



Comparison of cisplatin and carboplatin nephrotoxicity in paediatric patients with malignant extra-cranial germ cell tumours

Author:

Dr Lané Bothma
MBBCh (Wits), DCH (SA)
Department of paediatrics and child health
Charlotte Maxeke Johannesburg Academic Hospital
Faculty of Health Sciences
University of the Witwatersrand
Email: lanebothma08@gmail.com

Co-Authors:

Professor Jennifer Geel
MBChB (UCT), FC Paed (SA), Cert Med Onc (Paed), MMed (Wits)
Paediatric Oncology, Charlotte Maxeke Johannesburg Academic Hospital
Faculty of Health Sciences
University of the Witwatersrand
Email: Jennifer.Geel@wits.ac.za

Dr Cecil Levy
MBBCH, FC Paed (SA), Cert Paed Nephrology (SA)
Paediatric Nephrology, Nelson Mandela Children's Hospital
Faculty of Health Sciences
University of Witwatersrand
Email: Cecil.Levy@nmch.org.za

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Declaration

I, **Dr Lané Bothma**, student number **2522538**, declare that this Research Report is my own work. It is being submitted for the degree of Masters of Medicine in Paediatrics and Child Health, at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination.

A handwritten signature in black ink, consisting of a stylized 'L' and 'B' intertwined.

Dr Lané Bothma

17/07/2024

Dedication

I would like to dedicate this to all the wonderful people in my life. To my husband, this is as much yours as it is mine. Working on our dreams together has been the most difficult, yet the most rewarding adventure we've had so far. Thank you for spending countless nights with me, supporting and encouraging me through every challenge. Even when it's tough, I cherish every moment of doing life with you.

To all my friends and family who have supported me tirelessly, understood my absences from gatherings and celebrations, and always believed in me more than I believed in myself. Thank you for sticking with me through this journey and reminding me to never give up.

And then lastly to the brave children fighting cancer, this work is dedicated to you. May this effort on my part contribute in some way to making a big difference in your lives.

Acknowledgements

I am deeply grateful to Prof. Jennifer Geel, whose unwavering guidance and encouragement have been invaluable throughout my journey to achieve a Masters in Medicine in Paediatrics. Her support and mentorship were crucial for the successful completion of this degree. She consistently inspired me to strive for excellence and always believed in my ability to achieve what I once thought was beyond my reach.

A special thank you to Dr. Cecil Levy, who graciously stepped in as my second supervisor. His willingness to guide me, combined with his kindness and calm demeanour, provided a sense of reassurance and support that was unmatched.

Special acknowledgment goes to the patients, families, and healthcare providers at Charlotte Maxeke Johannesburg Academic Hospital, for their input and ongoing dedication to patient care.

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Author's Guidelines for Intended Journal

This Master of Medicine in Paediatrics will be submitted for examination in the
'Submissible Format.'

The Manuscript will be submitted to the SA Journal of Oncology.

The link to the guidelines for submission to this journal
can be found online at: https://sajo.org.za/index.php/sajo/pages/view/submission-guidelines#part_1

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), and how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, and clearly present the overall results and any meta-analysis.

Submission status	open
Word limit	3500-4000 words (<u>excluding</u> the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Aim, Setting, Methods, Results, Conclusion and Contribution
Main text	requires structural headings, refer to the full structure 'Ethical considerations' is a sub-section in the manuscript and must include: • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the Vancouver referencing style
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the Formatting requirements page and the AOSIS house style guide
Compulsory supplementary file(s)	the Authorship, disclosure statements, copyright, and license agreement form , Ethical Clearance/Waiver Documentation and any other relevant form applicable to your submission
Ethical clearance/waiver documentation	evidence of ethical clearance for the study, such as the study approval letter or certificate from the Institutional Review Board (IRB), a waiver from the IRB et cetera

Article

Comparison of cisplatin and carboplatin nephrotoxicity in paediatric patients with malignant extra-cranial germ cell tumours: a retrospective review

Authors: Lané Bothma¹, Cecil Stephen Levy^{1,2}, Jennifer Ann Geel^{1,3}

Author affiliations:

1. Department of Paediatrics and Child Health, Faculty of Health Sciences, School of Clinical Medicine, University of the Witwatersrand
2. Division of Paediatric Nephrology, Nelson Mandela Children's Hospital
3. Division of Paediatric Haematology-Oncology, Charlotte Maxeke Johannesburg Academic Hospital

ORCID ID

Levy: <https://orcid.org/0000-0002-4986-9036>

Geel: <https://orcid.org/0000-0001-8792-3251>

Bothma: <https://orcid.org/0009-0001-3022-9848>

Abstract

Introduction: Survival rates of children with malignant extra-cranial germ cell tumours (MEGCT) have increased, shifting the focus from survival to reducing long-term effects. Current literature reveals significant gaps in understanding short-term and chronic kidney outcomes, as well as relapse and survival rates when comparing cisplatin and carboplatin chemotherapy for these malignancies. This study aims to compare survival and nephrotoxicity rates between cisplatin- and carboplatin-based regimens in children with MEGCT.

Methods: We retrospectively analysed data from 70 patients treated at two paediatric oncology units between 1979 and 2019: 47 received cisplatin, and 23 received carboplatin. We assessed nephrotoxicity rates through estimated glomerular filtration rates (eGFR) and electrolyte evidence of tubulopathies, with Kaplan-Meier survival curves estimating survival.

Results: The cisplatin group experienced a greater decline in eGFR and a higher incidence of tubulopathies, with 38% experiencing acute kidney injury ($p=0.002$) and 19% requiring electrolyte supplementation ($p=0.025$). Both patients who required kidney replacement therapy received cisplatin. Chronic kidney disease was more prevalent in the cisplatin group (30%) compared to the carboplatin group (13%) at the two-year follow-up ($p=0.054$). Persistent tubulopathies affected 9% of patients in the cisplatin group, and none in the carboplatin group ($p=0.295$). Four-year overall survival was 79% in the carboplatin group and 91% in the cisplatin group ($p=0.313$).

Conclusion: The incidence of kidney dysfunction was higher in the cisplatin group. Given the comparable survival outcomes, we advise avoidance of cisplatin when possible in patients of standard risk. However, caution is warranted due to the small sample size, which may limit the generalizability of these findings.

1. Introduction

Advances in the management of childhood cancer over recent decades have led to a growing population of survivors. As a result, the global prevalence of long-term complications arising from therapeutic interventions has increased.(1) In children with cancer, the aetiology of kidney complications may be multifactorial and include cytotoxic chemotherapy, concomitant use of nephrotoxic antibiotics, dehydration due to poor oral intake and excessive vomiting, tumour compression, surgery, irradiation and stem cell transplantation.(2) Therapy-induced nephrotoxicity can present in various forms such as acute kidney injury (AKI), progressive chronic kidney dysfunction (CKD) or specific impairments of the kidney tubular cells. Clinical manifestations include hypertension, tubulopathies with electrolyte disturbances and proteinuria, and varying degrees of kidney dysfunction.(3)

Malignant germ cell tumours (GCT) make up approximately 3% of cancers in children 0-18 years and the incidence rises with the onset of puberty, with malignant extra-cranial germ cell tumours (MEGCTs) accounting for 14% of adolescent malignancies.(4) Chemotherapy is reserved for stage 2-4 disease but should be considered for patients raised tumour markers, even in the absence of clinical or radiological disease. In cases where upfront surgery is deemed excessive, neoadjuvant chemotherapy may be appropriate, while elevated tumour markers post-surgery would likely indicate the need for adjuvant chemotherapy.(5)

Treatment regimens for paediatric MEGCTs were historically based on clinical trials performed in adult men with testicular GCTs, who represent the largest population affected.(6) In the adult population, cisplatin-based protocols resulted in reasonable systemic tumour control, but local relapses and recurrence occurred without adequate local treatment.(7) Although cisplatin-containing regimens such as bleomycin, etoposide and cisplatin (BEP) were associated with satisfactory survival rates, they resulted in substantial immediate and often permanent adverse effects such as nephrotoxicity and ototoxicity. Since 1989, carboplatin replaced cisplatin in treatment regimens such as JEB (bleomycin, etoposide and carboplatin) with decreased short-term toxicities including nephrotoxicity.(8) This was adapted for use in children, with PEb (cisplatin-based) and JEb (carboplatin-based) regimens, where bleomycin was given once per cycle.

The Malignant Germ Cell International Consortium (MaGIC) compared 25 years of paediatric data, demonstrating no significant differences in observed outcomes between cisplatin and carboplatin-containing regimens. Good prognostic factors included patients <11 years, stage II-III ovarian cancer, or stage II extragonadal cancer. Testicular primary tumours generally had a more favourable prognosis.(9) A similar comparison has not been performed in Africa.

