Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: Relevance of age and dose as risk factors ☆

Roderick Skinner[a,c,1,*], Annie Parry[a], Lisa Price[a], Michael Cole[b], Alan W. Craft[c], Andrew D.J. Pearson[c,d]

[a]Department of Paediatric and Adolescent Oncology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom
[b]Northern Institute for Cancer Research, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH, United Kingdom
[c]Sir James Spence Institute of Child Health, School of Clinical Medical Sciences, University of Newcastle upon Tyne, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom
[d]Institute of Cancer Research, Royal Marsden Hospital, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom

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ABSTRACT

Purpose: The long-term outcome of platinum-induced nephrotoxicity is unknown. This prospective single-centre longitudinal cohort study evaluated long-term changes following treatment in childhood.

Methods: 63 children treated with platinum (27 cisplatin, 24 carboplatin and 12 both) were studied at the end of treatment (End), 1 year and 10 years later. No child received ifosfamide. Glomerular filtration rate (GFR), serum calcium and magnesium (Mg) were measured, and total nephrotoxicity score (N_s) was graded.

Results: There was no significant overall change in renal function over time in any treatment group (cisplatin, carboplatin or combined). Apart from marginally reduced median GFR (84 ml/min/1.73 m^2) and Mg (0.68 mmol/l) at End of cisplatin, median GFR, Ca and Mg were normal at all times in each group. At 10 years, GFR was <60 ml/min/1.73 m^2 in 11%, N_s grade was severe in 15% and oral Mg supplements were required in 7% cisplatin patients. After cisplatin, older age at treatment was correlated with lower GFR at 10 years ($p = 0.005$), and higher N_s at End and 10 years (both $p = 0.02$). After carboplatin treatment, older age was associated with lower GFR at all times, and with higher N_s at End and 1 year (all $p < 0.03$). Higher cisplatin dose rate (>40 mg/m^2/day) was associated with higher N_s at 1 year ($p = 0.02$) and higher carboplatin dose with lower Mg at 1 year and with higher N_s at 1 and 10 years (all $p < 0.008$).

Conclusions: Platinum nephrotoxicity did not change significantly over 10 years. Its severity was correlated to older age at treatment, and at some time points to higher cisplatin dose rate and higher cumulative carboplatin dose.

* *Corresponding author:* Address: Sir James Spence Institute of Child Health, School of Clinical Medical Sciences, University of Newcastle upon Tyne, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, United Kingdom. Tel.: +44 191 282 5543; fax: +44 191 202 3060.
   E-mail address: Roderick.Skinner@ncl.ac.uk (R. Skinner).
 [1] Dr. R. Skinner was an MRC Training Fellow at the commencement of this study.

1. Introduction

The long-term survival in about 75% of children presenting with malignancy in the 1990s[1] has been achieved only at the cost of late and chronic toxicities in some survivors. Cure has been the paramount aim in most poor and many average prognosis malignancies, overruling concerns about chronic toxicity. However, the development of late adverse effects of treatment is an increasingly important issue now that 1 in 715 young adults in developed countries is a long-term survivor of malignancy.[2] Therefore, in view of the success of contemporary treatment, the philosophy of management in good prognosis malignancies is now to cure whilst minimising late toxicity.[3]

This trend is illustrated by developments in the use of platinum drugs. Cisplatin is highly effective and has an important role in the treatment of children with neuroblastoma, osteosarcoma and some brain tumours, but chronic ototoxicity, neurotoxicity and especially nephrotoxicity[4] have encouraged the development of several less toxic platinum analogues, principally carboplatin. Although it has a subtly different therapeutic profile, carboplatin has been introduced successfully into some protocols for germ cell tumours (GCTs), neuroblastoma and certain brain tumours.[5,6] Carboplatin nephrotoxicity appears less frequent and severe than cisplatin nephrotoxicity.[7]

It is extremely important that long-term nephrotoxicity is documented to inform the future development of effective but safer treatments. However, there is very little published information about renal function more than 3 years after the completion of platinum chemotherapy, and there are no very long-term longitudinal data.

The main aim of this prospective longitudinal single-centre cohort study was to document changes in renal toxicity over 10 years after the completion of cisplatin or carboplatin treatment (or both) in children. An additional aim was to determine risk factors for long-term nephrotoxicity.

