Aspects of the management of children with cancer in Malawi

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Malnourished Malawian patients presenting with large Wilms tumours have a decreased vincristine clearance rate

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Abstract

**Introduction** In developing countries, patients with a Wilms’ tumour often present late with a high degree of malnutrition and large tumours. We investigated whether this affects vincristine pharmacokinetics.

**Methods** Patients newly diagnosed with Wilms’ tumour in Malawi and the UK were included. We documented anthropometric parameters, nutritional status and tumour size. Vincristine (1.50 mg/m²) was administered as part of the standard chemotherapy regimen. Vincristine plasma concentrations were measured at several time points by liquid chromatography-mass spectrometry. Vincristine pharmacokinetic parameters (clearance and area under the curve) were calculated by non-compartmental analysis.

**Results** 11 Malawian and 8 UK patients were included. Mean Z-score of (corrected) weight for height was significantly lower in the Malawian patients than in the UK patients (-2.3 versus 0.42, p <0.0001). Mean tumour weight at diagnosis was significantly larger in Malawian patients (2.8 kg versus 0.7 kg, p=0.007). Mean vincristine logClearance was lower in Malawian as compared to UK patients (2.2 versus 2.6 ml/min, p=0.001). Mean logAUC values were higher in Malawian than in UK patients (3.8 versus 3.5 μg/ml.min, p=0.003). This difference is reflected in the, on average, 1.98-fold larger vincristine AUC values for Malawian patients. The difference in AUC values was statistically significantly explained by nutritional status (p =0.043).

**Conclusion** Malnourished patients in Malawi exhibited lower vincristine clearance rates and thus higher AUC values than a comparable patient population with a better nutritional status in the UK. In malnourished patients, dose reductions may need to be considered to prevent an increased incidence and severity of toxicity.
Introduction

The incidence of Wilms’ tumour worldwide in children under 15 years of age is approximately eight per million children per year. Over the past 40 years, the development of a multidisciplinary treatment approach, consisting of a combination of chemotherapy, surgery and, in selected cases, radiotherapy, has improved overall long term survival rates to 85-90% in Europe and the US.\textsuperscript{1} In Europe, preoperative chemotherapy is given to shrink the tumour, reduce the risk of surgical complications such as tumour rupture and induce a more favourable tumour stage at surgery.\textsuperscript{2-4} Preoperative chemotherapy according to the International Society of Paediatric Oncology (SIOP) protocol for localized disease consists of a combination of intravenous vincristine and actinomycin D for four weeks.\textsuperscript{5} This protocol, in line with many others, recommends that vincristine is dosed empirically on the basis of body surface area. The vincristine dosing regimen recommended by SIOP for the treatment of Wilms’ tumour is 1.5 mg/m\textsuperscript{2} given as an intravenous bolus infusion on each of weeks 1 - 4. A 33% dose reduction is implemented for children with a body weight < 12 kg.\textsuperscript{4}

In developing countries, patients with a Wilms’ tumour often present late with large tumours and a marked degree of malnutrition.\textsuperscript{5-7} Eleven of 20 patients with Wilms’ tumour in Malawi (55%) were acutely malnourished at diagnosis, indicated by an arm muscle area < 5\textsuperscript{th} percentile.\textsuperscript{8} Mean tumour volume at diagnosis was 2500 ml (range 500 – 8200 ml), compared to a mean tumour volume of 470 ml in European patients in the SIOP 9 study.\textsuperscript{4,8} Patients in Malawi are treated with preoperative chemotherapy according to the SIOP protocol described above. Dosing regimens implemented for the treatment of Wilms’ tumour patients may be particularly important as vincristine, in common with many other anticancer drugs, has a relatively narrow therapeutic index and is associated with potentially life-threatening toxicity in the form of neuropathy. There are a limited number of reports concerning the pharmacokinetics of vincristine in children. Considerable intra- and inter-patient variation in pharmacokinetic parameters have previously been reported.\textsuperscript{9-11} Further clinical pharmacology studies in defined patient populations are required in order to obtain information which may be used to improve its future therapeutic potential.\textsuperscript{12-18}

The pharmacokinetics of drugs can be profoundly influenced by body composition, with changes in drug disposition observed in numerous studies in both obese and malnourished patient populations.\textsuperscript{19,20} In this respect, altered pharmacokinetics of doxorubicin have previously been reported in malnourished children.\textsuperscript{21} Differences in vincristine pharmacokinetics between children with normal nutritional status and those with malnutrition may be expected, relating to altered liver and renal function and differences in body composition, which may impact on drug distribution.
Additionally, as vincristine exhibits a relatively high level of plasma protein binding, decreased concentrations of plasma proteins in malnourished children may affect plasma protein binding and the proportion of free drug.\textsuperscript{22}

This study aimed to evaluate the pharmacokinetics of vincristine in Malawian patients with a Wilms’ tumour presenting with malnutrition and large tumours, as compared to patients diagnosed and treated in the UK.