Levels of tumour markers helped to assign risk group (low, medium or high) which guided treatment intensity.(6) This above risk stratification identified patients for individualised treatment, reducing intensity for some and intensifying treatment for others.(10) In South African children, a carboplatin-based regimen was shown to be effective, convenient and affordable, with minimal toxicity.(11)

Adult patients in the USA with low-risk GCT showed complete response rates which were equivalent for both cisplatin and carboplatin. However, at follow-up of 22 months, more patients in the carboplatin arm had relapsed (12% vs 3%, no p-value given). Studies done in Russia(12), Europe(13) and the Netherlands(14) all concluded that cisplatin was superior to carboplatin in the treatment of adult GCT, with better overall survival rates and fewer treatment failures.(11) Similar randomised controlled trials have not been performed in children.

Mudi et al. demonstrated an association between prolonged childhood cancer survival and increased likelihood of kidney dysfunction, with a threefold increased risk of post-treatment kidney dysfunction for patients with pre-existing kidney impairment. This finding underscores the need for heightened vigilance and surveillance of kidney function of at-risk patients.(15) Appropriate hydration is the fundamental strategy for reducing the risk of cisplatin-induced nephrotoxicity in all patients. However, evidence-based recommendations for specific hydration protocols in the paediatric population, such as duration, volume, electrolyte supplementation and mannitol forced diuresis, are limited.(23)

Research on the acute and long-term renal effects in African populations is limited. We aimed to compare survival outcomes and kidney toxicities in patients treated for MEGCT with cisplatin- and carboplatin-containing regimens.

2. Patients and methods

2.1 Patient selection:

This study included children under the age of 18 years with histologically proven, previously untreated MEGCT. Exclusion criteria included patients with stage 1 disease (not requiring chemotherapy) and those lacking complete records of histology or cumulative doses of chemotherapy administered. (See Figure 1.)

2.2 Study design and data collection:

This retrospective study collated data from 1979 to 2019, with data gathered from a clinical database and cross-referenced with patient files. The cisplatin group consisted of patients treated with a cisplatin-based regimen (PEb) from 1979 to November 2011, and the carboplatin group received a carboplatin-based regime (JEb) from December 2011 to December 2019. This date coincided with the implementation of the new protocol at both units, for the treatment of MEGCT on 30 November 2011. Anonymised data was entered into a password-protected REDCap database.

2.3 Site of study:

Data was collected from the paediatric oncology units of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Wits Donald Gordon Medical Centre (WDGMC), both situated in Johannesburg, Gauteng. Permission to perform this study was obtained from the University of the Witwatersrand Human Research Ethics Committee (M211162).

2.4 Methods:

We recorded kidney function and electrolyte values at baseline, during chemotherapy and six-monthly thereafter up to two years after completion of chemotherapy. Values included sodium, potassium, chloride, bicarbonate, urea, creatinine, calcium, magnesium and phosphate.

Patients were risk-stratified at baseline. If risk stratification was not conducted during the initial presentation, patients were retrospectively assigned to risk groups based on age, tumour site and stage, and serum lactate dehydrogenase (LDH), beta-human chorionic gonadotropin (β -HCG) and alpha-fetoprotein (α FP). The SACCSG MEGCT-2016 guidelines were used to categorize GCT histology into non-seminomatous and seminoma groups, with each group classified by prognostic categories (Good, Intermediate, Poor) based on clinical and laboratory features. For patients without documented upfront risk staging in their files,

risk categorization was done retrospectively. In non-seminomatous GCT, risk is assessed based on factors such as primary tumour location, alpha-fetoprotein (AFP) levels, and the presence of visceral metastases. For seminoma, risk factors include tumour size, presence of metastases, and levels of tumour markers like AFP and lactate dehydrogenase (LDH). Elevated levels of AFP, beta-human chorionic gonadotropin (BHCG), and LDH beyond specified upper limits (UL) indicate a higher risk.

Serum creatinine levels of patients treated in the public sector were measured at the National Health Laboratory Services (NHLS) using the Roche/Hitachi system, which employs an isotope dilution mass spectrometry (IDMS)-traceable, compensated kinetic Jaffe method. Specimens from patients in the private sector were analyzed at QPath Lancet Laboratories using the Kinetic Jaffe method on the Abbott Architect c16000.(20)

eGFR was calculated using the modified Schwartz formula, with an eGFR of less than 90ml/min/1.73m² considered abnormal.(21) A standardised definition of paediatric AKI by the Kidney Disease: Improving Global Outcomes (KDIGO) AKI working group in 2012, defined AKI as a decline in estimated GFR (eGFR), increase of the serum creatinine from baseline and decreased urine output.(16) Stages are defined as stage 1: an increase of $\geq 26\mu\text{mol/l}$ within 48 hours or an increase ≥ 1.5 -1.9 times baseline creatinine; stage 2: an increase 2-2.9 times baseline creatinine; and stage 3: an increase ≥ 3 times baseline creatinine, or an increase of $354\mu\text{mol/l}$, or need for renal replacement therapy regardless of stage as per KDIGO classification.(16) CKD reflects irreversible kidney damage associated with a gradual loss of kidney function over time, persisting for three or more months.(17) This definition has been formulated for the adult population, where CKD is a common and well-known health problem, but the KDIGO guidelines do not fully apply to the paediatric population, as it has unique clinical features which can significantly affect both childhood and future adult health.(17) Tubulopathies are disorders with specific transport defects involving one or multiple solutes, with little or no glomerular impairment. Clinical outcomes vary from isolated alterations of specific solutes in the blood or urine, to life-threatening disruption of homeostasis, with unrecognised tubulopathies linked to progressive interstitial nephropathy, glomerular impairment and chronic kidney failure.(18,19) This included electrolyte abnormalities, proteinuria, haematuria and/or glycosuria in the absence of other causes, and was staged from 1 to 5 based on the eGFR or the need for kidney replacement therapy, following the KDIGO guidelines.(17)

Serum phosphate levels below 1.0mmol/L and serum magnesium levels below 0.7mmol/L were regarded as abnormal, as per the NHLS reference ranges. Hypertension was defined as systolic or diastolic blood pressure equal to or greater than the 95th percentile for sex, age and height on three separate occasions.(22)

Throughout the two-year follow-up, surveillance imaging and serological testing (α FP and β -HCG) were conducted to monitor for long-term complications, including kidney dysfunction and disease relapse. Survival outcomes were categorised as alive and disease-free, alive with disease, lost to follow-up or demised. Patients considered lost to follow-up included those who were not contactable or failed to return for subsequent assessment and follow-up visits upon completion of therapy. This study also identified patients who had relapsed and required further chemotherapy.

2.5 Data analysis:

Long-term kidney outcomes, including dysfunction, hypertension and tubulopathies, were analysed by the Wilcoxon rank sum test, and Chi-square or Fisher's Exact test as appropriate. A two-tailed test was used at baseline because we had no prior hypothesis about which group might have worse kidney functioning at the start of the study, allowing detection of differences in either direction. During chemotherapy, a one-tailed test was used, as we hypothesized that cisplatin is more nephrotoxic than carboplatin, focusing on detecting if the cisplatin group had significantly worse kidney outcomes.

All results from univariate comparisons are reported with corrected p-values, using the Holm method for correction. Primary outcomes were analysed using t-test (eGFR in cisplatin group versus carboplatin group), and ordinal logistic regression (KDIGO staging in both cohorts). Overall survival was estimated using Kaplan-Meier curves with Cox regression analysis.

Potential differences between independent groups were assessed using multivariable ordinal regression modelling, controlling for demographics, tumour type and complications. In all cases, statistical significance was defined as a p-value < 0.05. All analyses were performed using R version 4.3.2.

3. Results

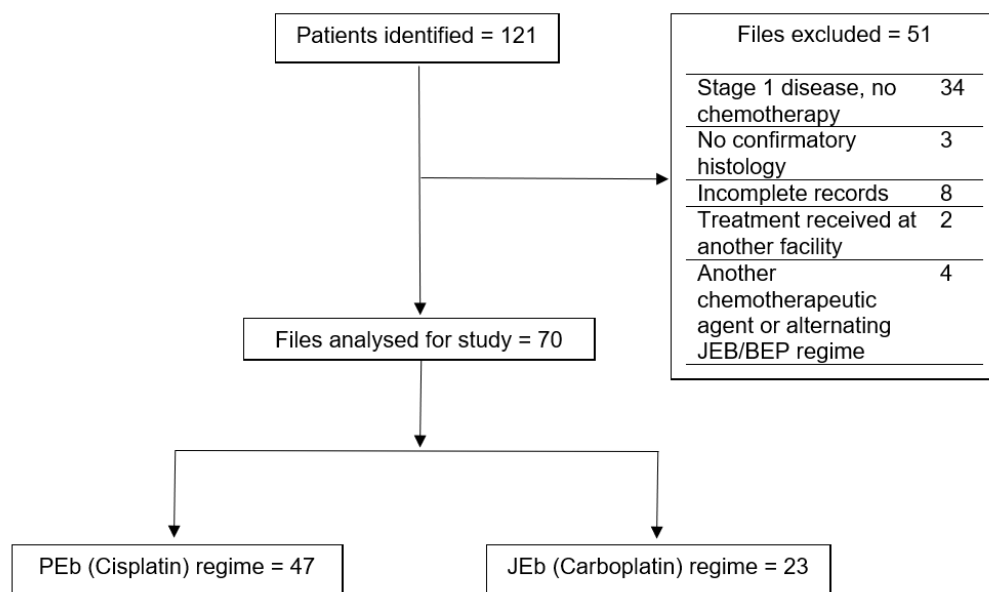


Figure 1. Patient grouping and exclusion criteria. JEb: bleomycin, etoposide and carboplatin; PEb: bleomycin, etoposide and cisplatin.