2. Patients and methods

2.1. Patients and treatment

68 children and adolescents (<18 years age at treatment) who commenced platinum treatment in Newcastle between 1981 and 1996 survived at least 10 years after the completion of treatment. Three patients were lost to follow-up (two treated with cisplatin and one with carboplatin), one patient treated with cisplatin declined investigation and one patient treated with carboplatin moved out of the region; however, follow-up by the Northern Region Young Persons' Malignant Disease Registry confirmed that all five patients were alive 10 years post-treatment. The other 63 survivors were studied; 27 received cisplatin only, 24 carboplatin only and 12 both. No patient who commenced platinum treatment during 1981–1996 died from nephrotoxicity. In Table 1 further patient and treatment characteristics are given. One child had a reduced glomerular filtration rate (GFR) (42 ml/min/1.73 m^2) prior to cisplatin treatment due to pre-renal glomerular impairment

at presentation of malignancy, one underwent unilateral nephrectomy before receiving carboplatin and another had renal invasion by neuroblastoma before combined platinum treatment. No other patient had significant renal dysfunction (raised serum creatinine or GFR <60 ml/min/1.73 m^2), radiological evidence of urinary tract obstruction or renal involvement prior to platinum treatment.

Several cisplatin administration schedules were employed, all incorporating intravenous hyperhydration. The cisplatin dose was 60–200 mg/m^2/course, given as a continuous infusion (40–100 mg/m^2/day) over 1–5 days, except in the four survivors with GCTs (given over 20 min), and one survivor with osteosarcoma (120 mg/m^2 over 1 h). Neuroblastoma and brain tumour protocols employed a cisplatin dose rate of 40 mg/m^2/day (15 children), whilst those for osteosarcoma, GCTs and hepatic tumours utilised higher rates (>40–120 mg/m^2/day, 24 children). All high-dose (200 mg/m^2) cisplatin courses were given over 5 days at 40 mg/m^2/day.

The carboplatin dose was 300–1200 mg/m^2/course. Carboplatin was given on one day only except in 6 children with brain tumours who received two doses (500–600 mg/m^2/dose) per course, on consecutive days. Each dose was given over 1 h, without hyperhydration. Six children with neuroblastoma received high-dose carboplatin (1000 mg/m^2) prior to autologous bone marrow transplantation.

High-dose melphalan (180–200 mg/m^2) was given prior to autologous bone marrow transplantation in nine children with neuroblastoma, including the six who were also receiving high-dose carboplatin. Eight patients also received intravenous intermediate (1 g/m^2)- or high (8 g/m^2)-dose methotrexate. Other chemotherapies received included actinomycin D, bleomycin, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, teniposide and vincristine. No child received ifosfamide. Treatment courses were repeated every three weeks except in 13 children on rapid scheduling protocols with chemotherapy every 10–14 days. Supportive care protocols included aminoglycosides (with therapeutic level monitoring) and amphotericin.

A small area of kidney was included in the radiotherapy fields in three children, or received a small amount of scatter in a further five. All these children received carboplatin only. No child developed haemolytic uraemic syndrome (HUS).

2.2. Assessment of renal function

Renal function was investigated approximately one month (End), 1 year and 10 years after the completion of platinum treatment. Glomerular (GFR) and proximal tubular function (serum calcium [Ca] and magnesium [Mg] concentrations) were assessed, and nephrotoxicity grading (Table 2) was calculated, using a standardised protocol.[8,9] Age-related reference ranges were used. Since it is difficult to perform creatinine clearance measurements accurately in children, GFR was calculated from ^{51}Cr-labelled ethylenediaminetetra-acetic acid (^{51}Cr-EDTA) plasma clearance,[10] which gives a more accurate value than calculated GFR.[11] Significant adverse clinical consequences of chronic nephrotoxicity (GFR <60 ml/min/1.73 m^2, tetany, convulsions, cardiac arrhythmias

Table 1 – Patient and treatment characteristics.

