

Drug Therapy Problems and Associated Factors in Management of Wilms' Tumor Among Pediatric Patients in Kenyatta National Hospital

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Drug therapy problems are common during the management of pediatric cases of Wilms' tumor. They can lead to events requiring further medical attention thus complicating the therapy process and increasing the cost of treatment. The objective of this study was to determine drug therapy problems and the associated factors among pediatric Wilms' tumor patients at Kenyatta National Hospital. A cross-sectional study recruiting pediatric patients (0 - 15 years) and their guardians was implemented. Data collection was done using a questionnaire and data abstraction tools. Chi square test and logistic regression in STATA version 15, were applied to identify possible associations between drug therapy problems and sociodemographic and clinical factors. Significance was set at ≤ 0.05 . Between February and August 2023, 66 children were enrolled, mostly female (53%) with a median age of 4 (IQR 2-6) years. The most common drugs used were vincristine and cyclophosphamide/ doxorubicin combination. Drug therapy problems found were the need for additional therapy, adverse drug reactions and unnecessary drug therapy. Stage I of Wilms' tumor was associated with unnecessary drug therapy (cOR 18, 95% CI 2.71 – 119.79, $p = 0.003$). Need for additional therapy, adverse drug reactions and unnecessary drug use were the drug therapy problems identified. Continuous review and education of patients during therapy would be beneficial to reduce occurrence of drug therapy problems.

Key Words: Wilms' Tumor, drug therapy problems

INTRODUCTION

A drug therapy problem (DTP) is defined as an event that patients experience, which is not desirable, that involves or is suspected to involve therapy with medications and that interferes with achieving the goals of therapy and requires medical intervention.¹ Drug therapy problems present a challenge as they affect the patient's outcomes which result in longer hospital stays, increased cost of treatment, enhanced morbidity and mortality.² Management of cancer patients presents a great risk of DTP occurrence due to the toxic nature of chemotherapeutic agents³, narrow therapeutic range and their potential to cause serious adverse effects at therapeutic doses.⁴

The DTPs are classified into several categories including unmanaged indication, medication use without indication, sub-therapeutic dose, overdose of medication, adverse drug reaction, inappropriate drug selection, and failure to receive the prescribed medication.¹ Drug

therapy problems cost billions of dollars in healthcare costs annually in America.¹ DTPs occur worldwide with studies conducted in specific countries showing a prevalence of 3.2% in France, 6.2% in Germany, 1.8% in India among hospitalized patients.⁵ A study on DTPs among cervical cancer patients at Kenyatta National Hospital (KNH) showed a prevalence of 93.8% with adverse drug reactions being the most prevalent at 69% and drug interactions at 47%.⁶

Wilms' tumor (WT) accounts for more than 90% of primary renal tumors in the pediatric population and is therefore the most prevalent.⁷ Among all childhood cancers, WT accounts for about 5% of childhood cancers worldwide.⁸ In Kenya, about 8% of pediatric cancers in children aged 1-5 years are due to WT.⁸ Over a 20 year span (2001-2021), the incidence of WT has risen to 8.5% from 5% in Kenya.

Oncology patients generally require multiple drug therapy predisposing them to DTPs.⁹ The

DTPs observed among cancer patients in Kenya are reported to be mostly drug-drug interactions due to polypharmacy, adverse drug reactions and need for additional therapy.⁷ However, there is a dearth of information regarding DTPs among WT patients treated at KNH. The aim of this study was to identify the DTPs among pediatric WT patients and the factors associated with them.

MATERIALS AND METHODS

A hospital based cross-sectional study was implemented in February - August 2023 at the KNH. The study participants were pediatric Wilms' tumor patients aged 0 - 15 years and admitted in KNH for management of Wilms' tumor within the study period. The inclusion criteria entailed a diagnosis of Wilms' tumor, age ≥ 15 years, informed consent from the guardian/parent or child (>5 years age) and at least one chemotherapeutic drug for management of WT administered not more than one week prior. Patients who fitted the following criteria were excluded; psychologically challenged children without a caregiver or guardian to fill the questionnaire, comorbid with any acute condition that would limit their participation in the study and those under 10 years, without a guardian or caregiver.

The calculated sample size using the Cochran formula¹⁰ was 77 participants, who were selected using simple random sampling, through the lottery method without replacement. Approval for the study was granted by Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH-ERC/A/151). Furthermore, authority to carry out the study was also granted by the Department of Research and Programs at KNH (KNH/PAEDS/48). Informed consent was obtained for all participants whilst maintaining patient confidentiality by eliminating direct patient identifiers with use of codes instead.