We identified 121 patients with MECGCT and excluded 51 who did not meet the inclusion criteria (see Figure 1). Seventy patients were included in the analysis. Patient characteristics are shown in Table 1. The majority of patients were female with a female-to-male ratio of 3:1 in the cisplatin group and 11:1 in the carboplatin group with a similar age distribution.

In the cisplatin group, tumour sites included ovaries, pelvis, testes, retroperitoneum, and mediastinum while in the carboplatin group sites included ovaries, sacrococcyx, neck and pelvis. The predominant histologies in the cisplatin group included yolk sac tumours (34%), dysgerminomas (30%), mixed GCT (15%), immature teratomas (9%), embryonal carcinoma (4%) and testicular seminomas, Sertoli-Leydig cell tumour, juvenile granulosa cell tumour and unspecified GCT each comprising of 2% of cases. In the carboplatin group, mixed GCT (48%) were most observed, followed by dysgerminomas (26%), yolk sac tumours (22%), and immature teratomas (4%). Differences in distribution of sites and histological subtypes were not significant (See Table 1).

Table 1. Demographic and tumour characteristics

Characteristic	Cisplatin group N = 47		Carboplatin group N = 23		p-value
Age (years)	7.5	2.0 - 11.8	7.3	1.9 - 12.1	0.951
Sex					0.122
Female	35	74%	21	91%	0.214
Male	12	26%	2	9%	
Type of tumour					
Dysgerminoma	14	30%	6	26%	
Embryonal carcinoma	2	4%	0	0%	
GCT NOS	1	2%	0	0%	
Immature teratoma	4	9%	1	4%	
Juvenile granulosa cell	1	2%	0	0%	
Mixed GCT	7	15%	11	48%	
Seminoma of testes	1	2%	0	0%	
Sertoli-Leydig cell tumour	1	2%	0	0%	
Yolk-sac tumour	16	34%	5	22%	0.058
Site of tumour					
Head and neck	0	0%	1	4%	
Mediastinum	4	9%	1	4%	
Ovary	25	53%	13	58%	
Pelvis	4	9%	1	4%	
Pubic	1	2%	0	0%	
Retroperitoneum	4	9%	0	0%	
Sacroccoccyx	3	6%	7	30%	
Testis	5	10%	0	0%	
Vaginal	1	2%	0	0%	
Tumour stage					0.160
Stage I	9	19%	8	35%	0.653
Stage II	10	21%	7	30%	
Stage III	14	30%	6	26%	
Stage IV	14	30%	2	9%	
Risk stratification					
Good risk	10	21%	7	30%	
Intermediate risk	6	13%	3	14%	
Poor risk	30	64%	12	52%	
Missing	1	2%	1	4%	
Kidney function					0.075
eGFR (ml/min/1.73m ²)	88	5 - 179	98	7 - 157	0.075
Normal kidney function, with eGFR >90 ml/min/1.73m ²	18	38%	15	65%	

eGFR: estimated glomerular filtration rate was calculated using the modified Schwartz formula, with an eGFR of less than 90ml/min/1.73m² considered abnormal. GCT: germ cell tumour

As seen in Table 1, tumour staging in the cisplatin group included Stage 1 disease in nine patients (19%), Stage 2 in ten patients (21%), and Stage 3 and 4 in 14 patients each (30%). In the carboplatin group, tumour staging included eight patients in Stage 1 (35%), seven patients in Stage 2 (30%), six patients in Stage 3 (26%) and two patients in Stage 4 (9%). In both groups, the majority of patients were categorised into the poor-risk group (64% in the cisplatin group and 52% in the carboplatin group).

Patients in the cisplatin group received a mean of six cycles of chemotherapy and cumulative dose of cisplatin of 595 mg/m² (range 523 - 602 mg/m²). Patients in the carboplatin group also received a median of six treatment cycles, with a mean of 2478 mg/m² (range 2144 - 3221 mg/m²). In our study, patients in the cisplatin group received 99 mg/m² per cycle, while those in the carboplatin group received 414 mg/m² per cycle. These doses are close to the recommended maximums of 100 mg/m² per cycle of cisplatin and 600 mg/m² per cycle of carboplatin.

In the cisplatin group, the mean eGFR at baseline was 88mL/min/1.73m², with 26 patients (56%) showing abnormal kidney function, and three patients (7%) had no recorded creatinine at baseline. Among the abnormal results, eight (31%) had hydronephrosis on imaging, and four (15%) had hypertension at baseline. In the carboplatin group, the mean baseline eGFR was 98mL/min/1.73m², and eight patients (35%) had abnormal results. Of the abnormal results, two (25%) had hypertension and five (63%) had hydronephrosis. There were no statistically significant differences detected between the two groups at baseline (p=0.075).

Table 2. Interventions and adverse events during chemotherapy

Characteristic	Cisplatin group N = 47		Carboplatin group N = 23		p-value
AKI	18	38%	1	4%	0.002
Tubulopathy	9	19%	0	0%	0.025
Hypertension	6	13%	0	0%	0.168
Kidney replacement therapy	2	4%	0	0%	>0.999
Febrile neutropaenia	23	49%	8	35%	0.263
Gastrointestinal symptoms	21	45%	8	35%	0.430
Nephrotoxic antimicrobial therapy given	33	70%	13	57%	0.533

AKI (acute kidney injury) stages are defined as stage 1: an increase of $\geq 26\mu\text{mol/l}$ within 48 hours or an increase ≥ 1.5 -1.9 times baseline creatinine; stage 2: an increase 2-2.9 times baseline creatinine; and stage 3: an increase ≥ 3 times baseline creatinine, or an increase of $354\mu\text{mol/l}$, or need for renal replacement therapy regardless of stage.

During chemotherapy, 18 patients (38%) in the cisplatin group and one patient in the carboplatin group developed AKI ($p=0.002$). Two patients (4%) in the cisplatin group required haemodialysis and one patient required haemodialysis after receiving a single dose of cisplatin; subsequently, the treatment regime was switched to carboplatin for the remainder of the chemotherapy course. This patient was excluded from the final analysis following this adjustment. In the cisplatin group, nine patients (19%) developed a tubulopathy requiring electrolyte supplementation, while none were identified in the carboplatin group ($p=0.025$).

Hypertension developed in six patients (13%) in the cisplatin group, none of whom had baseline hypertension. In comparison, one patient in the carboplatin group with baseline hypertension continued to experience elevated blood pressure during chemotherapy ($p=0.168$). No new cases of hypertension were identified during chemotherapy. Table 2 compares the interventions and adverse events during chemotherapy between the two groups.

Throughout the course of chemotherapy administration, across all cycles, 31 patients (53%) developed febrile neutropaenia, 29 (41%) had gastrointestinal symptoms including diarrhoea, severe nausea, persistent and prolonged vomiting and 15 (21%) had myelosuppression. Of the patients with suspected febrile neutropaenia, 29 (41%) received nephrotoxic antimicrobials including aminoglycosides, 13 (18%) received glycopeptides and five patients (7%) received antifungal therapy. No patients received non-steroidal anti-inflammatory drugs (NSAIDs).

Table 3. Kidney function at various time points

Characteristic	Cisplatin group N = 47						Carboplatin group N = 23						p-value
	Normal		Abnormal		Missing		Normal		Abnormal		Missing		
Baseline AKI	8	38%	26	56%	3	6%	15	65%	8	35%	0	0%	0.075
During therapy	9	62%	18	38%	0	0%	22	96%	1	4%	0	0%	
6 months	5	10%	13	28%	9	62%	13	57%	2	9%	8	34%	0.002
12 months	2	4%	6	13%	39	83%	12	51%	3	13%	8	34%	
18 months	1	2%	7	15%	39	83%	10	43%	3	13%	0	43%	
24 months	4	9%	14	29%	29	62%	13	57%	3	13%	7	30%	
													0.054

Normal referring to an eGFR of >90 ml/min/1.73m². AKI (acute kidney injury) stages are defined as stage 1: an increase of $\geq 26\mu\text{mol/l}$ within 48 hours or an increase ≥ 1.5 -1.9 times baseline creatinine; stage 2: an increase 2-2.9 times baseline creatinine; and stage 3: an increase ≥ 3 times baseline creatinine, or an increase of $354\mu\text{mol/l}$, or need for renal replacement therapy regardless of stage.