Patients and methods

All patients younger than 18 years who presented at the Queen Elizabeth Central Hospital with a renal mass compatible with a clinical and ultrasound diagnosis of Wilms’ tumour were eligible. As a control group, patients younger than 18 years, diagnosed with a localized Wilms tumour in the UK were eligible. The UK patients were required to have central venous access and were included only if samples up to 24 hours post vincristine administration had been taken. Informed consent from the parents was required for all patients entered onto the study. The study was approved by the appropriate ethical bodies related to the institutions where the study was performed.

Age, sex, body weight and height were documented for all patients and serum levels of total protein, albumen, prealbumen, creatinine, alkaline phosphatase (AP), aspartate amino transferase (AST) and alanine amino transferase (ALT) were determined for Malawian patients.

Tumour size was determined by ultrasonography (Malawian patients), CT scan or MRI analysis. The tumour was measured in three dimensions and the tumour volume calculated using a standard ellipsoid formula ($\text{length} \times \text{width} \times \text{height} \times 0.523$).\textsuperscript{23} Corrected weight (body weight – estimated tumour weight) was calculated and Z-scores for (corrected) weight for height (WHZ) were derived in reference to the 1978 NCHS growth curve (HANES data) to express the degree of acute malnutrition.\textsuperscript{24}

Vincristine (1.50 mg/m$^2$) was administered by intravenous bolus injection as part of the standard chemotherapy regimen that each patient was receiving. Dose reductions to 2/3 of the standard dose were implemented if the body weight of the patient was below 12 kg.

Blood samples for measurement of vincristine concentration were obtained prior to administration and at the following time points: 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 24 h. The actual times that samples were taken were recorded on each day of treatment and these accurate sampling times were used for pharmacokinetic analysis. In Malawian patients, additional blood samples were taken at 15 min and
6 h to determine unbound vincristine concentrations. Following withdrawal, blood samples were centrifuged at 1,200 g for 10 min at 4°C and plasma was stored at -20°C prior to transport to reference laboratories in Amsterdam and Newcastle for analysis.

For the quantification of vincristine in samples analysed in Amsterdam, a previously described high-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method was used. Analysis of samples in Newcastle was carried out using a validated liquid chromatography-mass spectrometry (LC-MS) assay. These methods have a lower limit of quantification (LLOQ) of 0.25 and 0.50 ng/ml respectively. Cross-validation of the assays was carried out involving analysis of a selected number of patient samples in both Amsterdam and Newcastle laboratories. For the quantification of the protein-unbound vincristine fraction, ultrafiltrate was prepared from plasma.

Vincristine pharmacokinetic parameters were calculated for all patients by non-compartmental analysis using the Stata (Release 10) software package for intravenous bolus injection. The area under the plasma concentration-time curve (AUC) was calculated from 0 to 24 hours using the trapezoidal rule.

Statistical differences in numerical patient characteristics between the patient populations were investigated using the independent sample t-test. Because of small sample size t-test results were verified with a non-parametric Mann-Whitney U test. Since the tests coincided, only t-test results are denoted. Difference in categorical characteristics were tested with a Fisher Exact test. Pharmacokinetic parameters (vincristine clearance and AUC) were 10log-transformed before analysis, because of their skewed distribution. Again population differences were tested with an independent t-test. Linear regression was used to assess the correlation between logAUC and patient characteristics that might influence pharmacokinetics.

Results

Patient characteristics

A total of nineteen patients with localized Wilms tumour were entered onto the study, including 11 patients from Malawi and 8 patients from the UK. The mother of one Malawian patient refused informed consent. The study population had a mean age of 4.6 years (range 1.0 – 9.6 years), mean bodyweight of 17.1 kg (range 9.3 – 39.7 kg) and mean surface area of 0.71 m² (range 0.44 – 1.3 m²) and included 6 girls and 13 boys. Patient characteristics for the 19 evaluable patients are given in Table I.
Mean age was comparable in both groups; 4.5 years in Malawian children, 4.6 years in children from the UK (p = 0.91). Mean body weight was lower in Malawian children (15.0 kg) than in UK children (20.2 kg), but not statistically significant (p = 0.09). Body surface area was lower in Malawian children but not statistically significant (0.65 m² versus 0.79 m²; p = 0.11).