Data was collected using a pretested questionnaire. The data collected included participants' demographics and clinical data.

The data was entered into Microsoft Excel spreadsheet (Microsoft Inc, Redmont, WA, USA) and exported to Stata version 15 (Stata Corp LLC, College Station, TX, USA). Chi Square test for association was used and variables with p-value greater than 0.25 subjected to bivariate and multivariate logistic regression. Associations with $p \leq 0.05$ were considered statistically significant.

RESULTS

Sixty-six children who were placed on treatment for Wilms' tumor were studied for DTPs. There were more female (35,53%) than male (31, 47%) patients as shown in Table 1. The median age was 4 years, with an interquartile range of 2 to 6 years. Most patients (48, 72.7%) had a BMI below 18.5 kg/m^2 . Six patients were diagnosed at stage 1, three at stage 2, twenty-one at stage 3, twenty-eight at stage four disease, while among them, thirty-two had left sided disease, twenty-six with right sided disease and eight had bilateral disease. Most patients (56, 85%) were on post-operative therapy.

Twenty-nine participants reported symptoms that required additional therapy while thirty-seven had no complaints. The most prevalent complaint was nausea and vomiting as listed in Table 2. The most common drugs were vincristine as a single drug (39.4%) and cyclophosphamide/ doxorubicin combination (21.2%) (**Figure 1**). Majority of the study participants, 55 (83.3%) needed additional drug therapy, adverse drug reactions were found in 30 (45.5%) patients while 10 (15.2%) patients received medication that was deemed unnecessary.

Anaemia, leucopenia and pain were the most commonly experienced adverse drug reactions while anti-emetic therapy and prophylactic antibiotics were the most commonly used drugs which were not required. Most patients with an unmet need required hematinics and management of hyperkalemia (**Table 3**).

Table 1: Sociodemographic and clinical characteristics of study participants

Variable	n (%)
Sex	
Female	35 (53)
Male	31 (47)
Age	
<5	46 (69.7)
>5	20 (30.3)
BMI	
<18.5	48 (72.7)
18.5 – 24.9	10 (15.2)
25 – 29.9	8 (12.1)
Stage of cancer	
1	6 (9.1)
2	3 (4.6)
3	21 (31.8)
4	28 (42.4)
5	8 (12.1)
Primary tumor site	
Left Kidney	32 (48.5)
Right Kidney	26 (39.4)
Bilateral	8 (12.1)
Adverse symptoms	
Yes	29 (43.9)
No	37 (56.1)
Treatment phase	
Post op	56 (84.9)
Pre op	10 (15.2)

Table 2: Symptoms reported by Wilms' tumor patients

Symptom	Frequency (%)
Poor appetite	27 (40.9)
Weight Change	23 (34.8)
Pain	14 (21.8)
Dizziness	1 (1.5)
Tinnitus	1 (1.5)
Epistaxis	2 (3)
Hemoptysis	1 (1.5)
Hypertension	6 (9.1)
Dyspnea	3 (4.5)
Wheezing	2 (3)
Heart burn	10 (15.2)
Nausea & Vomiting	31 (47)
Diarrhea	7 (10.6)
Constipation	8 (12.1)
Rash	1 (1.5)
Dehydration	1 (1.5)
Hyponatremia	19 (28.8)
Hyperkalemia	23 (34.8)
Hematuria	2 (3)
Anxiety	1 (1.5)

A combination of cyclophosphamide and doxorubicin had significant association with the need for additional drug therapy at bivariable regression (cOR 0.14, 95% CI 0.04 – 0.58, $p = 0.006$) but lost significance at multivariable regression while Stage 1 of Wilms' tumor was significantly associated with the use of unnecessary drug therapy at bivariable level (cOR 18, 95% CI 2.71 – 119.79, $p = 0.003$), but could not undergo multivariable analysis as it was the only statistically significant factor (**Table 4**).