	Cisplatin alone		Carboplatin alone		Cisplatin and carboplatin	
Number of patients (males)	27 (11 Males)		24 (14 Males)		12 (9 Males)	
Age at treatment commencement (years)	7.7 (0.6–17.8)		4.4 (0.4–15.8)		1.9 (0.1–6.2)	
Total dose (mg/m^2)	500 (300–960)		2400 (560–8800)		Cisplatin 473 (240–739)	
					Carboplatin 1500 (750–4200)	
Diagnoses	Osteosarcoma	12	Germ cell tumour	9	Neuroblastoma	9
	Germ cell tumour	4	Medulloblastoma	5	Brain tumour	3
	Brain tumour	3	Other brain tumour	5		
	Liver tumour	3	Neuroblastoma	3		
	Epithelial carcinoma	1	CCSK	1		
	Ewing's sarcoma	1	Retinoblastoma	1		
	Nasophayrngeal carcinoma	1				
	Neuroblastoma	1				
	Salivary gland carcinoma	1				

Age and dose expressed as median (range).
CCSK, clear cell sarcoma of kidney.

Table 2 – Grading of cisplatin nephrotoxicity in children.[a]

Nephrotoxicity grade	GFR	Mg	
		<2 Years	$\geqslant$2 Years
0	$\geqslant$90	$\geqslant$0.75	$\geqslant$0.70
1	60–89	0.60–0.74	0.55–0.69
2	40–59	0.50–0.59	0.45–0.54
3	20–39	No symptoms, but 0.40–0.49	0.35–0.44
4	<20	Tetany or convulsion or <0.40	<0.35

A score of 4 in an individual aspect of grading (e.g. GFR) constitutes severe toxicity in that aspect.
Total nephrotoxicity score (N_s) = sum of GFR + Mg.
0, No nephrotoxicity; 1, Mild nephrotoxicity; 2–3, Moderate nephrotoxicity; $\geqslant$4, Severe nephrotoxicity.
GFR, glomerular filtration rate (ml min^{-1} 1.73 m^{-2}); Mg, serum magnesium concentration (mmol l^{-1}).

or hypertension) were recorded using standard definitions,[8,12] and ongoing treatment with electrolyte supplements was documented, at each time point.

The study protocol was approved by the Joint Ethics Committee of Newcastle Health Authority and the University of Newcastle. Informed consent was obtained from the parents and, where appropriate, the patient.

2.3. Statistics

For analysis of changes with time, the results of renal function investigations were both expressed as raw values and categorised as either normal or abnormal (i.e. below the age-related reference range). 'No' or 'mild' nephrotoxicity (N_s 0–1) was categorised as a normal N_s, and 'moderate' or 'severe' nephrotoxicity ($N_s \geqslant 2$) as abnormal. Changes between End and 1 year, End and 10 years and 1 and 10 years were analysed by the Wilcoxon sign rank test (paired raw values) and McNemar's test for paired proportions (percentages of normal and abnormal results, and the presence or absence of a severe nephrotoxicity score ($N_s \geqslant 4$), clinically significant complications or ongoing supplementary treatment). Statements describing percentages (and changes in percentages) of normal or abnormal results apply to paired data only.

Analysis of platinum dose as a risk factor for the development of nephrotoxicity at each time point was performed using linear regression (cumulative dose) and the unpaired t-test (cisplatin dose intensity, comparing 40 with >40 mg/m^2/day). The outcome measures were GFR, Ca, Mg and N_s. Linear regression was used to evaluate age at treatment as a risk factor for GFR, Ca and N_s. However, since the lower limit of the reference range of Mg is age-related, and the calculation of N_s incorporates Mg, the mean ages of those survivors with normal results and those with abnormal results for these variables were compared using unpaired t-tests. Risk factor analysis was not performed for the combined cisplatin and carboplatin group due to small numbers.

3. Results

The 1- and 10-year post-treatment studies were performed at a median (range) of 1.1 (0.7–2.3) and 10.3 (9.0–12.3) years, respectively, after the completion of chemotherapy. The timing did not differ between the cisplatin, carboplatin and combined groups. Table 3 summarises the results of renal function investigations and the percentages of normal results at End, 1 year and 10 years.

Table 3 – Renal function investigations at end of, one year and ten years after platinum treatment.

