0.001$

Abbreviations: *SCr*, serum creatinine; *AKI*, acute kidney injury; *eAKI*, electrolyte-AKI; *CKD*, chronic kidney disease; *HTN*, hypertension; *OR*, odds ratio; *CI*, confidence interval

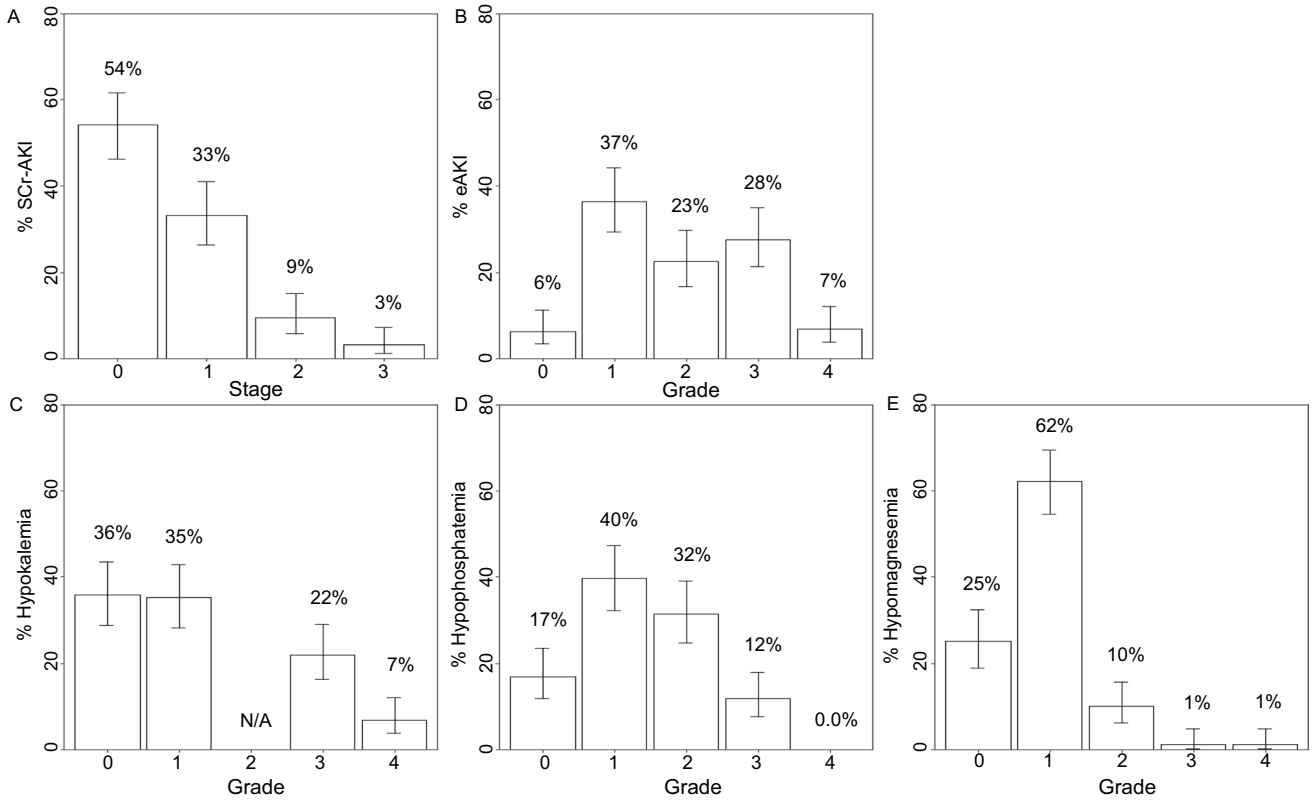

Fig. 2 Description of AKI severity during cisplatin therapy. Proportions of participants with each AKI stage or grade are shown. Point estimates are written above each bar in each graph. Error bars represent the upper and lower 95% confidence intervals. Panel **A**: SCr-AKI during cisplatin therapy. Panel **B**: eAKI during cisplatin therapy. Panel **C**: hypokalemia during cisplatin therapy. Grade 2 hypokalemia was not applicable (not assessed) since criteria for grade 1 hypokalemia could not be differentiated from grade 2 hypokalemia solely based on serum potassium concentration. Grade 1 hypokalemia: < lower limit of normal for age—3.0 mmol/L. Grade 2 hypokalemia: < lower limit of normal for age—3.0 mmol/L, symptomatic, intervention indicated. Panel **D**: hypophosphatemia during cisplatin therapy. Panel **E**: hypomagnesemia during cisplatin therapy. Abbreviations: SCr, serum creatinine; AKI, acute kidney injury; *eAKI*, electrolyte-AKI; *N/A*, not applicable

In most adjusted models, age less than 3 years at cisplatin commencement was associated with 2–6-month CKD and HTN and male sex was associated with 2–6-month HTN (Table 6).