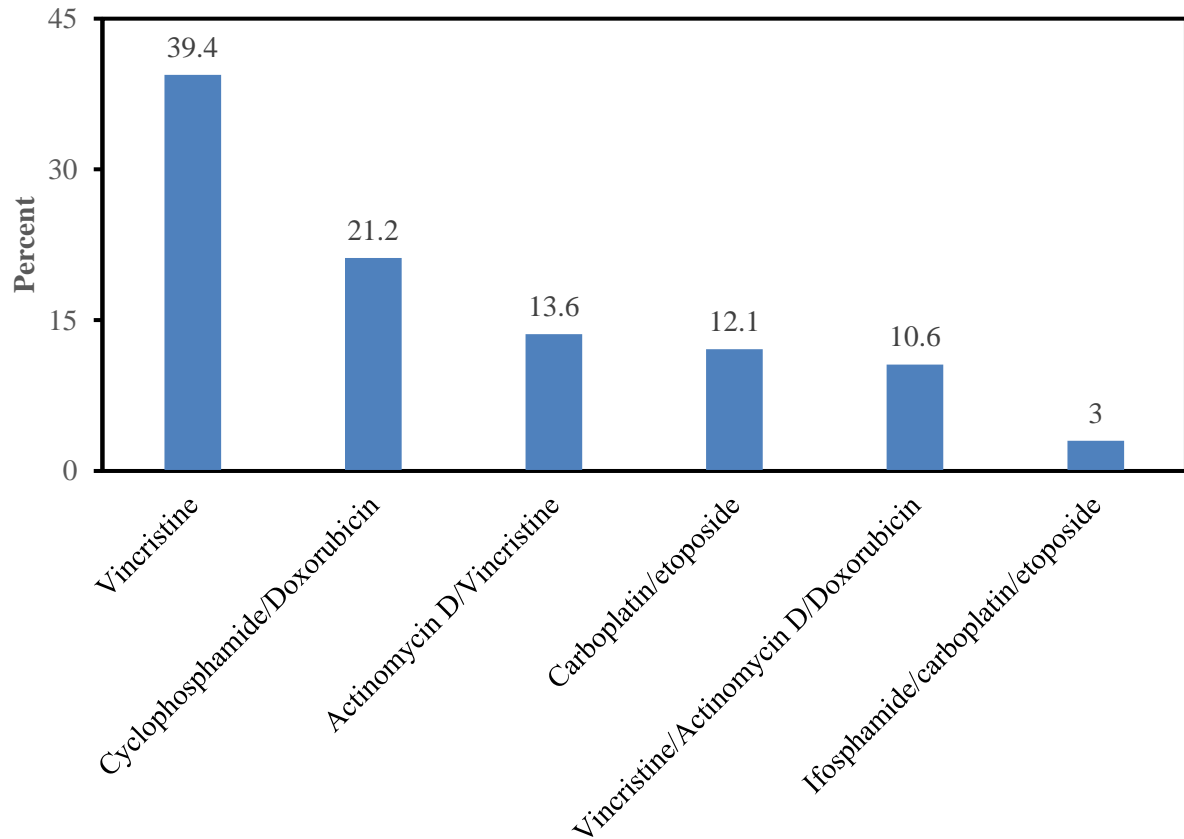


Figure 1: Frequency of chemotherapy drugs used in the management of pediatric Wilms' tumor.

Table 3: Summary of drug therapy problems.

ADR	n (%)	Needs Additional Therapy	n (%)	Unnecessary Drug Therapy	n (%)
Anaemia	16 (19.75)	Hematinic drug	30 (19.61)	Anti-emetic	6 (50)
Leucopenia	15 (18.52)	Hyperkalemia medication	22 (14.38)	Prophylactic antibiotic	1 (8.33)
Pain	13 (16.05)	Analgesic	20 (13.07)		
Hyperkalemia	9 (11.11)	Sodium supplement	18 (11.76)		
Hyponatremia	8 (9.88)	Appetite medication	16 (10.46)		
Nausea	5 (6.17)	Prophylactic antibiotic	16 (10.46)		
Constipation	5 (6.17)	GCSF	7 (4.58)		
Diarrhea	4 (4.94)	Laxative	7 (4.58)		
Hyperacidity	2 (2.47)	Anti-diarrhea	6 (3.92)		
		Antihypertensive	5 (3.27)		
		Antiemetic	3 (1.96)		
		Bronchodilator	2 (1.31)		

Table 4: Bivariate and multivariate logistic regression for associated factors of the drug therapy problems