As shown in Table 3 at 6 months post-treatment, 13 out of 18 patients (72%) in the cisplatin group and two out of 15 (13%) in the carboplatin group had abnormal kidney function (excluding missing data). At 12 months, these percentages were 75% (6 out of 8 patients) for the cisplatin group and 20% (3 out of 15 patients) for the carboplatin group (excluding missing data). At 18 months, 88% (7 out of 8 patients) in the cisplatin group and 23% (3 out of 13 patients) in the carboplatin group had abnormal kidney function (excluding missing data). At 24 months, 78% (14 out of 18 patients) in the cisplatin group had abnormal results, and from those six (43%) were KDIGO Stage 2, 7 (50%) were KDIGO Stage 3, and one (7%) was classified as KDIGO Stage 5. In the carboplatin group, 19% (3 out of 16 patients) had abnormal kidney function where all three patients (100%) were KDIGO Stage 2. Here, the cisplatin group exhibited a significantly lower eGFR compared to the carboplatin group; odds ratio for cisplatin versus carboplatin (95% CI = 0.05 (0.01, 0.25); $p < 0.001$). The precision of the estimate (95% CI of the odds ratio) was low owing to the small sample size. See Figure 2.

Four (9%) cisplatin recipients required ongoing electrolyte supplementation due to persistent tubulopathy at the two-year mark. No patients in the carboplatin group had similar features. After accounting for demographic factors, tumour characteristics and pre-existing kidney dysfunction, there was no statistically significant association between the type of platinum drug used and KDIGO stage at two years post-chemotherapy mark ($p=0.054$).

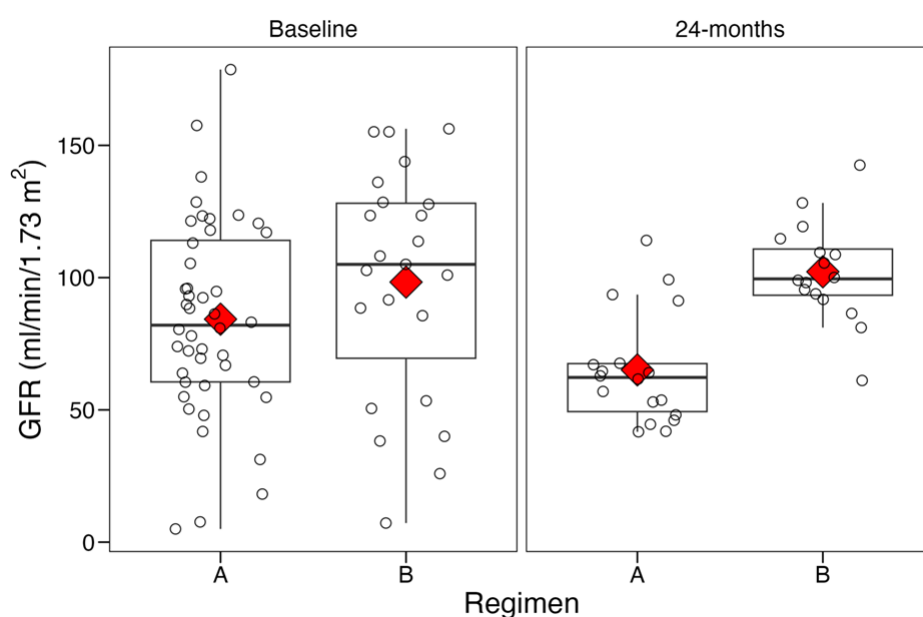


Figure 2. Tukey box-and-whisker plot of baseline glomerular filtration rate (GFR) by type of platinum-based treatment at baseline and 24-months after treatment. Group A: Cisplatin group, Group B: Carboplatin group. The clear circles are individual data points. The red diamonds indicate the group means.

Table 4. Two-year and long-term characteristics of the cohorts

Characteristic	Cisplatin group N = 47		Carboplatin group N = 23		p-value
2-year post-chemotherapy CKD staging	Abnormal results in 14 patients		Abnormal results in 3 patients		0.054
stage 2	6/14	43%	3/3	100%	
stage 3	7/14	50%	0/3	0%	
stage 5	1/14	7%	0/3	0%	
Missing data	29/47	62%	7/23	30%	
2-year post-chemotherapy tubulopathy	4/47	9%	0/23	0%	0.295
2-year post-chemotherapy outcomes					0.819
Alive	36	76%	17	74%	
Dead	8	18%	3	13%	
Lost to follow-up	3	6%	3	13%	
Long-term follow-up time (years)	5.7	2.5 - 11.5	3.9	2.2 - 5.9	0.114
Long-term follow-up: relapse requiring chemotherapy	9/47	19%	5/23	22%	0.408
Long-term follow-up: survival					0.313
Alive	37/47	79%	21/23	91%	

CKD = chronic kidney disease, with irreversible kidney damage associated with a gradual loss of kidney function over time, persisting for three or more months. KDIGO stage 2: eGFR 60-89(ml/min/1.73m²); KDIGO stage 3: eGFR 30-59(ml/min/1.73m²); KDIGO stage 4: eGFR 15-29(ml/min/1.73m²) and KDIGO stage 5: eGFR <15(ml/min/1.73m²).

At the two-year time point (Table 4), 33 (70%) patients in the cisplatin group were alive and disease free, three (6%) were alive with disease, eight (18%) had died and three (6%) were lost to follow-up. Similarly, in the carboplatin group, 16 patients (70%) were alive and disease-free, one (4%) was alive with disease, three (13%) had died and three patients (13%) were lost to follow-up. Kaplan-Meier estimation yielded a two-year survival rate of approximately 83% for the cisplatin group and 90% for the carboplatin group.

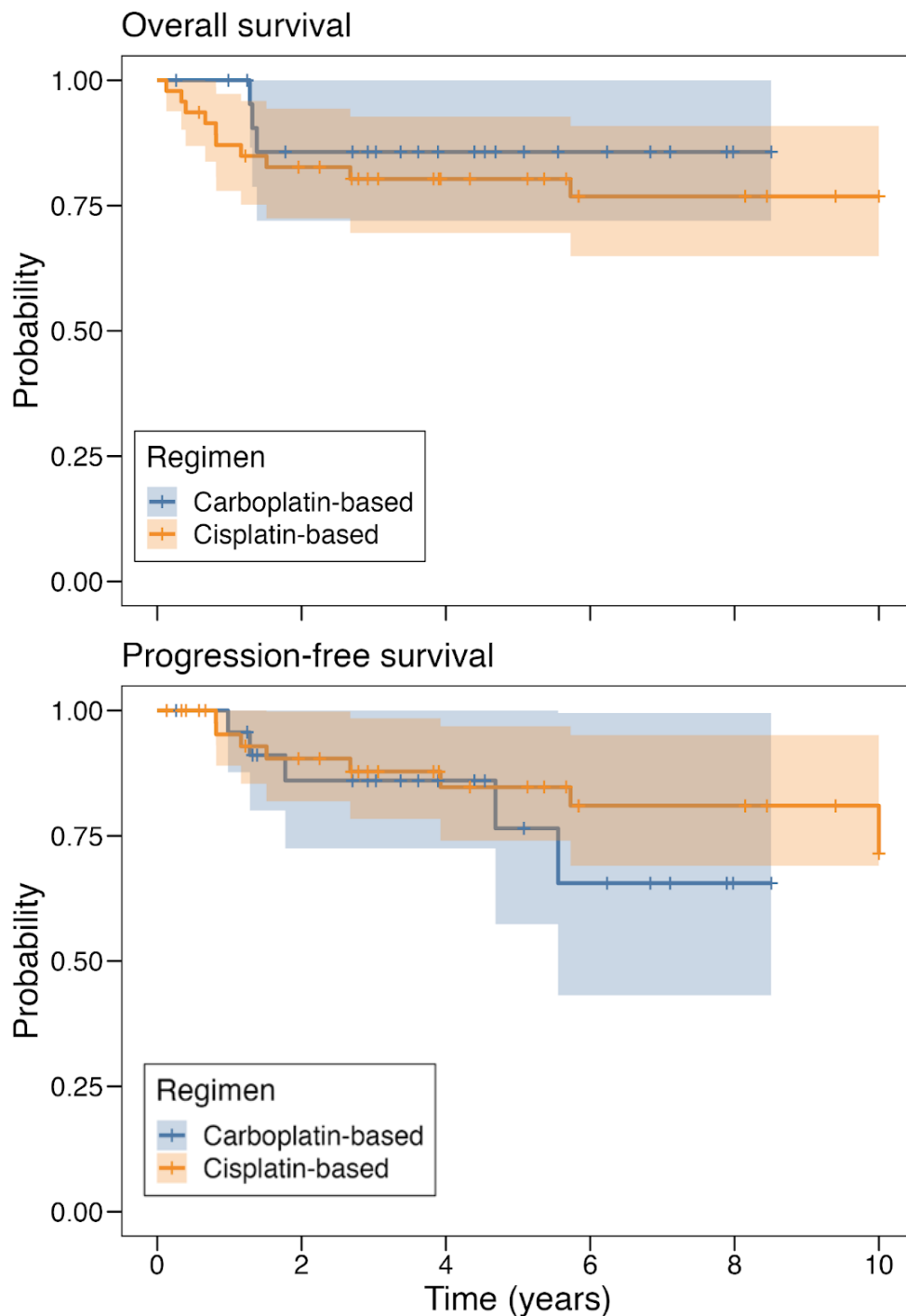


Figure 3: Kaplan-Meier overall and progression-free survival curves for patients with MEGCT treated on cisplatin-containing regimens and carboplatin-containing regimens.