Sensitivity analyses

When excluding 24-h creatinine clearance results to ascertain baseline measured or estimated GFR, SCr-AKI vs. non-SCr-AKI differences in baseline measured or estimated GFR were similar (Online Resource 11). When the strict 3-month visit window was applied (Online Resource 12) and when participants with indeterminable 2–6-month composite outcomes were assumed not to have the outcome (Online Resource 13), AKI-outcome associations were similar in direction and magnitude. AKI associations with low eGFR for age at 2–6 months remained similar in direction and magnitude (Online Resource 14). When evaluating AKI rates in patients who were cisplatin naïve upon enrollment versus not, AKI rates remained similar except for SCr-AKI, which was higher in patients who were cisplatin naïve *vs.* not (59% vs. 28%; $P < 0.001$; Online Resource 15).

Discussion

This is one of the first multi-centre, prospective paediatric studies to comprehensively evaluate post-cisplatin CKD and HTN associations with AKI. Almost half of the children experienced AKI during cisplatin treatment. At 2–6 months post-cisplatin, nearly half had signs of CKD and one in seven developed HTN. Although SCr-AKI was not associated with CKD and HTN, severe eAKI was associated with 2–6-month CKD *or* HTN and composite-AKI was associated with HTN.

The SCr-AKI rate in our cisplatin-treated cohort was in the literature-described range (5–77%) [2, 4, 6, 36, 37]. AKI is rarely defined by electrolyte disturbances outside of the cancer setting. Although we acknowledge that electrolyte

Table 3 Adjusted associations of baseline risk factors for AKI during cisplatin therapy

SCr-AKI during cisplatin therapy ($n = 159$; $n = 73$ with AKI)[a]	
Variable	**Adjusted OR (95% CI)**
Age at cisplatin treatment start < 3 years[b]	1.73 [0.85–3.53]
Cancer diagnosis[c]	
Osteosarcoma	1 (reference)
CNS tumour	***3.43 [1.29–9.16]***
Neuroblastoma	2.42 [0.86–6.81]
Other cancer[d]	1.92 [0.59–6.20]
Severe eAKI during cisplatin therapy ($n = 159$; $n = 55$ with AKI)[e]	
Variable	**Adjusted OR (95% CI)**
Age at cisplatin treatment start < 3 years[b]	1.85 [0.84–4.06]
Cancer diagnosis[c]	
Osteosarcoma	1 (reference)
CNS tumour	0.46 [0.18–1.15]
Neuroblastoma	***0.12 [0.04–0.38]***
Other cancer[d]	0.47 [0.15–1.45]
Composite-AKI during cisplatin therapy ($n = 159$; $n = 30$ with AKI)[f,g]	
Variable	**Adjusted OR (95% CI)**
Age at cisplatin treatment start < 3 years[c]	*2.84 [1.26–6.40]*

Significant Odds Ratios are italicized and bolded

Only baseline (pre-cisplatin) risk factors were considered

[a]Model for SCr-AKI: variables evaluated were age < 3 years, cancer type and baseline estimated or measured GFR

[b]Age was categorized as age < 3 years since there was an increased AKI risk in this group and to increase clinical usefulness. Age less than 3 years was forced into all models (a priori)

[c]Based on distribution and AKI risk, cancer type was expressed in four categories: (1) osteosarcoma, (2) CNS tumour, (3) neuroblastoma, (4) other cancers (germ cell tumours, hepatoblastoma, and others)

[d]Other cancer diagnoses include germ cell tumours, hepatoblastoma, lymphoma, and nasopharyngeal carcinoma

[e]Model for Severe eAKI: variables evaluated were age < 3 years, cancer type, and methotrexate (in 2 weeks pre-cisplatin)

[f]SCr-AKI *and* severe eAKI

[g]Model for composite-AKI: variables evaluated were age < 3 years and cancer type

Abbreviations: *SCr*, serum creatinine; *AKI*, acute kidney injury; *CNS*, central nervous system; *eAKI*, electrolyte-AKI; *OR*, odds ratio; *CI*, confidence interval

abnormalities may occur for other reasons (e.g. emesis, diarrhoea, tumour type, etc.), we believe a novel term similar to "eAKI" should be used or acknowledged in the cisplatin context to reflect electrolyte disturbances occurring due to cisplatin kidney injury. Almost all participants developed eAKI, 35% with severe eAKI. In the literature, cisplatin-associated electrolyte abnormalities are poorly described, but hypomagnesemia occurs in 14–94% of children [3, 4, 36, 38, 39]. CNS tumours were associated with increased SCr-AKI risk relative to osteosarcoma for unclear reasons. Specific treatment combinations or high single cisplatin infusion dose may have contributed. Consistent with our previous findings on AKI during individual cisplatin infusions, age less than 3 years at cisplatin start was associated with SCr-AKI during cisplatin therapy [8]. Neuroblastoma *vs.* osteosarcoma was associated with lower odds of severe eAKI perhaps because osteosarcoma treatment includes a high cumulative cisplatin dose with methotrexate and sometimes ifosfamide.