Type of DTP	Independent variable	Bivariate analysis		Multivariate analysis	
		cOR (95% CI)	p-value	aOR (95% CI)	p-value
ADR	Vincristine (No/ Yes)	0.479 (0.173-1.327)	0.157	0.563 (0.195-1.620)	0.286
	Vincristine + Actinomycin D + Doxorubicin (No/Yes)	3.4 (0.609-18.972)	0.163	2.656 (0.45-15.69)	0.281
Need additional drug therapy	Age ($\leq 5, >5$)	0.45 (0.119-1.696)	0.238	0.587 (0.16-2.95)	0.518
	Vincristine (Yes, No)	8.333 (0.997-69.637)	0.050	5.244 (0.516-53.346)	0.161
	Cyclophosphamide + Doxorubicin (Yes, No)	0.142 (0.035-0.577)	0.006	0.326 (0.038- 2.773)	0.305
	Stage IV	0.353 (0.092-1.353)	0.129	0.916 (0.135-6.208)	0.929
Unnecessary drug therapy	Stage 1	18 (2.705-119.79)	0.003	N/A	

DISCUSSION

The chemotherapy regimens administered to pediatric Wilms' tumor patients in this study encompassed a variety of drug combinations. Vincristine was the most frequently used drug, followed by a combination of cyclophosphamide and doxorubicin. The DTP classes found were the need for additional therapy which was the most prevalent, followed by ADRs and unnecessary drug therapy. In this study, stage I Wilms' tumor was associated with unnecessary drug therapy. However, ADRs and the need for additional drug therapy had no associated factors.

The use of vincristine for both localized and metastatic disease and combination of cyclophosphamide and doxorubicin for metastatic disease aligns with the International Society of Pediatric Oncology (SIOP) guidelines from where the institutional protocol has been developed. This also agrees with findings by Breslow *et al.* and Jesper *et al.*, which found that use of vincristine alone or in

combination therapy pre and post operatively was associated with better prognosis for Wilms' tumor.^{11,12}

Among the DTP classes observed, majority of the patients had unmet need that required additional drug therapy. The need for hematinics, potassium lowering agents and analgesics were highlighted in the study. A study conducted in pediatric population in Ethiopia reported that there is high prevalence of the need for additional drug therapy among the pediatric population.¹³

Unnecessary drug therapies were also reported in this study with the overuse of antiemetics and prophylactic antibiotics being highlighted. In concordance with our study, overtreatment of cancer patients has been reported in various studies especially on the overuse of antiemetics and prophylactic antibiotics.¹³⁻²⁰ Schnipper *et al.* also reported overuse of cytotoxics in early cancer stages.²¹ In a general study on drug related problems in pediatric population in Ethiopia, unnecessary drug therapies were also

reported.¹³

Among the ADRs reported, anemia, leucopenia and pain were highly prevalent. In a study by Wahlang *et al.*, anemia and leucopenia were reported as the most common toxicities though in the same study, vomiting, constipation, and anorexia were the most prevalent.²² Schulte *et al.* reported that procedure and treatment related pain is common among pediatric cancer patients.²³

There was no association between age, sex and DTPs. A study done in a pediatric ward of Southwestern Ethiopian hospital found out that being a neonate was significantly associated with high prevalence of medication related problems.¹³ Lavan *et al.* reported that sex was not a predictor of ADRs in cancer patients.²⁴ These findings are however inconsistent with other studies which have reported that the female sex is at an increased risk of developing serious ADRs which even at times may require hospital admission.^{25–28}

Chemotherapeutic regimens used in management of Wilms' tumor were not associated with DTPs. Combination therapy which would directly contribute to polypharmacy has been significantly associated with occurrence of DTPs in pediatrics.²⁹ The difference in study findings was probably because even with the combination therapy, pediatrics rarely received five or more drugs that meet the threshold of polypharmacy as defined by Bjerrum *et al.* and Erika *et al.*^{30,31}

Cancer stage was neither associated with ADRs

nor need for additional drug therapy. In a study done at a tertiary hospital in Kenya, advanced cancer stage was associated with adverse drug reactions.⁶ However, it is paramount to note that this relationship was observed in patients aged 50 years and above who in addition to the cancer itself may present with higher prevalence of comorbidities.

Stage I of Wilms' tumor was associated with unnecessary drug therapy at bivariable level and being the only significant factor, it was not subjected to multivariable analysis. This stage is associated with better prognosis and require less intensive therapy as described in SIOP protocol.³²

The main limitation of this study was the small sample size. Despite that, a report on the presence of DTPs among this previously unstudied group of pediatric patients was made.

CONCLUSION

The management of Wilms' tumor entails the use of a variety of drug combinations which was evident in this study. This complexity of treatment regimens places patients at risk of DTPs. In the present study, majority of patients required additional therapy, further supporting the need for critical review of Wilms' tumor patients to address any unmet need. The use of drug monitoring tools and drug interaction checkers is encouraged to limit the occurrence of DTPs during the management of Wilms' tumor patients.

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