The median follow-up was 5.7 years (range 2.5-11.5 years) in the cisplatin group and 3.9 years (2.2-5.9 years) in the carboplatin group. In the cisplatin group, nine patients (19%) relapsed and required further treatment, while five (22%) relapsed in the carboplatin group. Overall survival was 85% for the entire cohort at the four-year time point, with survival rates of 79% for the cisplatin group, and 91% for the carboplatin group ($p=0.313$); (relapse: $p=0.408$).

4. Discussion

We aimed to compare the efficacy and nephrotoxicity of cisplatin- and carboplatin-based regimens in the treatment of paediatric MEGCT. We found that patients treated with a cisplatin-based regimen were more likely to develop various forms of nephrotoxicity than those treated with a carboplatin-based regimen. Kidney function worsened in both groups during chemotherapy, with higher grades of kidney dysfunction seen in the cisplatin group and lasting effects observed up to two years later. The differences in overall survival between the two groups were not statistically significant, although the numbers in this study are relatively small.

We found no correlation between histology, tumour site, site of malignancy, stage or risk group and the development of nephrotoxicity. More children in the cisplatin group were affected, but the observed kidney dysfunction was generally of mild to moderate severity, with a minority experiencing deterioration necessitating kidney replacement therapy. While various studies(15) have examined the kidney outcomes in survivors of childhood cancer, these have primarily focused on nephrotoxicity during the acute treatment phase rather than the long-term consequences.

The nephrotoxicity of cisplatin is a major dose-limiting side effect. In patients where the pre-treatment eGFR is below 60 ml/min/1.73m², treatment regimens should be adjusted by reducing or omitting the drug where possible. Many patients who received cisplatin experience varying degrees of kidney injury, with up to 30% being detected following initial treatment.(23) This was similar in our study, in which nearly 40% of patients developed a degree of AKI during the administration of chemotherapy.

A direct relationship between the total cisplatin dose administered and the extent of nephrotoxicity has been noted, with higher doses associated with more severe and longer-lasting kidney impairment.(24) This emphasises the importance of careful dosing and close monitoring during and after treatment. While the prognosis for long-term recovery or stability of kidney function is optimistic, data in the paediatric population remains limited. The study also demonstrated significant renal tubular dysfunction, primarily characterized by hypomagnesaemia due to magnesium loss from tubular damage. This required supplementation and was found to persist long-term.(24) Similarly in our data, tubulopathy was found to persist at the two-year time point.

Carboplatin causes less nephrotoxicity than cisplatin, with myelosuppression being the dose-limiting side effect. Unlike cisplatin, it does not undergo biotransformation by the kidney tubules, thereby preventing the formation of toxic metabolites, with reduced nephrotoxicity. Carboplatin rarely causes clinically significant reductions in GFR and hypomagnesaemia.(3) Dose reductions are required if creatinine clearance decreases, particularly for patients with kidney failure from obstructive uropathy. Carboplatin can be adjusted based on eGFR and is suitable even for patients on dialysis, making it a viable option for those with severe kidney impairment. Consequently, the literature suggests replacing cisplatin with carboplatin in cases of renal failure to reduce nephrotoxicity while maintaining effective chemotherapy.(25)

It is widely acknowledged that the likelihood of long-term kidney damage rises as survival rates improve. In high-income countries, among every 715 young adults, one might be a survivor of childhood cancer, possibly burdened with additional complications from treatment, with up to 60% experiencing one or more chronic health issues.(26)

GFR is a useful indicator of kidney function and progression of disease but determining true GFR by measurement of excretion of radioisotope (nuclear GFR) is costly, time-consuming, difficult to perform and involves radiation exposure.(25) The eGFR using the Schwartz formula has not been well validated in patients younger than two years of age, as the GFR progressively increases after birth and only reaches adult levels at 18 months to two years of age.(26) In the cisplatin group, 12 patients were under two years of age, compared to six patients in the carboplatin group. Our study estimated the frequency of kidney dysfunction during a two-year monitoring period for children treated with platinum-based chemotherapy. Kidney dysfunction was observed more frequently and persisted longer in the cisplatin group compared to the carboplatin group.

As there are no validated pharmacological interventions for AKI, early detection and prevention of further injury are the mainstays of treatment.(2) A study done by Skinner et al, demonstrated decreased eGFR and magnesium wasting as the predominant manifestation of kidney dysfunction, but normalisation was usually seen after one year. Moderate to severe renal impairment was shown at various time-points and the impairment was not dose-dependent, although higher doses were associated with prolonged impairment even after one year. Conversely, most carboplatin-treated participants maintained normal kidney function and electrolyte levels throughout the study.

Although both agents induce similar kidney damage, this occurred less frequently and with milder effects in patients treated with carboplatin compared to cisplatin.(26) Our study had similar findings, and showed that cisplatin had a higher incidence of AKI, hypertension, tubulopathies and CKD. Nevertheless, it is crucial to interpret these findings with caution due to significant gaps in the clinical records.

Febrile neutropaenia, leads to increased administration of possibly nephrotoxic antibiotics, possibly compromising an already vulnerable organ system. Despite the known nephrotoxic effects of treatment of the malignancy and febrile neutropaenia, we did not demonstrate statistically significant impacts on kidney function in either group.

Some limitations of this study included missing data for eGFR, which could not be calculated at all time points. Additionally, there were no urine dipstick results documented, precluding assessment of proteinuria, haematuria or glycosuria. The two-year post-treatment data needs to be interpreted with caution because of the large amount of missing data. Acknowledging the impact of missing data on our interpretation, our statistical analysis doesn't definitively confirm poorer outcomes in the cisplatin group. This raises questions about the accuracy of our findings, highlighting the need for further investigation into the true effects of these drugs. Comparing historical cohorts can be problematic due to potential confounding factors, such as changes in nutrition, variations in access to medical care over time, and differences in clinical management.

The primary method for estimating GFR involves measuring serum creatinine, which is closely linked to muscle mass and partially eliminated by the kidneys. However, this method may not detect early declines in GFR or acute changes in kidney function. Serum creatinine levels vary with age, sex, ethnicity and kidney function, leading to different equations for estimating GFR. More accurate GFR measurements require exogenous substances that are solely eliminated by the kidneys, but these tests are impractical, costly and time-consuming, particularly in children. Although nuclear GFR is the gold-standard for the measurement of kidney function, it was not routinely performed on this cohort of patients.

Understanding platinum-induced kidney damage is complex, and the precise interactions of the drug remains unclear, hindering the development of protective treatments and limiting the broader use of platinum drugs. Understanding the long-term effects is crucial for cautious administration of platinum agents, yet limited information exists about how its

intensity and severity changes over time. This study provides crucial insights into the nephrotoxicity associated with cisplatin and carboplatin in paediatric patients, highlighting the need for tailored treatment strategies within the current national protocol. Given the significant differences in nephrotoxicity rates observed, it is essential to consider incorporating prospective analyses of kidney function and nephrotoxicity into the national protocol. This could enhance monitoring and support measures, ultimately optimizing patient outcomes and mitigating long-term renal complications.

The current protocol includes an alternative regimen with cisplatin and carboplatin, but this was excluded from the analysis. Future research should investigate this regimen's potential to reduce nephrotoxicity while maintaining high cure and survival rates.

5. Conclusion

This study is the first comprehensive comparison of cisplatin and carboplatin regarding short- and long-term kidney health in paediatric cancer survivors. While both agents are effective in tumour control, cisplatin is linked to significantly higher rates of acute and chronic nephrotoxicity. Personalized treatment approaches, vigilant monitoring, and early referral to paediatric nephrologists are crucial to optimizing outcomes and minimizing treatment-related toxicities. The more recent cohort in the carboplatin group may have benefitted from enhanced supportive care, potentially contributing to reduced nephrotoxicity.

As survival rates for children with malignant extra-cranial germ cell tumours (MEGCT) improve, prioritizing chemotherapy regimens that protect renal function while maintaining efficacy is imperative. Certain subgroups of patients may benefit from a more intensive cisplatin-based regimen, and we await the results of local and international collaborative research efforts to guide this decision. Avoiding cisplatin may not be feasible for all children with MEGCT, particularly those at standard risk. Continued research is essential to better understand the long-term effects on kidney health and to develop sensitive markers for early detection of dysfunction.

6. Conflicts of interest statement

No conflicts of interest to declare.

7. Authors' contributions

All authors have played integral roles in shaping this manuscript. Each author contributed significantly to its conception, design, analysis and interpretation. L.B., as principal author, took the lead in drafting the manuscript, with all co-authors providing critical feedback and revisions that were essential to finalizing the article for publication.