Literature estimates of kidney abnormalities at 1 year or more after childhood cancer treatment are highly variable (range: 0–84%) [9]. Studies have typically been small, conducted in single centres, used inconsistent outcome definitions, or were performed in adults treated for cancer as children in the past [9, 40, 41]. This has created roadblocks in developing clear kidney follow-up guidelines post-chemotherapy. Few studies have evaluated post-cisplatin CKD using standardized definitions [4, 9]. At variable time points post-cisplatin, some studies described that low GFR occurs in 0–74% and albuminuria occurs in 0–60% [4, 5, 7, 42–44],

Table 4 Description of individual 2–6-month kidney and blood pressure measures in participants with and without SCr-AKI during cisplatin therapy

2–6-month study visit characteristic	All ($n=149$)	SCr-AKI during cisplatin therapy ($n=66$)	No SCr-AKI during cisplatin therapy ($n=83$)
CKD characteristics[a]			
uACR, median (IQR), mg/mmol	2.7 (1.4–5.0) $N=118$	2.7 (1.5–5.0) $N=49$	2.6 (1.4–4.5) $N=69$
Albuminuria for age, No. (%)[b]	43/118 (36%)	18/49 (37%)	25/69 (36%)
Severe albuminuria, No. (%)[c]	4/118 (3%)	2/49 (4%)	2/69 (3%)
Measured or estimated GFR, mean (SD), ml/min/1.73 m^2[2d]	140 (39) $N=135$	138 (41) $N=56$	142 (38) $N=79$
Low measured or estimated GFR for age, No. (%)[e]	11/135 (8%)	6/56 (11%)	5/79 (6%)
Measured or estimated GFR < 60 ml/min/1.73 m^2, No. (%)	1/135 (0.7%)	1/56 (2%)	0/79 (0.0%)
Measured or estimated GFR ≥ 150 ml/min/1.73 m^2 (hyperfiltration), No. (%)	50/135 (37%)	21/56 (38%)	29/79 (37%)
CKD, No. (%)	53/119 (45%)	23/51 (45%)	30/68 (44%)
Low potassium, magnesium, or phosphate, No. (%)	29/143 (20%)	11/61 (18%)	18/82 (22%)
Potassium, magnesium, phosphate, or bicarbonate supplements, No. (%)	47 (32%)	19 (29%)	28 (34%)
Hypokalemia or potassium supplements, No. (%)	20/144 (14%)	8/62 (13%)	12/82 (15%)
Hypomagnesemia or magnesium supplements, No. (%)	49/145 (34%)	24/63 (38%)	25/82 (31%)
Hypophosphatemia or phosphate supplements, No. (%)	11/144 (8%)	6/62 (10%)	5/82 (6%)
BP Characteristics[f]			
SBP percentile, median (IQR)[g]	50 (25–73) N = 124	55 (31–77) N = 52	43 (23–69) $N=72$
Elevated SBP or worse, No. (%)[h,i]	12/127 (10%)	4/54 (7%)	8/73 (11%)
Systolic HTN, No. (%)[i]	8/127 (6%)	4/54 (7%)	4/73 (6%)
DBP percentile, median (IQR)[g]	59 (37–83) N = 124	68 (44–85) N = 52	57 (37–81) $N=72$
Elevated DBP or worse, No. (%)[i,j]	21/127 (17%)	9/54 (17%)	12/73 (16%)
Diastolic HTN, No. (%)[i]	12/127 (10%)	7/54 (13%)	5/73 (7%)
Taking anti-hypertensive medications (in 2 weeks prior to 2–6-month visit), No. (%)[k]	2/128 (2%)	2/55 (4%)	0/73 (0.0%)
Elevated BP or worse or taking anti-hypertensive medication, No. (%)[l]	28/128 (22%)	12/55 (22%)	16/73 (22%)
HTN or worse or taking anti-hypertensive medication, No. (%)[m]	18/128 (14%)	10/55 (18%)	8/73 (11%)
Stage 2 HTN, No. (%)[n]	3/128 (2%)	2/55 (4%)	1/73 (1%)