**Nutritional status at diagnosis**

We used the Z-score of corrected weight for height (Z-score Wt/Ht) to assess nutritional status. In Malawian patients the mean Z-score Wt/Ht was significantly lower (−2.3, SD 1.3) than in UK patients (0.42, SD 0.8) (p < 0.0001). Seven of the eleven Malawian patients (64%) had a corrected weight for height Z score < -2, indicating severe acute malnutrition. Figure 1 shows the range of Z-scores observed for Wilms’ tumour patients studied in both Malawi and the UK.

<table>
<thead>
<tr>
<th></th>
<th>Malawi N=11</th>
<th>UK N=8</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9 -82%</td>
<td>4 -50%</td>
<td>0.319</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>4.5 ± 2.6</td>
<td>4.6 ± 2.1</td>
<td>0.912</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>15 ± 3.9</td>
<td>20 ± 8.4</td>
<td>0.091</td>
</tr>
<tr>
<td>Surface area (m²)</td>
<td>0.65 ± 0.13</td>
<td>0.79 ± 0.22</td>
<td>0.113</td>
</tr>
<tr>
<td>Tumour weight (kg)</td>
<td>2.8 ± 2.1</td>
<td>0.7 ± 0.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Z-score corrected weight for height</td>
<td>-2.3 ± 1.3</td>
<td>0.4 ± 0.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± sd

![Fig 1 Z-scores (corrected weight for height) observed in UK and Malawian Wilms tumour patient populations](image_url)
Tumour weight at diagnosis
For Malawian patients, the estimated tumour weight at diagnosis also represented the tumour weight when the pharmacokinetic study was carried out. For UK patients, the pharmacokinetic study was carried out at a later date, with a mean time interval of 1.1 months (range 0.7 – 24 months). In Malawian patients, mean tumour weight at diagnosis was higher than in UK patients, with mean tumour weights of 2.8 kg (SD 2.1, range 0.9 to 8.2 kg) and 0.7 kg (SD 0.4, range 0.4 to 1.3 kg) calculated in the two patient populations respectively (p = 0.007).

Vincristine treatment
The mean dose of vincristine administered across the study population was 1.0 mg (range 0.4 – 2.0 mg) or 1.43 mg/m² (range 0.91 – 1.57 mg/m²). Dose reductions (to 2/3 of the dose) were implemented in two Malawian patients and one UK patient because their body weight was below 12 kg. Vincristine doses were not significantly different between the two groups. Malawian patients received a mean dose of 0.94 mg (SD 0.28, range 0.5-1.4 mg) as compared to a mean dose of 1.16 mg (SD 0.41, range 0.55 – 2.0 mg) in UK patients (p = 0.2). Doses were also comparable when expressed in terms of body surface area. Malawian patients received 1.41 mg/m² (SD 0.21, range 0.91 – 1.57) compared to 1.45 mg/m² (SD 0.19, range 1.0 – 1.56 mg/m²) in UK patients (p= 0.7). Details of vincristine doses administered to all patients are provided in Table II.

Vincristine pharmacokinetics
Plasma samples were obtained from 19 patients prior to vincristine administration and over a 24h period after administration of vincristine. A total of 6 samples were obtained from each of the 11 Malawian study patients, with 5-7 samples obtained from 8 patients studied in the UK. All vincristine plasma concentrations in post-administration samples were above the lower limit of quantification for the assays utilised.

Clearance
Median vincristine clearance (Cl) values of 211.3 ml/min (range 93.5 to 896.5 ml/min) or 278.0 ml/min/m² (range 125.5 – 825.3 ml/min/m²) were observed across all patients, both Malawian and UK, studied. Mean logClearance was lower in Malawian as compared to UK patients, with meanlogCl values of 2.2 ml/min (SD 0.17, range 2.0 to 2.5) and 2.6 ml/min (SD 0.26, range 2.1 to 3.0) respectively (p=0.001). Expressed in terms of body surface area, mean logCl in Malawian patients was 2.4 ml/min/m² (SD 0.14, range 2.1 to 2.6) as compared to 2.7 ml/min/m² (SD 0.21, range 2.2 to 2.9) in UK patients (p = 0.001). Figure 2A shows a
comparison of vincristine logClearance values in Wilms tumour patients treated in the UK and Malawi.