8. Acknowledgments

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Appendix I:
Ethics clearance certificates

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--	--

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr L Bothma
School of Clinical Medicine
Department of Paediatrics and Child Health
Medical School
University

E-mail: 2522538@students.wits.ac.za

CC: Supervisor: Professor J Geel and Dr S Iruen
<Jennifer.Geel@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/01/19

REF: R14/49

PROTOCOL NO: **M211162** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Comparison of cisplatin and carboplatin nephrotoxicity in paediatric patients with malignant extra-cranial germ cell tumours: a retrospective review*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.



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R49 Dr L Bothma

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M211162**

NAME:
(Principal Investigator)

Dr L Bothma

DEPARTMENT:

School of Clinical Medicine
Department of Paediatrics and Child Health
Medical School
University

PROJECT TITLE:

*Comparison of cisplatin and carboplatin nephrotoxicity
in paediatric patients with malignant extra-cranial
germ cell tumours: a retrospective review*

DATE CONSIDERED:

2021/11/26

DECISION:

Approved unconditionally

CONDITIONS:

NOTE:

If contact information regarding student study participants is required,
please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR:

Professor J Geel and Dr S Irusen

APPROVED BY:


Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL:

2022/01/19

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

Appendix II:
Faculty protocol approval letter



Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

07 October 2021
Person No: 2522538
PAG

Dr L Bothma
11 6th Avenue
Melville
2092
South Africa

Dear Dr Lane Bothma

Master of Medicine in Paediatrics: Approval of Title

We have pleasure in advising that your proposal entitled *Comparison of cisplatin and carboplatin nephrotoxicity in paediatric patients with malignant extra-cranial germ cell tumours: a retrospective review* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely



Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix III:
Plagiarism declaration



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Lané Bothma (Student number: 2522538) am a student registered for the degree of Masters of Medicine in Paediatrics in the academic year 2024.

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Author affiliations:

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2. Division of Paediatric Hematology, Netter Mandela Children's Hospital
3. Division of Paediatric Haematology-Oncology, Charlotte Maxeke Johannesburg Academic Hospital

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Appendix V:
Protocol



Research Protocol

Comparison of cisplatin and carboplatin nephrotoxicity in paediatric patients with malignant extra-cranial germ cell tumours: a retrospective review

Candidate:

Dr Lané Bothma

MBChB (Pret), DCH (SA)

Student no: 2522538

Degree: Masters of Medicine in the discipline of Paediatrics

Supervisors:

Prof Jennifer Geel

MBChB (UCT), FC Paed (SA), Cert Med Onc (Paed), MMed (Wits)

Consultant paediatric oncologist and Head of Clinical Unit, Paediatric Haematology/Oncology, CMJAH

Dr Cecil Levy

MBBCH, FC Paed (SA), Cert Paed Nephrology (SA)

Consultant paediatric nephrologist and Head of Clinical Unit, Paediatric Nephrology, NMCH

Protocol date: August 2021

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1. Abbreviations

AKI:	acute kidney injury
BMAT:	bone marrow aspirate and trephine
CKD:	chronic kidney disease
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
CT:	Computed tomography
FDA:	Food and Drug Administration
FIGO:	International Federation of Gynaecology and Obstetrics
GCTs:	germ cell tumours
GFR:	glomerular filtration rate
eGFR:	estimated glomerular filtration rate
MaGIC:	Malignant Germ cell International Consortium
MRI:	Magnetic resonance imaging
MEGCTs:	Malignant extra-cranial germ cell tumours
WDGMC:	Wits Donald Gordon Medical Centre

2. Introduction

Malignant extra-cranial germ cell tumours (MEGCT) are a heterogeneous group of neoplasms that display remarkable variability concerning age at presentation, histology and site of presentations. MEGCTs share a common embryological origin and an extraordinary responsiveness to chemotherapy when treated with platinum compounds.¹ As the long-term survival of these patients is relatively high, it is important to look at the long-term toxic effects of the treatment given. There is currently a lack of data regarding the renal outcomes of paediatric patients treated with a cisplatin-based regime compared to a carboplatin-based regime.

3. Background

MEGCTs are derived from a pluripotent primordial germ cell and can be divided into gonadal (ovary and testes) and extra-gonadal types (sacroccygeal area, retroperitoneum or mediastinum). These tumours are subdivided according to cell morphology, immunohistochemistry and tumour marker secretion.²

Epidemiology and incidence

MEGCT have an annual incidence of approximately 4 per million in patients younger than 15years.² Malignant germ cell tumours make up about 3% of cancers in children 0-18 years and the incidence rises with the onset of puberty, when MEGCTs account for 14% of malignancies diagnosed in adolescence.^{1, 3}

Diagnosis

Diagnosis of MEGCT relies on a combination of clinical presentation, raised tumour markers, radiology findings and biopsy results. Not all MEGCT require histological confirmation for diagnosis, as the diagnosis may be made on the basis of raised tumour markers and radiological findings, although this will be considered once definitive surgery has been performed.²

Staging

Staging modalities include a chest X-ray, ultrasound, computed tomography scan (CT) or Magnetic Resonance Imaging (MRI) of the primary lesion as well as bone marrow aspirate and trephine (BMAT). Metastatic disease occurs in about 20% of paediatric cases, and is mainly to the lungs, but there may be bone, bone marrow and liver involvement.² Levels of

tumour markers help to assign risk group (low, medium or high) which guides treatment intensity.³

Chemotherapy is reserved for stage 2-4 disease, while patients with stage 1 disease can be observed, as only 25% of these patients will have recurrence.² Chemotherapy is given to patients with raised tumour markers, even when no clinical or radiological diseases is apparent, and when risk of upfront surgery is deemed excessive.²

Treatment

Treatment regimens for paediatric MEGCTs have historically been based on clinical trials done in adult men with testicular GCTs, who represent the largest population of patients affected with GCTs.³ Currently the standard adjuvant chemotherapy regime for adults is BEP (Bleomycin, Etoposide and Cisplatin), and has found to have a 88% 5-year event free survival rate in the paediatric and adolescent population, but with significant associated side effects.⁴ Cisplatin-based protocols result in reasonable systemic tumour control, but local relapses and recurrence can occur in patients without adequate local treatment.⁴ Cisplatin chemotherapy was approved by the Federal Drug Association in 1978 and the increasing use of this agent contributed to a significant rise in survival, but multiple reports later documented nephrotoxicity.⁵ Since 1989, cisplatin has been substituted with carboplatin (JEB according to the Paediatric UK regime) with improved short-term toxicities, including nephrotoxicity, ototoxicity, peripheral neuropathies and acute gastrointestinal toxicities.⁵

In a case series from Red Cross War Memorial Children's Hospital between 1992 and 2008, it was confirmed that a carboplatin-based regime combined with surgery is an example of a treatment approach with high success and low toxicity rates that limit hospitalisation. This treatment regime matched the needs of patients in a resource-limited setting, afforded them treatment with high cure rates, and was shown to be cost-efficient and convenient to the patient and their caregivers. All chemotherapy was given in the outpatient department, and no deaths were reported due to infection or chemotherapy-related toxicity.⁶

Table 1: Comparison of cisplatin and carboplatin (adapted from Hendricks et al) ⁶

Cisplatin used in PEB	Carboplatin used in JEB
Effective in malignant germ cell tumours, including high risk groups	Decreased efficacy in comparison with cisplatin in high risk malignant GCT

Significant nephrotoxicity	Less nephrotoxicity than cisplatin
More cost effective at recommended dose (100mg/m ² at US \$127.50)	More expensive at the recommended dose (550mg/m ² at US \$264.14)
Requires overnight admission for pre and post hydration to prevent nephrotoxicity	Decreases cost by reducing the need for admission and inpatient care
Requires monitoring of glomerular filtration rate (GFR)	Monitoring of glomerular filtration rate not required

In a study comparing cisplatin and carboplatin use in low risk germ cell tumours (GCT) in adult patients in Minnesota, USA, and complete response rates were found to be equivalent. However, at follow-up of 22 months, more patients in the carboplatin arm relapsed (12% v 3%, no p value given). Multiple studies done in Russia, Europe and the Netherlands all concluded that cisplatin is superior to carboplatin in the treatment of adult GCT, with better overall survival rates, fewer treatment failures, including relapse and treatment-related deaths.⁷

In an analysis of MaGIC data (Malignant Germ Cell International Consortium) where 25 years of clinical data in the paediatric population was pooled, the outcomes of cisplatin and carboplatin in the use of MEGCT were directly compared. This was an analysis of clinical trials and data rather than randomised control trials but showed no significant difference in the outcomes observed when comparing age, site or stage of disease in paediatric patients with MEGCT. In the paediatric regimen, a higher doses of carboplatin is used (350-500mg/m² in adults vs 600mg/m² in children), with an adequate dose density, and the tumours were found to be more sensitive as the underlying biology is different than that of adults.⁸ Some factors in MaGIC data predicted worse outcomes in paediatric patients: patients aged ≥11 years, advanced staging and/or ovarian or extra-gonadal primary tumours. This led to a proposed risk stratification, identifying patients where therapy and toxicity can be appropriately reduced for some patients and intensified for others.⁸