Total $N=149$. Denominator N is indicated when it is not 149. There were no statistically significant differences between AKI and non-AKI groups ($P>0.05$)

[a]Excludes 8 participants with a low estimated or measured GFR for age at baseline

[b]Defined using age-based thresholds: if age < 2 years, uACR ≥ 7.5 mg/mmol; if age ≥ 2 years, uACR ≥ 3 mg/mmol

[c]Defined as uACR > 30 mg/mmol

[d]Composition of measured or estimated GFR at 2–6 months: GFR estimated using the study measured SCr ($n=123$); routine care nuclear medicine measured GFR ($n=4$); routine care 24-h creatinine clearance measured GFR ($n=0$); GFR estimated using a routine care SCr value ($n=8$)

[e]Defined using age-based thresholds: aged ≤ 1 month, GFR < 43 mL/min/1.73 m^2; aged 1–4 months, GFR < 47 mL/min/1.73 m^2; aged 4–8 months, GFR < 58 mL/min/1.73 m^2; aged 8 months–1 year, GFR < 65 mL/min/1.73 m^2; aged 1–1.5 years, GFR < 74 mL/min/1.73 m^2; aged 1.5–2 years, GFR < 76 mL/min/1.73 m^2; age > 2 years, GFR < 90 mL/min/1.73 m^2)

[f]Excludes 8 participants with HTN at baseline

[g]Two participants were excluded from these measures because they were aged above 18 years at BP measurement; 2 other participants were excluded from these measures because they were taking anti-hypertensive medications

[h]Defined as per paediatric and adult HTN guidelines [23, 32]: SBP percentile ≥ 90th percentile (if age < 13 years); SBP ≥ 120 mmHg

[i]One participant was excluded from these measures because they were only classified as having HTN due to being on anti-hypertensive medications (i.e. BP was unavailable)

[j]Defined as per paediatric and adult HTN guidelines [23, 32]: DBP percentile ≥ 90th percentile (if age < 13 years); DBP ≥ 80 mmHg

[k]Including angiotensin II receptor blocker, beta blocker, calcium channel blocker, vasodilator and/or alpha blocker

[l]Defined as per paediatric and adult HTN guidelines [23, 32]: SBP/DBP percentile ≥ 90th percentile (if age < 13 years); SBP/DBP ≥ 120/80 mmHg; taking anti-hypertensive medication

[m]Defined as per paediatric and adult HTN guidelines [23, 32]: SBP/DBP percentile ≥ 95th percentile (if age < 13 years); SBP/DBP ≥ 130/80 mmHg; taking anti-hypertensive medication

[n]Defined as per paediatric and adult HTN guidelines [23, 32]: SBP percentile ≥ 95th percentile + 12 mmHg *or* SBP ≥ 140 mmHg or DBP percentile ≥ 95th percentile + 12 mmHg or DBP ≥ 90 mmHg (if age < 13 years); SBP/DBP ≥ 140/90 mmHg (if age ≥ 13 years)

Abbreviations: *SCr*, serum creatinine; *AKI*, Acute kidney injury; *CKD*, chronic kidney disease; *uACR*, urine albumin-to-creatinine ratio; *GFR*, glomerular filtration rate; *HTN*, hypertension; *BP*, blood pressure; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *IQR*, interquartile range

Table 5 Characteristics of the cohort by CKD status and by HTN status at the 2–6-month study visit

Characteristic	CKD ($n=53$)	No CKD ($n=66$)	HTN ($n=18$)	No HTN ($n=110$)
Baseline (prior to 1st cisplatin infusion)				
Age at cisplatin treatment start, median (IQR), years	4 (2–10)	7 (4–12)	2 (2–4)	7 (3–12)**
Age at cisplatin treatment start < 3 years, No. (%)	22 (42%)	13 (20%)**	11 (61%)	26 (24%)**
Male, No. (%)	29 (55%)	32 (49%)	16 (89%)	50 (46%)**
Race				
Aboriginal, No. (%)	2 (4%)	2 (3%)	0 (0.0%)	7 (6%)
American Indian/Alaskan, No. (%)	1 (2%)	0 (0.0%)	0 (0.0%)	1 (1%)
Caucasian/White, No. (%)	43 (81%)	51 (77%)	15 (83%)	80 (73%)
Black/African American, No. (%)	1 (2%)	1 (2%)	1 (6%)	3 (3%)
Asian, No. (%)	2 (4%)	8 (12%)	1 (6%)	10 (9%)
Mixed Race, No. (%)	4 (8%)	4 (6%)	1 (6%)	8 (7%)
Hispanic, No. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1%)
Cancer diagnosis				
Osteosarcoma, No. (%)	8 (15%)	18 (27%)	1 (6%)	29 (26%)
Germ cell tumour, No. (%)	4 (8%)	5 (8%)	2 (11%)	7 (6%)
Neuroblastoma, No. (%)	17 (32%)	20 (30%)	6 (33%)	24 (22%)
CNS Tumour, No. (%)[a]	21 (40%)	18 (27%)	7 (39%)	41 (37%)
Hepatoblastoma, No. (%)	3 (6%)	3 (5%)	2 (11%)	7 (6%)
Other, No. (%)[b]	0 (0.0%)	2 (3%)	0 (0.0%)	2 (2%)
Baseline measured or estimated GFR, mean (SD), mL/min/1.73 m^{2}[c]	154 (45)	141 (35)	145 (48)	137 (39)
Low baseline measured or estimated GFR for age, No. (%)[d]	0 (0.0%)	0 (0.0%)	2 (11%)	6 (6%)
Kidney medical history, No. (%)[e]	6 (11%)	5 (8%)	0 (0.0%)	5 (5%)
Nephrotoxic drug (in 2 weeks prior to 1st cisplatin), No. (%)[f]	13 (25%)	8 (12%)	2 (11%)	20 (18%)
Loop diuretics (in 2 weeks prior to 1st cisplatin), No. (%)[g]	3 (6%)	0 (0.0%)	2 (11%)	0 (0.0%)*
NSAIDS or ASA (in 2 weeks prior to 1st cisplatin), No. (%)[h]	3 (6%)	9 (14%)	4 (22%)	11 (10%)
During cisplatin/cancer treatment (between first and last cisplatin infusion)				
Cancer involves one or both kidneys, No. (%)	7 (13%)	2 (3%)	1 (6%)	7 (6%)
Flank (left or right), whole abdomen, or total body radiation given or planned, No. (%)	6 (11%)	11 (17%)	3 (17%)	13 (12%)
Total cumulative cisplatin dose, median (IQR), mg/m^{2}	343 (253–410)	396 (293–447)	355 (240–410)	386 (282–466)
Radiation in chemotherapy protocol, No. (%)[i]	25 (47%)	38 (58%)	7 (39%)	56 (51%)
Stem cell transplant in chemotherapy protocol, No. (%)	30 (57%)	24 (36%)*	13 (72%)	37 (34%)**
Infection, No. (%)[j]	23 (43%)	20 (30%)	8 (44%)	37 (34%)
Sepsis, No. (%)	5 (9%)	0 (0.0%)*	0 (0.0%)	5 (5%)
Kidney infection or UTI, No. (%)[k]	4 (8%)	2 (3%)	4 (22%)	4 (4%)**
PICU Admission, No. (%)	4 (8%)	5 (8%)	5 (28%)	5 (5%)**
Between last cisplatin infusion and 2–6-month visit				
Veno-occlusive disease, No. (%)	2 (4%)	2 (3%)	1 (6%)	3 (3%)
Nephrectomy, No. (%)	1 (2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Radiation to abdomen, No. (%)	2 (4%)	2 (3%)	1 (6%)	5 (5%)
Aminoglycosides, No. (%)[l]	7 (13%)	9 (14%)	1 (6%)	15 (14%)
Nephrotoxic drug (in 1 month prior to 2–6-month visit), No. (%)[m]	27 (51%)	17 (26%)**	9 (50%)	42 (38%)
Time between cisplatin treatment end and 2–6-month visit, median (IQR), days	89 (71–104)	85 (75–108)	80 (70–104)	91 (80–111)
BMI percentile at 2–6-month visit, median (IQR)	22 (3–57)	40 (18–61)	39 (20–52) $N=17$	35 (8–67)

Table 5 (continued)

[a]CNS Tumours: astrocytoma, choroid plexus tumour, ependymoma, medulloblastoma, primitive neuroectodermal tumour, atypical teratoid/rhabdoid tumour

[b]Other cancer: lymphoma and nasopharyngeal carcinoma

[c]Baseline measured or estimated GFR was assessed using measured GFR if available or 24-h creatinine clearance if unavailable; if both were unavailable. GFR was estimated (using the lowest 3-month pre-cisplatin SCr level). Composition of baseline measured or estimated GFR: routine care nuclear medicine measured GFR ($n=98$); routine care 24-h creatinine clearance measured GFR ($n=9$); GFR estimated using the study measured SCr or a routine care SCr value ($n=52$)

[d]Defined using age-based thresholds: aged ≤ 1 month, GFR < 43 mL/min/1.73 m^2; aged 1–4 months, GFR < 47 mL/min/1.73 m^2; aged 4–8 months, GFR < 58 mL/min/1.73 m^2; aged 8 months–1 year, GFR < 65 mL/min/1.73 m^2; aged 1–1.5 years, GFR < 74 mL/min/1.73 m^2; aged 1.5–2 years, GFR < 76 mL/min/1.73 m^2; age > 2 years, GFR < 90 mL/min/1.73 m^2)

[e]Kidney medical history (based on medical chart review): hypertension, treatment with antihypertensives, family history of kidney disease, chronic kidney disease, dialysis, congenital kidney anomaly, kidney stones, vesicoureteral reflux, urinary tract infection, serum electrolyte abnormality requiring treatment or AKI

[f]Nephrotoxic drugs include acyclovir, amphotericin, aminoglycosides (gentamycin, tobramycin, amikacin), vancomycin, angiotensin-converting enzyme inhibitor, ganciclovir/valganciclovir, ifosfamide or methotrexate

[g]Furosemide, ethacrinic acid, bumetanide

[h]Ibuprofen, naproxen, cox-inhibitors, diclofenac, ketorolac, or any form of aspirin

[i]Radiation information was extrapolated from each participant's chemotherapy protocol

[j]Only infections with a positive culture and documentation were tabulated

[k]Kidney infection or UTI includes any infection with a specimen originating from the kidneys or UTI

[l]Gentamycin; tobramycin; amikacin

[m]Nephrotoxic drugs include: acyclovir, amphotericin, aminoglycosides (other than gentamycin, tobramycin, and amikacin), vancomycin, angiotensin-converting enzyme inhibitor, ganciclovir/valganciclovir, ifosfamide or methotrexate

[*]Stands for significant difference between Outcome and No Outcome groups: *$P<0.05$; **$P<0.01$; ***$P<0.001$

Abbreviations: *CKD*, chronic kidney disease; *HTN*, hypertension; *IQR*, interquartile range; *CNS*, central nervous system; *GFR*, glomerular filtration rate; *NSAIDS*, nonsteroidal anti-inflammatory drugs; *ASA*, acetylsalicylic acid; *UTI*, urinary tract infection; *PICU*, paediatric intensive care unit; BMI, body mass index

compared to our 2–6-month rates of albuminuria (36%), low GFR (8%) and CKD (45%, ≥ eight times that of the general paediatric population) [45]. The main CKD contributor, albuminuria, was associated with higher GFR, perhaps indicative of pathologic hyperfiltration. Few studies have described post-cisplatin HTN rates (range: 0–15%) [4, 5, 7, 43, 44]; our 2–6-month HTN rate of 14% (≥ six times that of the general paediatric population) is comparable [46]. The early and common occurrence of CKD and HTN are important since they are treatable cardiovascular risk factors [15, 16].

Age less than 3 years at cisplatin start was associated with 2–6-month CKD and HTN and males had increased odds for HTN, similar to other studies [43, 47]. High baseline GFR was associated with SCr-AKI, and 2–6-month outcomes, possibly due to hyperfiltration, decreased muscle mass, and/or SCr dilution from hydration [8]. Recent acyclovir use, SCT, and non-osteosarcoma were identified as 2–6-month outcome covariates. Future studies should explore independent associations of other factors (medication doses, duration; treatment combinations; etc.) with kidney outcomes to better risk-stratify patients for follow-up.

Some paediatric studies in non-cancer settings have found a link between AKI and CKD or HTN, but others have not [12–14]. A possible explanation for the lack of association between SCr-AKI and 2–6-month outcomes in this cohort may be the short follow-up duration. Kidney abnormalities may emerge later. There could be subtle kidney damage at 2–6 months, undetectable by traditional kidney markers. New biomarkers of fibrosis or tubular damage should be studied [48]. There were different AKI-outcomes associations depending on AKI definitions used, suggesting it is important to consider the characteristics of injury, including tubulopathy-induced electrolyte abnormalities. Severe eAKI was a risk factor for 2–6-month abnormalities, suggesting this may better reflect tubular injury, which may be more important in HTN progression, possibly due to unfavourable hemodynamics, increased renin release from damaged tubulointerstitium or angiotensin II hypersensitivity [11, 49].

Study strengths included the prospective pan-Canadian design, detailed data, tailored cisplatin-AKI definition, and standardized CKD/HTN definitions. The study also had limitations. Generalizability to non-Canadian children may be limited. Despite the large sample size relative to other paediatric cisplatin studies, we were limited in adjusted analyses and evaluating specific treatment combinations. In the multivariable analyses, we included only risk factors associated with both AKI and the outcome (CKD; HTN;

Table 6 Multivariable associations between AKI during cisplatin therapy and 2–6-month outcomes

SCr-AKI during cisplatin therapy (as main exposure of interest)			
	CKD ($n=119$; 53 with CKD)[a]	HTN ($n=128$; 18 with HTN)[b]	CKD *or* HTN ($n=111$; 57 with CKD *or* HTN)[c]
Variable	Adj OR (95% CI)	Adj OR (95% CI)	Adj OR (95% CI)
SCr-AKI	0.67 [0.29–1.53]	1.58 [0.51–4.89]	0.78 [0.33–1.84]
Age < 3 years at cisplatin start[d]	***2.78 [1.16–6.66]***	***6.15 [1.95–19.39]***	***3.31 [1.18–9.26]***
Female Sex	0.63 [0.28–1.40]	***0.08 [0.02–0.40]***	0.56 [0.24–1.27]
Baseline estimated or measured GFR[e,f]	***1.01 [1.00–1.02]***		1.01 [0.99–1.02]
Acyclovir (1 month before 2–6-month visit)[e]	2.55 [0.72–9.06]		
Stem cell transplant in cancer protocol[f,g]			1.63 [0.62–4.28]
Osteosarcoma[f]			0.67 [0.22–2.02]
Severe eAKI during cisplatin therapy (as main exposure of interest)			
	CKD ($n=119$; 53 with CKD)[i]	HTN ($n=128$; 18 with HTN)[b]	CKD *or* HTN ($n=111$; 57 with CKD *or* HTN)[c]
Variable	Adj OR (95% CI)	Adj OR (95% CI)	Adj OR (95% CI)
Severe eAKI	1.92 [0.84–4.40]	2.31 [0.74–7.24]	***2.65 [1.04–6.74]***
Age < 3 years at cisplatin start[d]	2.25 [0.90–5.64]	***6.25 [1.96–19.88]***	***2.85 [1.01–8.03]***
Female Sex	0.68 [0.30–1.56]	***0.09 [0.02–0.43]***	0.55 [0.24–1.28]
Baseline estimated or measured GFR[e,f]	1.00 [0.99–1.02]		1.01 [0.99–1.02]
Acyclovir (1 month before 2–6-month visit)[e]	1.98 [0.54–7.23]		
Stem cell transplant in cancer protocol[f,g]	1.54 [0.62–3.79]		1.69 [0.63–4.55]
Osteosarcoma[f]			0.49 [0.15–1.61]
Composite-AKI during cisplatin therapy (as main exposure of interest)[h]			
	CKD ($n=119$; 53 with CKD)[i]	HTN ($n=128$; 18 with HTN)[b]	CKD *or* HTN ($n=111$; 57 with CKD *or* HTN)[c]
Variable	Adj OR (95% CI)	Adj OR (95% CI)	Adj OR (95% CI)
Composite-AKI	1.35 [0.46–3.90]	***3.64 [1.05–12.62]***	2.25 [0.72–7.05]
Age < 3 years at cisplatin start[d]	2.25 [0.88–5.71]	***5.27 [1.62–17.20]***	***2.82 [1.01–7.94]***
Female Sex	0.68 [0.30–1.54]	***0.08 [0.02–0.41]***	0.54 [0.23–1.23]
Baseline estimated or measured GFR[e,f]	1.00 [0.99–1.01]		1.01 [0.99–1.02]
Acyclovir (1 month before 2–6-month visit)[e]	2.04 [0.56–7.50]		
Stem cell transplant in cancer protocol[f,g]	1.38 [0.57–3.34]		1.80 [0.67–4.85]
Osteosarcoma[f]			0.72 [0.24–2.22]

Significant odds ratios are italicized and bolded

[a]Adjusted CKD model for SCr-AKI: age < 3 years + sex + AKI + baseline GFR + acyclovir pre-visit

[b]Sex- and age-adjusted HTN model: age < 3 years + sex + AKI. Due to low HTN rate, HTN models only included age, sex and AKI

[c]Adjusted CKD *or* HTN model: age < 3 years + sex + AKI + baseline GFR + stem cell transplant in protocol + osteosarcoma

[d]Age was categorized as age < 3 years since there was an increased AKI risk as well as increased CKD and HTN risk in this group and to increase clinical usefulness. Age < 3 years at cisplatin start was forced into all models (a priori)

[e]Baseline GFR and acyclovir (in 1 month prior to 2–6-month visit) were kept in the CKD model because they were important confounders (caused a ≥ 20% change in the point estimate of other covariates)

[f]Baseline GFR, stem cell transplant in cancer protocol and osteosarcoma were kept in the CKD *or* HTN model because they were important confounders (caused a ≥ 20% change in the point estimate of other covariates)

[g]Both stem cell transplant and carboplatin in cancer protocol were associated with AKI and CKD and CKD *or* HTN. However, there was significant overlap between these two variables Therefore, we decided to only include stem cell transplant because associations were stronger

[h]SCr-AKI *and* severe eAKI

[i]Adjusted CKD model for severe eAKI and composite-AKI: age < 3 years + sex + AKI + baseline GFR + stem cell transplant in protocol + acyclovir pre-visit

Abbreviations: *CKD*, chronic kidney disease; *HTN*, hypertension; *SCr*, serum creatinine; *AKI*, acute kidney injury; *Adj*, Adjusted; *OR*, odds ratio; *CI*, confidence interval; *GFR*, glomerular filtration rate; *eAKI*, electrolyte-AKI

CKD *or* HTN); other important risk factors only associated with CKD or HTN may have been missed.

A large proportion of participants treated with SCT also received carboplatin; therefore, it remains unclear whether SCT, carboplatin, or both are associated with nephrotoxicity. We surmise that patients treated with SCT also get exposed to several other nephrotoxins, which we were unable to fully capture (e.g. antibiotics used to treat febrile neutropenia episodes). It is challenging to tease out risk factors since there may be many potential confounding relationships (e.g. cancer type with age with cisplatin dose; cancer type with other chemotherapies or other nephrotoxins); for example, total cumulative cisplatin dose did not emerge as a risk factor. This may simply be due to a lack of sample size; with a larger sample, we may have seen a relationship emerge. Because of the multiple nephrotoxic therapies received (e.g. SCT), we cannot be certain that AKI and subsequent complications are due to cisplatin; rather, outcomes must be viewed as having occurred in children who received cisplatin.

Although the internationally accepted KDIGO AKI definition was used to define AKI, this definition also has limitations, for instance, it can be easier (only small changes needed) for children with a low baseline SCr to attain AKI criteria [17]. We evaluated the worst AKI during cisplatin therapy; however, we did not evaluate the impact of repeated AKI episodes. In the paediatric literature, most studies have used a single peak SCr during a certain time period (maximal AKI severity) to ascertain AKI and evaluate associations with kidney outcomes [13, 14, 50]. For eAKI, we utilized nadir electrolyte values to determine severity, which may not only reflect the severity of kidney injury but also reflect how aggressive healthcare teams were in correcting electrolyte disturbances. This eAKI definition is relatively simple and reproducible for future studies and also likely reflects the more severe forms of eAKI.

The study cohort was heterogeneous in cancer types and cisplatin dosing; this may in part explain why no associations were found with SCr-AKI and outcomes, however, this also highlights the challenges associated with studying this unique but important population. Ascertainment of baseline eGFR was not perfect; multiple methods were used, including measured GFR, 24-h creatinine clearance, and eGFR. Moreover, for 2–6-month GFR, we had to use a nuclear medicine measured GFR for 4 patients. Ideally, we would have used SCr or nuclear medicine GFR in everyone. However, this was a small number and this is a challenge when weighing the risks and benefits of losing participants versus trying to address missing data using relatively valid methods. Also, for one participant, we had to use the average of the child and adult eGFR equations, which did not impact the results. However, this highlights how this is a problem in paediatric to adult transition research. We likely overestimated albuminuria from the random urine collections, which are susceptible to orthostatic proteinuria and/or urine dilution effects. For feasibility, BP was not measured at three separate visits, which may overestimate HTN. Also, most participants (59%) had 3 BP measurements, however, 39% of participants only had one BP measurement; inadvertently, this could have led to overestimation of HTN. Future studies should consider using gold standard outcome measurements (e.g. 24-h ambulatory BP monitoring; first-morning urine).

SCr-eGFR equations may overestimate true GFR, implying that decreased GFR may be more common than what we reported [42]. Other markers of kidney function (e.g. cystatin C) should be evaluated. Outcomes were evaluated at a single visit, which may not represent chronicity. Moreover, the post-cisplatin therapy end follow-up duration was only 2–6 months; this mirrors the initial follow-up suggested by the KDIGO guidelines [17], but longer follow-up will be needed to determine if and in whom abnormalities worsen or improve. Although the majority of participants had their 2–6-month follow-up performed around 3 months or later, some were evaluated slightly before the 3-month mark; thus it is possible that these few patients had resolving AKI. Also, we could not rule out a time-dependent effect on outcomes.

Few studies have characterized in detail CKD and HTN in children 2–6 months post-cisplatin therapy. This study indicates that kidney health of children treated with cisplatin must be closely monitored and presence of severe electrolyte abnormalities during cisplatin therapy should be viewed as a marker of kidney injury. Kidney follow-up guidelines need to be clearer in terms of follow-up duration, risk-assessment and outcomes to ascertain and act on. Future research should evaluate impact of post-cisplatin CKD and HTN on cardiovascular health.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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