	End of treatment	One year after treatment	Ten years after treatment	Percentage of normal results		
				End of treatment	One year after treatment	Ten years after treatment
Cisplatin alone	(n = 20–22)	(n = 21–22)	(n = 26–27)			
GFR (ml/min/1.73 m^2)	84 (18–197)	98 (25–130)	96 (29–142)	40 (19–64)	62 (38–82)	60 (39–79)
Serum Ca (mmol/l)	2.45 (2.02–2.60)	2.47 (2.19–2.66)	2.38 (2.18–2.53)	90 (70–99)	100 (87–100)	100 (89–100)
Serum Mg (mmol/l)	0.68 (0.32–0.93)	0.70 (0.44–0.95)	0.73 (0.37–0.83)	48 (26–70)	50 (28–72)	68 (45–86)
Nephrotoxicity score	1 (0–5)	1 (0–4)	1 (0–4)	57 (34–78)	64 (41–83)	63 (42–81)
Carboplatin alone	(n = 20–23)	(n = 21–23)	(n = 24)			
GFR (ml/min/1.73 m^2)	120 (68–207)	109 (63–161)	110 (66–171)	80 (56–94)	81 (58–95)	79 (58–93)
Serum Ca (mmol/l)	2.42 (2.25–2.59)	2.48 (2.34–2.58)	2.39 (2.28–2.59)	100 (88–100)	100 (87–100)	100 (88–100)
Serum Mg (mmol/l)	0.77 (0.42–0.89)	0.78 (0.51–0.90)	0.77 (0.54–0.94)	74 (52–90)	73 (50–89)	83 (61–95)
Nephrotoxicity score	0 (0–4)	0 (0–2)	0 (0–2)	91 (71–99)	95 (77–100)	96 (79–100)
Cisplatin and carboplatin	(n = 10–11)	(n = 12)	(n = 11–12)			
GFR (ml/min/1.73 m^2)	91 (45–160)	93 (55–131)	92 (66–135)	80 (44–97)	75 (43–95)	55 (23–83)
Serum Ca (mmol/l)	2.39 (2.18–2.61)	2.46 (2.24–2.55)	2.36 (2.23–2.53)	100 (76–100)	100 (80–100)	100 (76–100)
Serum Mg (mmol/l)	0.74 (0.62–0.98)	0.80 (0.68–0.89)	0.81 (0.68–0.92)	55 (23–83)	92 (62–100)	91 (59–100)
Nephrotoxicity score	1 (0–3)	0 (0–2)	0 (0–2)	82 (48–98)	92 (62–100)	92 (62–100)

Values of the renal function investigations are expressed as median (range).
Percentage of patients with normal renal function investigations are expressed as percentage (95% confidence limits).

Substantial inter-individual variability was observed with some survivors showing improvement and others deterioration in glomerular, tubular or overall renal function during follow-up (Fig. 1). However, there was no significant change with time in any of the measures of nephrotoxicity in any treatment group, nor in the proportion with clinically significant complications or ongoing treatment with supplements.

3.1. Cisplatin alone

Median GFR and Mg were both slightly reduced at End (84 ml/min/1.73 m^2 and 0.68 mmol/l, respectively), but were normal at 1 and 10 years. Median Ca was normal at all time points. Moderate nephrotoxicity was present in 6 (29%), 7 (32%) and 6 (22%), and severe nephrotoxicity in 3 (14%), 1 (5%) and 4 (15%) evaluable survivors at End, 1 year and 10 years.

GFR was <90 and <60 ml/min/1.73 m^2, respectively, in 12 (60%) and 4 (20%) evaluable survivors at End, 9 (43%) and 1 (4%) at 1 year and 13 (48%) and 3 (11%) at 10 years. Tetany was documented in 1 (4%) patient at each time point. No patient experienced a convulsion related to cisplatin-induced hypomagnesaemia or hypocalcaemia, but 1 (4%) patient had suffered a serious cardiac arrhythmia due to hypomagnesaemia shortly before End. Six (22%), 2 (7%) and 2 (7%) survivors were receiving magnesium supplements at End, 1 year and 10 years post-treatment, respectively. One (4%) patient had stage 1 hypertension at 10 years, but none was on antihypertensive medication.