Nephrotoxicity

Acute kidney injury (AKI) is defined as a decline in GFR, doubling of the serum creatinine from baseline and a decrease in urine output. The incidence, prevalence and aetiology are not well defined in the paediatric population. In oncology patients the aetiology of AKI may be multifactorial due to cytotoxic drugs administered, concomitant use of nephrotoxic

antibiotics, dehydration due to poor oral intake and excessive vomiting, irradiation and stem cell transplantation.⁹

A standardised definition of AKI was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) AKI working group in 2012, and has subsequently been validated in the paediatric population. The definition identifies and stages AKI based on serum creatinine and urine output. Baseline creatinine is defined as the lowest serum creatinine in the preceding three months, thus estimating the baseline GFR using the original Schwartz equation.¹⁰ Serum creatinine has limitations as a biomarker for AKI, and is insensitive to small changes in the GFR. It is not a real time indicator, may rise up to 72 hours following an insult and may not change until up to 50% of kidney function is lost. The concentration of creatinine is also affected by age, sex, muscle mass and volume status of a patient.¹¹

GFR is a useful indicator of kidney function and kidney disease progression but determining true GFR by measurement of excretion of radio-isotope (nuclear GFR) is time-consuming, difficult to perform, involves exposure to radiation and is costly. Formulas are thus needed to estimate GFR in children. The Schwartz formula which uses serum creatinine, height and an empirical constant to estimate GFR, was devised in the mid-1970s, but recent data suggests that this formula overestimates GFR.¹² Determining the estimated glomerular filtration rate (eGFR) with the Schwartz formula is not validated in patients < two years of age as the GFR progressively increases after birth and only reaches adult levels at 18 months to two years of age.¹³ As there are no validated pharmacological interventions for AKI, early detection and prevention of further injury is the mainstay of treatment.⁹ In oncology patients, eGFR is usually overestimated by the Schwartz formula, as these patients have reduced muscle mass, and thus may delay the diagnosis of AKI.⁹

Cisplatin is a platinum-based antineoplastic chemotherapy agent used in the treatment of multiple malignancies. Cisplatin is eliminated predominantly by the kidneys, and more than 50% of the drug is excreted in the urine in the first 24 hours after administration. The concentration in the renal cortex is several times higher than that of other organs or plasma. Cisplatin leads to injury in the S3 segment of the proximal tubule (late straight segment), leading to a decrease in the GFR, although non-proliferating cells are generally less sensitive to the toxic effects.

Risk factors for toxicity include high free plasma concentrations, which could suggest that the cumulative dose of platinum may play a role in the development of nephrotoxicity.¹⁴ Carboplatin nephrotoxicity is similar in terms of pathogenesis, but less common and usually much less severe.¹⁵

Multiple mechanisms could contribute to renal impairment caused by cisplatin, as evidenced by a decline in the GFR. By exposing the renal tubular cells to toxic platinum metabolites, a complex signalling pathway is activated that can lead to tubular cell injury and even cell death. Injury to the renal vasculature and a profound inflammatory response results in vasoconstriction with decreased blood flow and subsequent ischaemic injury. This leads to tubular injury, apoptosis and finally renal dysfunction.¹⁶ This AKI which could be worsened when combined with other nephrotoxic agents often used in oncology patients such as aminoglycosides, glycopeptides and antifungal medication when treating febrile neutropaenia.¹⁴

Cisplatin has a 10-80% incidence of nephrotoxicity in treated patients, compared to 0-25% in carboplatin.¹⁵ Cisplatin administration could also lead to electrolyte wasting especially magnesium, and supplementation thereof could reduce renal tubular damage.¹⁷

In a study done in North Carolina, USA, nephrotoxicity was noted in 25-33% of patients who received only a single intravenous dose of cisplatin, at 50-75mg/m², intermediate dose. The majority of patients (50-75%) developed moderate to severe nephrotoxicity when they received cisplatin for five consecutive days at a daily dose of 15-20mg/m², low dose. Severe or irreversible nephrotoxicity was found in patients who received high dose cisplatin of >100mg/m².¹⁷ In clinical practice, up to a third of patients treated with cisplatin develop nephrotoxicity, which usually presents 10 days after treatment.¹⁷

Some studies have shown a benefit of mannitol forced diuresis as it reduces the concentration of cisplatin in the kidneys, but has not consistently been proven. The concern with mannitol is that of over-diuresis leading to dehydration which could further compromise the kidney. It was therefore suggested that mannitol should only to be used in patients receiving high-dose cisplatin ($\geq 100\text{mg/m}^2$).¹⁷ Despite multiple decades of research, concrete recommendations regarding volume, duration, hydration type, supplementation and forced diuresis remain unavailable and are limited in the paediatric population.

Chronic kidney disease (CKD) refers to a state of irreversible kidney damage that is associated with a gradual loss of kidney function over time that persists over a minimum of three months. This definition has been formulated for the adult population, where CKD is a common and well-known health problem, but the KDIGO guidelines for definition and staging are not fully applicable to the paediatric population.¹⁸

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guideline proposes the following definition of CKD:¹⁹

- Abnormalities of kidney structure or function that have been present for more than three months, with implications for the health of the patient, and either of the following:
 - Decreased GFR ($< 60 \text{ mL/min/1.73m}^2$) and/or
 - Presence of markers of kidney damage
 - Proteinuria (urine dipstick $\geq 2+$ or urine PCR five times the upper limit of normal)
 - Electrolyte and other abnormalities caused by tubular disorders
 - Histological abnormalities
 - Structural abnormalities detected by imaging
 - History of renal transplantation

The above mentioned definition does not apply to children < 2 years of age, where appropriate age adjusted GFR should be used, and also does not apply to children younger than three months.

For patients less than two years of age, concern should be raised when GFR values are more than one standard deviation below the mean for age.¹⁹

- Moderate reduction: an age specific GFR value between one to two standard deviations below the mean
- Severe reduction: an age specific GFR value more than two standard deviations below the mean.

Tubulopathies are defined as disorders with specific transport defects involving one or multiple solutes, with little or no glomerular impairment. The clinical outcomes can range from isolated alterations of specific solutes in the blood or urine, to life-threatening disorders

of homeostasis.²⁰ Tubulopathies, if not recognised, have been associated with progressive interstitial nephropathy, glomerular involvement and renal failure.²¹

Prognosis and follow-up:

Despite tumour stage or histology, 15% of patients with MEGCT who were treated with chemotherapy and surgery may relapse.² It is thus important to preserve renal function as second-line chemotherapy may cause further damage to the kidney. As the long-term survival of oncology patients is improving, it is important to address the side effects of treatment given.⁶

The new chemotherapy protocol for MEGCTs was changed on 30 November 2011, and implemented at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Wits Donald Gordon Medical Centre (WDGMC). This comprised of a substitution of Carboplatin for Cisplatin. Further studies are needed to assess if the consequences of platinum-based chemotherapy are avoidable without compromising survival in paediatric patients with MEGCTs, and to investigate the rates of nephrotoxicity in these patients.

4. Purpose of study

4.1 Research question

- Does a carboplatin-based chemotherapy regime have decreased incidence and severity of nephrotoxicity in paediatric patients with malignant extra-cranial germ cell tumours when compared to the previous cisplatin-based regime?
- What are the long term survival outcomes when comparing the two protocols in patients with malignant extra-cranial germ cell tumours?

4.2 Aims of the study

- To determine whether the change in chemotherapy protocol from a cisplatin-based to a carboplatin-based protocol has decreased the rates and severity of nephrotoxicity in paediatric patients with MEGCTs.
- To determine the two year survival rate in patients treated with carboplatin compared to cisplatin, as part of the management of MEGCTs.

4.3 Objectives

- To determine the rate and extent of nephrotoxicity in patients with MEGCT treated with a platinum-based chemotherapy regime, with emphasis on renal function testing and estimated glomerular filtration rate. The renal side effects of a cisplatin-based regime will be compared to that of a carboplatin-based regime.
- To identify patients who developed AKI and the cumulative doses of platinum chemotherapy used during treatment.
- To identify patients with long-term renal complications and the occurrence of CKD at the end of follow-up, two years after completing chemotherapy.

5. Methodology

5.1 Study design

- Retrospective cross-sectional study with data gathered from a clinical database with correlation of patient files.
- Group 1 will be those from 01 January 1983 to 30 November 2011 as a historical cohort to whom cisplatin-based chemotherapy was given, using an established database.
- Data will be compared to Group 2, who received carboplatin-based chemotherapy. This information will be collected from 01 December 2011 to 31 December 2019, as the new protocol for the treatment of MEGCT was implemented from 30 November 2011.

5.2 Site of study

- Paediatric oncology unit at CMJAH, a tertiary referral centre accepting patients from a large drainage area in Gauteng, other areas in South Africa and neighbouring African countries.
- Paediatric oncology practice at WDGMC, a private academic hospital in Johannesburg.
- Paediatric nephrology unit at CMJAH.

5.3 Study population and sample size

Patients seen at above mentioned paediatric oncology units, age 0 - 18 years who were diagnosed with MEGCT. Sample size approximately 55 in Group 1, and 30 in Group 2.

Newborns mostly present with benign tumours that do not require chemotherapy, but patients with malignant transformation would be included.