Area under the curve (AUC)

AUC values of 1.6 to 11.4 μg/ml.min were observed across the Wilms’ tumour population studied, with logAUC values of 3.2 to 4.1 μg/ml.min. Mean logAUC values were higher in Malawian than in UK patients, with mean values of 3.8 μg/ml.min (SD 0.15, range 3.6 to 4.1) and 3.5 μg/ml.min (SD 0.22, range 3.2 to 3.9) respectively (p = 0.003). This difference is reflected in, on average, 1.98-fold larger vincristine AUC values for Malawian patients than for UK patients (95% confidence interval (CI) 1.39, 2.99). A comparison of vincristine logAUC values in these two patient populations is shown in Figure 2B.
Analysis of variables possibly influencing AUC

We calculated the log(10)AUC to transform the AUC into a less skewed distributed variable which is a (pre)condition to perform a linear regression analysis as presented below. Across the whole patient population, age did not explain the difference in AUC ($p = 0.82$) and neither did vincristine dose as expressed per m$^2$ ($p = 0.42$). Body weight ($p = 0.3$) and vincristine dose ($p = 0.6$) did not significantly contribute to the difference in logAUC.

Fig 2 Vincristine logClearance (A) and logAUC (B) values in UK and Malawian Wilms’ tumour patient populations

Decreased vincristine clearance in malnourished patients
Nutritional status

Nutritional status, expressed as Z-score for corrected weight for height, was shown to significantly contribute to the difference in logAUC. Linear regression analysis indicated that a decrease of -1 in Z-score was associated with a change in log10AUC of +0.061 (p = 0.043). This translates into a 13% increase in AUC on the non-transformed scale, i.e. higher AUC values were exhibited by the more malnourished patients. This association is shown in Figure 3.

![Figure 3](image_url)

Fig 3 Relationship between patient nutritional status as determined by Z-score for corrected weight for height and logAUC of vincristine in patients with Wilms’ tumour.

Tumour weight

Tumour weight did not significantly contribute to the differences found in logAUC across the population studied (p=0.20). In UK patients, tumour weight was estimated at diagnosis and pharmacokinetics sampling carried out later. For this reason, we also analysed the relationship between tumour size and logAUC separately for the Malawian patients only. Again, no significant relationship between tumour weight and logAUC was observed (p=0.338).
Correlation nutritional status and tumour weight
Nutritional status, as determined by Z-score for corrected weight for height, and tumour weight were closely correlated \( r = -0.848, \ p<0.0001 \).

Laboratory values patients Malawi
Laboratory values and protein status at diagnosis were documented only for Malawian patients and are summarised in Table III. Liver enzymes and creatinine were analysed to screen for any dysfunction of liver and/or kidney in these malnourished children which might affect vincristine clearance. All laboratory values (creatinin, sodium, alkaline phosphatase (AP), alanineaminotransferase (ALT)) were within normal limits, except for a slightly increased potassium level in 3 patients with a maximum of 5.5 mmol/L and a slightly increased levels of aspartate aminotransferase (AST), with a maximum of 127 i.u./L, in 10 of 11 patients.

Protein binding of vincristine
Protein status was evaluated in this malnourished patient population to investigate whether this affected protein binding of the drug. Nine of 11 patients had an albumen level below the normal values of 37 – 55 g/L, with a mean value of 30 g/L (range 22 g/L to 38 g/L). Four of 11 patients had a total protein below the normal values of 60 - 80 g/L, with a mean value of 65 g/L (range 51 g/L to 82 g/L). The fraction of vincristine bound to protein in the Malawian patient population was found to be 69.4 % (SD 4.6, range 62.4 – 74.9 %).

Discussion
This study aimed to evaluate the pharmacokinetics of vincristine in Malawian patients with a Wilms’ tumour presenting with malnutrition and large tumours, as compared to control patients treated with a comparable vincristine dosing regimen in the UK.
A clear difference in nutritional status between the two patient populations was found, highlighted by the fact that the patient with the poorest nutritional status in the UK group had a higher Z-score than the least malnourished Malawian patient. A limitation in this assessment is that the actual pharmacokinetic study was carried out in the UK patients at variable times after the tumour weight was estimated. Assuming though that most tumours will shrink during preoperative chemotherapy, had tumour weight been estimated at the time of the pharmacokinetic study, the actual tumour weight would have been lower, the corrected weight higher and thus the difference between the two groups even larger. Similarly with respect
to tumour weights, which were higher in Malawian patients, it is likely that this difference would only have been larger if tumour weight in the UK patients had been determined at the time of the pharmacokinetic study.

A significantly lower vincristine clearance and correspondingly higher AUC was found in the Malawian children studied. This could be clinically relevant as the Malawian patients exhibited vincristine AUC values approximately 2-fold larger than those in UK patients.

Following linear regression analysis, nutritional status (as evaluated with Z-score for corrected weight for height) was shown to be a significant contributor to the differences in AUC found. A decrease of -1 in Z-score was associated with a 13% increase in AUC ($p=0.043$). In this study, we did not find statistically significant evidence for a contribution of tumour weight to the differences in AUC. However, we can not exclude a contribution of tumour weight per se in this study, bearing in mind that malnutrition and tumour size are highly correlated, the imperfect documentation of tumour size in the control patients in this study and the small sample size.

It would be interesting to know whether the increased vincristine AUC observed in Malawian patients is associated with an increased tumour response. This study does not provide data to support or reject that hypothesis. In a previously published study, involving many patients included in the current study, we found that tumour

### Table III. Laboratory values at presentation for the Malawian patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Alb g/L</th>
<th>Prot g/L</th>
<th>Sod mM</th>
<th>Pot mM</th>
<th>Creat μmol/L</th>
<th>AP iu/L</th>
<th>AST iu/L</th>
<th>ALT iu/L</th>
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<tbody>
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<td>2.</td>
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<td>4.</td>
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<td>4.8</td>
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<td>7.</td>
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<td>24</td>
<td>54</td>
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<td>6</td>
</tr>
</tbody>
</table>

Alb = albumen; Prot = Total protein; Sod = Plasma sodium; Pot = plasma potassium; Creat = plasma creatinin; AP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanineaminotransferase; g/L = gram/Litre, mM = mmol/Litre; iu/L = international units per litre.
responses in Malawian patients with localized disease were comparable to those documented in European patients in the SIOP 9 study. In the Malawian patients 6 of 11 (55%) showed a >50% reduction in tumour size, compared to 52 % of patients in the SIOP 9 study.\textsuperscript{5,9}

An additional question would be whether an increased vincristine AUC is associated with an increased toxicity in Malawian patients. In the previous study we found that toxicity was increased in Malawian patients compared to European patients.\textsuperscript{5,9}

The most important toxicity was haematological, with 6 of 10 Malawian children treated with two drugs (actinomycin/vincristine) and 5 of 8 children treated with three drugs (adding doxorubicin) experiencing grade 3/4 anaemia. It is unknown whether this increased toxicity is caused by a reduced patient tolerance, related to nutritional status, or due to an increased exposure to the drug in terms of AUC.

In our study, 69.4 % of the vincristine was found to be bound to proteins in Malawian patients. Despite their very low albumen and relatively low total protein levels, this percentage of binding is comparable to the percentage of 58% protein binding found by Donigian.\textsuperscript{24}

The laboratory values in Malawian patients do not indicate any liver or kidney dysfunction associated with malnutrition which would explain the decreased clearance and correspondingly higher AUC.

A limitation of this study is that pharmacogenetics in these, racially different, groups were not studied. Variation in drug metabolising enzymes such as CYP3A4 and CYP3A5, or drug transporters, many of which exhibit racial differences in prevalence of genetic variants, can not be ruled out. Expression of CYP3A5, which plays a key role in vincristine metabolism, varies significantly according to race, with a greater proportion of African-Americans and Asians being high expressors as compared to Caucasians.\textsuperscript{28} However, such an impact of CYP3A5 expression would cause an increased clearance in association with an increase in vincristine metabolism, i.e. the reverse of the trend observed in our study.

In conclusion, the results of this study show a significantly decreased clearance and increased AUC of vincristine in malnourished patients with larger tumours. A decrease in vincristine dose may need to be considered in malnourished patients, especially if they experience severe toxicity.

Acknowledgements

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Patient with IV drip for the pharmacokinetic study.

Documenting the time of the blood sampling.
References