Older age at treatment was correlated with lower GFR at 10 years (p = 0.005) (Fig. 2a) and with greater overall nephrotoxicity measured by higher N_s at End and 10 years (both p = 0.02), whilst the mean age of children with abnormal Mg at End (10.9 years) and N_s at 10 years (11.0 years) was higher than that of those with normal values (4.8 years for Mg at End, p = 0.006; 6.0 years for N_s at 10 years, p = 0.01). An
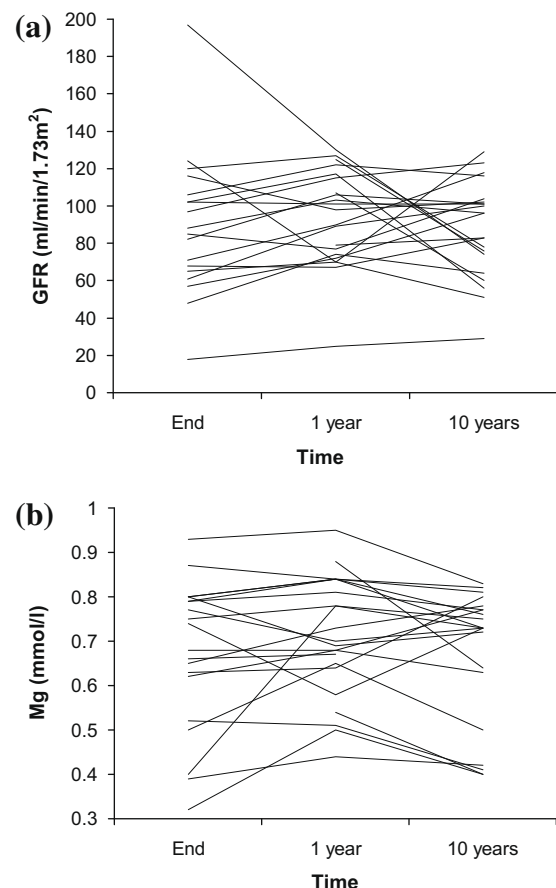

Fig. 1 – Renal function, measured by (a) GFR and (b) serum Mg at the end of, and 1 and 10 years after, cisplatin treatment. Joined lines show data from individual patients, and demonstrate considerable inter-patient variability in the severity of renal toxicity and in changes with time.
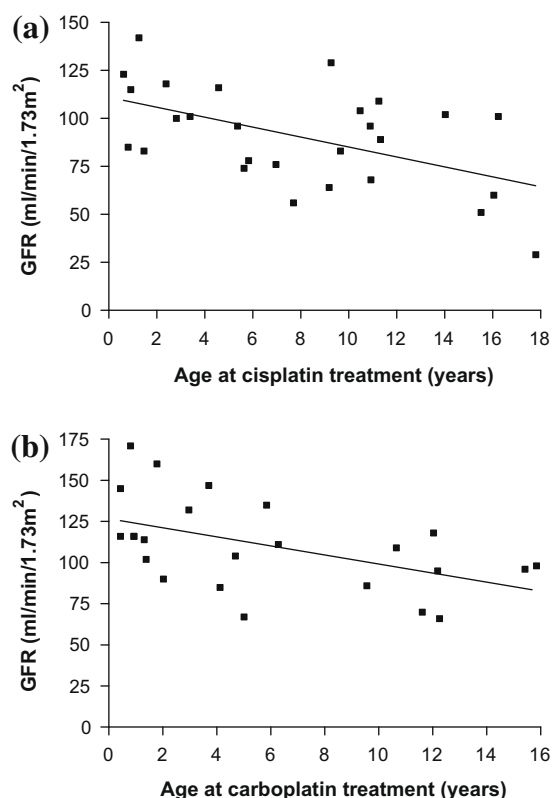
Fig. 2 – Scatter plots and regression lines showing relation between age at treatment with (a) cisplatin and (b) carboplatin, and GFR at 10 years after the completion of treatment. Older age at treatment predicts lower GFR ($p = 0.005$ for cisplatin, $p = 0.011$ for carboplatin).

increase of 5 years in age at treatment was associated with a fall in GFR (measured at 10 years post-treatment) of 13.0 (95% confidence intervals 4.5–21.5) ml/min/1.73 m^2. No relationship was seen between dose and the severity of toxicity, but higher dose rate was associated with higher N_s at 1 year ($p = 0.02$).

3.2. Carboplatin alone

Median GFR, Ca and Mg were all normal at all time points. Of evaluable survivors, moderate nephrotoxicity was present in 1 (5%) at each time point, whilst severe nephrotoxicity was present in 1 (5%) at End only.

GFR was <90 ml/min/1.73 m^2 in 4 (19%) evaluable survivors at End and at 1 year, and 5 (21%) at 10 years. No patient had a GFR <60 ml/min/1.73 m^2 at any time point, and none experienced tetany, convulsions or cardiac arrhythmia. Two (8%) and one (4%) survivors were receiving magnesium supplements at End and 1 year, respectively, whilst one (4%) was taking calcium supplements at 10 years. No patient was hypertensive or on antihypertensive medication.

Older age at treatment was correlated with lower GFR at End, 1 year and 10 years ($p = 0.018$, $p = 0.025$ and $p = 0.011$, respectively) (Fig. 2b) and with greater overall nephrotoxicity measured by higher N_s at End and 1 year ($p = 0.001$ and $p = 0.01$, respectively). In addition, the mean age of children with an abnormal Mg at End (11.4 years) was higher than that

of those with a normal value (4.2 years, $p = 0.008$). An increase of 5 years in age was associated with falls in GFR of 17.5 (3–5–31.5) when measured at End and of 13.8 (3.3–24.3) ml/min/1.73 m^2 at 10 years. Higher cumulative carboplatin dose was correlated with lower Mg at 1 year ($p = 0.001$) and with higher N_s at 1 and 10 years ($p = 0.008$ and $p = 0.003$, respectively). It was also correlated to lower Mg at End ($p = 0.037$), but the magnitude of this effect was very small with an increase of 600 mg/m^2 leading to a fall of only 0.015 (0.001–0.029) mmol/l.

3.3. Cisplatin and carboplatin

Median GFR, Ca and Mg were all normal at each time point. Moderate nephrotoxicity was present in 2 (18%), 1 (8%) and 1 (8%) evaluable survivors at End, 1 year and 10 years, whilst no patient had severe nephrotoxicity at any time point.

GFR was <90 and <60 ml/min/1.73 m^2, respectively, in 5 (50%) and 1 (10%) evaluable survivors at End, 4 (33%) and 1 (10%) at 1 year and 5 (45%) and none at 10 years. GFR was <60 ml/min/1.73 m^2 in 1 (10%) evaluable survivor at End and 1 year, but in none at 10 years. No patient experienced tetany, convulsions or cardiac arrhythmia. One (8%) child was receiving potassium supplements at End, but no patient subsequently required supplement treatment. One patient (8%) each had stage 1 and stage 2 hypertension at 10 years, but none was on antihypertensive medication.

4. Discussion

Glomerular or renal tubular toxicity, or both, occur in many children and adolescents treated with cisplatin.[4,8,13,14] The frequency of nephrotoxicity reported within three years of the completion of treatment has varied widely, probably due to differences in chemotherapy schedules and doses, and in timing and methodology of investigation. Nevertheless, a very consistent pattern of toxicity has been observed. A fall in GFR has been reported in 20–80% of children,[4,8,13] and may occasionally lead to chronic renal failure (CRF).[15] Hypomagnesaemia, the commonest feature of chronic proximal tubular toxicity,[16] occurs in 12–100% of children[8,13,14,17] due to impaired tubular magnesium reabsorption, and may cause paraesthesiae, tremor, tetany, convulsions and cardiac arrhythmias.[18] Less common features of cisplatin nephrotoxicity include hypokalaemic metabolic alkalosis,[19] hypocalcaemia (probably secondary to hypomagnesaemia),[20] hypertension (probably renovascular)[21] and rarely HUS.[22] Carboplatin nephrotoxicity is similar in nature but occurs less frequently and is usually much less severe than cisplatin nephrotoxicity. Mild glomerular impairment and hypomagnesaemia have each been reported in 0–25% of children.[7,23–25] Rarely, carboplatin may lead to CRF, usually in the context of high-dose conditioning chemotherapy in heavily pre-treated children undergoing autologous stem cell transplantation.[26]

There is very little information about the very long-term outcome of platinum nephrotoxicity and in particular about changes in severity with time. The Late Effects Surveillance System found that Mg increased slightly during the first year but then remained unchanged 1–3 years post-treatment.[17] Three short-term longitudinal studies have reported

persistent platinum nephrotoxicity in up to 40% survivors at a median of about 2 years after the completion of treatment, whilst case reports have described persistence of toxicity up to 20 years post-treatment.[7,8,13,19] Bergeron did not observe significant reductions in Mg or calculated GFR in 30 infants with neuroblastoma investigated 4.5–9 years after carboplatin treatment,[25] but GFR was assessed indirectly and the cumulative carboplatin dose was much lower than in this study.

Although it is likely that long-term retention of platinum in the kidney and involvement of renal tubular cells in platinum excretion are both important in the development of nephrotoxicity, detailed understanding of the complex pathophysiology and its relationship with platinum pharmacology remains elusive.[27] This has hampered efforts to develop nephroprotective agents, which are therefore not yet in widespread use.[27] Hence, it remains important to document the very long-term outcome of platinum nephrotoxicity and factors that determine its severity, to inform continued but safer use of these drugs, especially cisplatin.

This prospective longitudinal single-institution cohort study was based on the evaluation of the commonest and most important components of platinum-induced glomerular and tubular toxicities, using measures that have been used in many previous studies.[4,7,8,13,14,23,28,29] The grading score was designed to document and quantify clinically relevant nephrotoxicity.[8]

Although considerable inter-individual variability in renal toxicity was seen in many survivors during the course of the study, manifested by marked improvement or deterioration in one or more aspects of nephrotoxicity, there was no significant change in the frequency and severity of *overall* nephrotoxicity during the 10-year follow-up after treatment of children with cisplatin, carboplatin or both. In particular, there was no suggestion of deterioration in renal function with time. However, it is important to note that severe nephrotoxicity (i.e. $N_s \geqslant 4$) appears to be lasting, being persistent in 15% of survivors 10 years after the completion of cisplatin treatment. Although chronic nephrotoxicity is well documented during the first three years after the completion of treatment, this is the first report of very long-term nephrotoxicity in children. Improved understanding of the nature and severity of long-term platinum nephrotoxicity is crucial to direct follow-up of current survivors and to facilitate the development of future platinum-containing protocols by providing clearer information about the risks of severe or even life-threatening late toxicity.

An important new finding of this study, which contrasts with the results of previous studies,[8,13] is the importance of older age at treatment as a risk factor for cisplatin nephrotoxicity, both early (End) and late (10 years) after the completion of treatment. Although an early report suggested that higher cisplatin dose was correlated with greater acute nephrotoxicity in 28 adults,[16] larger medium-term studies[8,13] (in 35 and 40 children, respectively, studied at a median of about 2 years post-treatment) and this study have shown no relationship between cumulative cisplatin dose and chronic nephrotoxicity. However, this study confirms previous reports that high cisplatin dose rate may be more important as a risk factor for greater overall nephrotoxicity at 1 year, as evaluated by higher N_s.[8,28,29] Although these findings should be confirmed

in a larger patient population, it is feasible that they may allow continued use of this important chemotherapeutic agent with less concern about stringent restriction of cumulative dose.

The limited published literature concerning carboplatin nephrotoxicity in children has suggested that higher cumulative dose is associated with greater tubular toxicity (manifested by lower Mg).[7] This study has confirmed a correlation between higher cumulative carboplatin dose and increased tubular toxicity (lower Mg) at 1 year and greater overall nephrotoxicity at 1 and 10 years. A further and novel finding is that older age at treatment is correlated with greater glomerular toxicity (lower GFR) at all time points, tubular toxicity (lower Mg) at End and overall nephrotoxicity (N_s) at End and 1 year.

Although previous studies have not suggested that potentially nephrotoxic supportive drugs used in children with malignancy (e.g. aminoglycosides and amphotericin) are risk factors in terms of the overall frequency of platinum-induced nephrotoxicity,[8] it remains possible that they may be important factors in the development of renal damage in some individual survivors.

This study has provided the longest follow-up of long-term platinum nephrotoxicity in children, but since the number of patients in each group was still relatively small, the findings require confirmation in larger studies. Nevertheless, despite the well-known difficulties of long-term follow-up research, the study included 93% of a single-institution cohort of 10-year survivors. The findings are consistent with but extend considerably the previous experience with shorter follow-up. Although age-related variability in reference ranges may have limited the study's ability to detect changes in renal function, this likelihood was reduced by the categorisation of results as normal or abnormal.

In conclusion, platinum-induced nephrotoxicity persisted during the 10-year follow-up. An important new finding is that older age at treatment appears to be the major risk factor for nephrotoxicity, especially in carboplatin survivors, whilst higher cisplatin dose rate and cumulative carboplatin dose were also important predictors of some aspects of toxicity. The lack of late deterioration in renal function is reassuring and supports continued use of platinum chemotherapy in sensitive malignancies. However, further studies are required to evaluate very long-term renal function in view of the continued presence of severe toxicity at 10 years in 15% of cisplatin survivors, and to evaluate potentially modifiable risk factors that may allow future reduction of the prevalence of severe and potentially life-shortening chronic platinum-induced nephrotoxicity.

Conflict of interest statement

None declared.

Acknowledgements

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