Inclusion criteria:

- All patients with histologically proven diagnosis of MEGCT, on first-line chemotherapy.
- Age 0 – 18 completed years who were treated with a platinum-based chemotherapy regime during the study period.

Exclusion criteria:

- Patients with incomplete records, including histology results, no records of treatment received, for example dose of chemotherapy administered during treatment.
- Patients with stage 1 cancer who did not receive chemotherapy.
- Patients with intracranial germ cell tumours.
- Patients with benign germ cell tumours, including mature sacrococcygeal teratomas.

5.4 Data collection

Data will be manually collected from files and entered directly into a prepared REDCap database and will capture the following:

- Age
- Sex
- Pre-existing renal pathology and presence/absence of hydronephrosis secondary to tumour compression or other causes
- Type, site and staging of germ cell tumour
- Chemotherapy regime given and number of cycles.

- Cumulative dose of platinum agent across all cycles
- Serum electrolytes, serum urea, serum creatinine.
- Estimated glomerular filtration rate will be calculated based on age, sex and height/length. The Schwartz formula will be used to determine the eGFR, and will be done at various time points during chemotherapy, and every six months during the two year follow-up period.
- Urine dipsticks, urine protein: creatinine ratio, urine electrolytes if available
- Long term survival outcomes and renal status at end of follow-up period: alive with no CKD, progression of CKD, dead or lost to follow-up

5.5 Data management and analysis

Data will be entered directly into an electronic REDCap database that is password protected. SPSS will be used for data analysis.

Help with the data analysis will be sought by the Wits biostatistical unit.

- Descriptive statistics to describe the data in each sample group. They include means with standard deviations for normally distributed data and medians with interquartile ranges for non-parametric data.
- Kaplan-Meier survival analysis curves will be generated to determine actuarial five year survival rates, with Cox regression analysis to ascertain prognostic factors, which will include age, sex, stage, treatment (cisplatin-based or carboplatin-based),
- Univariate and multivariate analysis
- The chi-squared test to determine associations between categorical variables.
- Mann-Whitney U test to determine significant differences between two sets of data that have come from two different sets of subjects (early and late cohort).

6. Ethical considerations and confidentiality

Patient confidentiality will be maintained throughout the study and no identifying details such as names or dates of birth will be included into the database. The data to be used will be collected from the patient files and entered into a REDCap database which will be password protected.

The above protocol will be submitted for approval to:

- The Human Research Ethics committee of the University of Witwatersrand
- The University of Witwatersrand Faculty Post Graduate Studies Committee

- The clinical executive at CMJAH and WDGMC
- Head of the paediatric department and heads of the respective clinical units

7. Funding

The cost involved with this study will be borne by the researcher. A proposed budget:

Expense	Cost	Total cost
Online ethics short course	Free	Free
FAHS1595: Health Science Research Methodology online course	R300	R300
Statistical analysis:	Free at Wits University	Free at Wits University
Printing:	R0.97/A4 sheet	R97.00 for 100 pages
Binding:	R436.25	R436.25
Poster making for publication and presentation costs	R104.00/A1 poster	R104.00/A1 poster
Total presumed costing:	R937.25	

7. Limitations

- As this is a retrospective study, adequacy of data collection will rely on clinical notes and completeness of data filed on the database, and some data might not be recorded.
- Not every patient had urine dipsticks and electrolytes performed.
- Schwartz formula not validated < two years of age.
- Some patients may also be lost to follow-up, and thus long term side effects and complications may not be detected.
- Comparison of historical cohorts is not an ideal comparison as there may be confounding factors such as changes in nutrition, changes in access to medical care over time, different clinicians managing patients etc.

8. Study timelines

Year	2021										2022												2023		
Month	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
Literature review																									
Preparing protocol																									
Ethics application																									
Protocol assessment																									
Collecting data																									
Data Analysis																									
Writing and submission																									

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10. Appendices

Appendix 1: Kidney Disease: Improving Global Outcomes (KDIGO) staging of AKI ¹⁰

Stage	Serum creatinine	Urine output
1	Increase by 1.5 – 1.9 times baseline within 7 days OR Increase by ≥ 0.3 mg/dL (26.5 μ mol/L) within 48 hours	Less than 0.5 mL/kg/h for 6–12 hours
2	Increase by 2 – 2.9 times baseline	Less than 0.5 mL/kg/h for ≥ 12 hours
3	Increase by ≥ 3 times baseline OR Increase to ≥ 4 mg/dL (353.6 μ mol/L) OR Renal replacement therapy initiation OR In patients younger than 18 years, decrease in estimated GFR to < 35 mL/min/1.73 m ²	Less than 0.3 mL/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Appendix 2: Stages of CKD for children based on the KDIGO 2012 clinical practice guideline:¹⁹

GFR category	GFR (mL/min/1.73m ²)	Terms
G1	≥ 90	Normal or high
G2	60 – 89	Mildly decreased
G3a	45 – 59	Mildly to moderately decreased
G3b	30 – 44	Moderately to severely decreased
G4	15 – 29	Severely decreased
G5	< 15	Kidney failure*

*Kidney failure: defined as a state of permanent loss of kidney function, requiring long-term dialysis or kidney transplantation to sustain life.

Appendix 3: See REDCap data collection sheets

Appendix VI: Data collection sheets

Confidential

MMed Bothma
Page 1

Study information at diagnosis

Study ID

Hospital number

Age (years)

Gender

☐ Female
☐ Male

Comments

Demographic information

Study ID

Platinum based regime given

- ☐ Cisplatin-based (Group 1)
☐ Carboplatin-based (Group 2)

Hospital treated

- ☐ CMJAH
☐ WDGMC

Weight (kilograms)

Height/Length (cm)

BMI

Body surface area

Creatinine (umol/L)

Calculated GFR (ml/min/1.73m²)

Tumour information

Study ID

Type of tumour

- ☐ Ovarian dysgerminoma
 - ☐ Seminoma of testes
 - ☐ Choriocarcinoma
 - ☐ Yolk-sac tumour
 - ☐ Embryonal carcinoma
 - ☐ Extragenital germinoma
 - ☐ Mixed GCT
-

Site of tumour

- ☐ Ovary
 - ☐ Testis
 - ☐ Retroperitoneum
 - ☐ Sacrococcyx
 - ☐ Mediastinum
 - ☐ Head and neck
 - ☐ Other
-

Staging of tumour

Risk stratification

- ☐ Low risk
 - ☐ Medium risk
 - ☐ High risk
-

Pre-existing medical conditions:

- ☐ None
 - ☐ Renal dysfunction
 - ☐ Hydronephrosis
 - ☐ Other
-

Elaborate on comorbidities:

Chemotherapy given

Study ID

Chemotherapy protocol given

- ☐ BEP: cisplatin based
☐ JEB: carboplatin based

Duration/cycles of chemotherapy:

Cumulative platinum dose received:

Complications during chemotherapy:

- ☐ Neutropaenic sepsis
☐ Nephrotoxicity
☐ Ototoxicity
☐ Myelosuppression
☐ Gastrointestinal symptoms
☐ Other

Elaborate on complications:

Drugs given during chemotherapy:

- ☐ Aminoglycosides
☐ Glycopeptides
☐ Antifungal therapy
☐ Furosemide
☐ NSAIDS
☐ Other nephrotoxins

Special investigations

Study ID

Serum calcium:

Serum magnesium:

Serum phosphate:

Serum sodium:

Serum potassium:

Serum urea:

Serum creatinine:

Blood gas results:

Urine dipstick

- ☐ NAD
- ☐ Protein
- ☐ Glucose
- ☐ Leucocytes
- ☐ Nitrites

Urine protein:creatinine ratio

Urine electrolytes

Abdominal sonar:

- ☐ Yes
- ☐ No
- (if yes: Elaborate)

Other:

Follow-up visits

Study ID _____

Intervention for AKI:

- ☐ None needed
- ☐ Intravenous fluids
- ☐ Electrolyte supplementation
- ☐ Renal replacement therapy

Acute kidney injury:

- ☐ yes
- ☐ no
- ☐ not recorded

Staging of AKI:

- ☐ stage 1
- ☐ stage 2
- ☐ stage 3

Renal replacement therapy:

- ☐ not applicable
- ☐ dialysis
- ☐ transplantation

Chronic kidney disease:

- ☐ yes
- ☐ no
- ☐ not recorded

If yes for CKD: Staging

- ☐ stage 1
- ☐ stage 2
- ☐ stage 3
- ☐ stage 4
- ☐ stage 5

Long term renal pathology: (2years)

- ☐ normal kidney function
- ☐ chronic kidney disease
- ☐ tubulopathy
- ☐ dead
- ☐ lost to follow up

Long term survival: (2years)

- ☐ Alive and disease free
- ☐ Alive with disease
- ☐ Dead
- ☐ Lost to follow-up

Completion Data

Study ID

Has patient completed chemotherapy?

- ☐ No
☐ Yes
☐ Not recorded

Relapse, requiring further chemotherapy:

- ☐ Yes
☐ No

Last chemotherapy date:

Date of last visit:
