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BRIEF REPORT

Vincristine exposure in Kenyan children with cancer: CHAPATI feasibility study

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Abstract

The low incidence of vincristine-induced peripheral neuropathy (VIPN) in Kenyan children may result from low vincristine exposure. We studied vincristine exposure in Kenyan children and dose-escalated in case of low vincristine exposure (NCT05844670). Average vincristine exposure was high. Individual vincristine exposure was assessed with a previously developed nomogram. A 20% dose increase was recommended for participants with low exposure and no VIPN, hyperbilirubinemia, or malnutrition. None of the 15 participants developed VIPN. Low vincristine exposure was seen in one participant: a dose increase was implemented without side effects. In conclusion, the participants did not develop VIPN despite having high vincristine exposure.

KEYWORDS
feasibility study, individualized dosing, pediatric oncology, pharmacokinetics, sub-Saharan Africa, vincristine

Abbreviations: ALL, acute lymphoblastic leukemia; AUC, area under the curve; CTCAE, Common Terminology Criteria for Adverse Events; CYP450, cytochrome P450; IQR, interquartile range; OATP1B3, organic anion-transporting polypeptide 1B3; PD, pharmacodynamics; ped-mTNS, pediatric modified total neuropathy scale; PK, pharmacokinetics; VIPN, vincristine-induced peripheral neuropathy.

Gertjan Kaspers and Festus Njuguna contributed equally to this work.

1 | INTRODUCTION

Vincristine is an anticancer drug that is part of many childhood cancer treatment protocols.[1,2] It exerts its cytotoxic effect by binding to tubulin in tumor cells. However, tubulins are abundant in neurons as well, and the main side effect of vincristine is therefore vincristine-induced peripheral neuropathy (VIPN), a sensory-motor neuropathy that often presents with numbness or pain in the hands and feet or constipation.[1,2]

The vincristine dose is generally capped at 2.0 mg (1.5 mg/m^2) to avoid excessive toxicity. A trial in predominantly White children attempted to increase the dose to 2.0 mg/m^2 (maximum 2.5 mg), which led to severe VIPN.[3] Interestingly, this dose is standard-of-care for children treated in western Kenya and is well tolerated: less than 5% develop VIPN.[4,5] Indeed, several studies have established the lower risk of VIPN in Black children,[6–9] which might be explained by pharmacogenomics. Vincristine is metabolized by cytochrome P450 (CYP) 3A4 or 3A5, of which the latter is more efficient.[10,11] As Black patients more frequently express CYP3A5,[4,12,13] they likely metabolize vincristine quicker, leading to lower plasma concentrations[4] and a lower risk of VIPN.[14,15] Toxicity is generally something to be avoided, but as the mechanism underlying vincristine toxicity and efficacy is similar,[1,2] VIPN may be considered on-target toxicity. Indeed, higher systemic exposure is associated with an increased risk of VIPN and lower relapse rates.[14–16] Therefore, a pharmacokinetic (PK) study assessing vincristine exposure in the possibly underdosed Kenyan population is warranted.

In the CHAPATI feasibility study, we studied vincristine exposure in Kenyan children with cancer, and incorporated pharmacokinetically (PK)-guided dose escalation in case of low exposure.

2 | METHODS

2.1 | Participants

Eligible patients were between 5 and 14 years old, newly or previously diagnosed with acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), rhabdomyosarcoma, neuroblastoma, or nephroblastoma, and scheduled to receive at least two vincristine doses (Appendix SI). Based on findings from a previous study,[4] we performed a quality control of locally dispensed vincristine according to the European Pharmacopoeia (Ph. Eu.) method.[17] Patients were ineligible in case of moderate–severe malnutrition, hyperbilirubinemia, severe mental retardation, or peripheral neuropathy (Appendix SII).

Patients and their legal guardians provided informed written consent and assent as appropriate. The study was approved by Kenyan regulatory institutions (NCT05844670).

2.2 | Study intervention

Two milliliters of venous samples were collected at 60 (±15), 90 (±5), and 240 (±15) minutes after the end of vincristine intravenous (IV) push administration.[18] The samples were shipped temperature-controlled to the Netherlands, where the vincristine concentration was determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS).[19] Vincristine exposure was assessed using a pharmacometric nomogram in which the ratio between the individual observed concentration and the median concentration of European patients was determined.[18] A 20% dose increase was recommended for patients with low exposure and no VIPN, hyperbilirubinemia, and moderate/severe malnutrition; otherwise the standard-of-care dose was maintained. VIPN was assessed through Common Terminology Criteria for Adverse Events (CTCAE) version 5 items constipation, peripheral sensory and motor neuropathy, and neuralgia[20] and with the pediatric modified total neuropathy scale (ped-mTNS), with respective scores

TABLE 1 Demographic and descriptive data of the participants in the feasibility study.

	Total ($n = 15$)
Diagnosis, *n* (%)	
ALL	10 (66.7)
Nephroblastoma	2 (13.3)
NHL	2 (13.3)
Neuroblastoma	1 (6.7)
Age in years, median (IQR)	9.3 (8.2–10.3)
Male sex, *n* (%)	9 (60)
Dose in mg, median (IQR)	2.0 (1.7–2.2)
Number of on-study doses, median (IQR)	6 (5–8)
Nutrition status in SD score, median (IQR)	−0.5 (−1.9 to 0.5)
Bilirubin in μmol/L, median (IQR)	5.3 (3.1–17.5)
VIPN according to CTCAE, *n* (%)	0 (0)
VIPN according to ped-mTNS, *n* (%)	0 (0)
ped-mTNS score, median (IQR)	0 (0–3)
CTCAE score, median (IQR)	0 (0–0)
Exposure to vincristine	Total ($n = 30$ occasions)
$T = 60$ minutes, *n* (%)	
Low exposure	6 (20)
Normal exposure	24 (80)
$T = 90$ minutes, *n* (%)	
Low exposure	1 (3)
Normal exposure	29 (97)
$T = 240$ minutes, *n* (%)	
Low exposure	0 (0)
Normal exposure	30 (100)
Overall, *n* (%)	
Low exposure	1 (3)
Normal exposure	29 (97)

Abbreviations: ALL, acute lymphoblastic leukemia; CTCAE, Common Terminology Criteria for Adverse Events; IQR, interquartile range; NHL, non-Hodgkin lymphoma; ped-mTNS, pediatric modified total neuropathy score; SD, standard deviation.

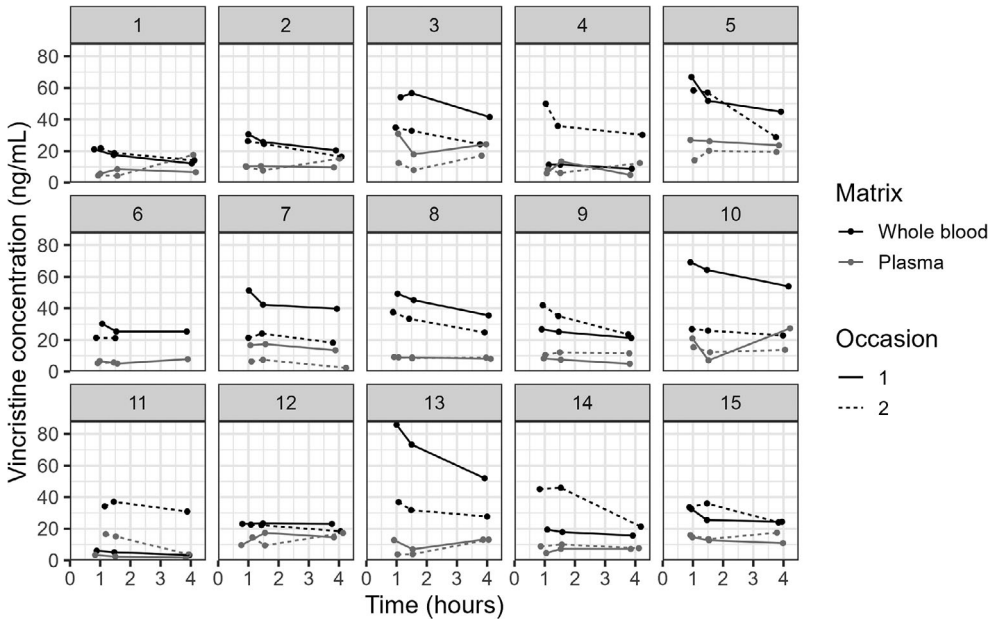

FIGURE 1 The individual time–vincristine concentration graphs of the participants. A dose increase was implemented for Patient 11 at Occasion 2. The $T = 240$-minute sample was missing in Patient 6.

of 2 and 5 and higher indicating VIPN.[21] VIPN assessments were performed at baseline, before, and 1 week after a dose, and at least monthly.

2.3 | Statistical methods

Descriptive and outcome data were summarized using frequency distributions, means with standard deviations (SD), and medians with interquartile ranges (IQR). Medians were tested with the Wilcoxon rank sum test. A two-sided p-value of $\leq .05$ was considered statistically significant. Analyses were conducted using R (version 4.2.1).[22]

3 | RESULTS

3.1 | Participants

Fifteen patients were included in the study, 10 of whom were diagnosed with ALL (Table 1, Figure S1). In one participant, the $T = 240$-minute sample was missing. Vincristine quality control showed 38% higher drug content than specified on the label claim (Appendix SIII).

3.2 | Outcomes

Vincristine exposure was significantly higher in the Kenyan participants than in the European patients used for the development of the nomogram: median plasma concentrations (ng/mL) and IQR at Time 1: Europeans = 3.89 (5.96), Kenyans = 9.81 (8.19), $p < .001$; Time 2: Europeans = 2.37 (0.95), Kenyans = 8.67 (6.15), $p < .001$; and Time 3: Europeans = 1.99 (3.07), Kenyans = 12.4 (9.41), $p < .001$)[18] (Figure 1, Figure S2A). The overall median plasma exposure was 150% higher in the Kenyan participants (10.00 ng/mL) than in the European participants (3.99 ng/mL). None of the participants developed VIPN (Table 1). Based on low vincristine exposure, a 20% dose increase (2.4 mg/m^2, 3.0 mg) was implemented in one participant without side effects (Table 1, Figure 1). Vincristine was given in 20–30 seconds as opposed to 2–3 minutes in 10 occasions; the median concentrations were however not significantly different (Figure S2B).

4 | DISCUSSION

This study showed that Kenyan participants had higher exposure to vincristine compared to European patients, but did not develop VIPN. It is therefore unlikely that a PK explanation accounts for this lack of VIPN.

The lower risk of VIPN in Black patients has been well established,[6–9] and is particularly apparent in Kenyan patients.[4] We hypothesized that this was due to more efficient metabolism and therefore lower blood concentrations. However, we found the opposite. This was partially, but not completely, explained by a higher dose as a consequence of a higher vincristine concentration in the drug product. A study comparing the PK of severely malnourished Malawian children to children from the United Kingdom also found that Malawian children had a higher exposure to vincristine.[23] These observations suggest that there is a difference between the PK of Black and non-Black children, which cannot solely be attributed to nutritional status.

Two recently published studies support individualized dosing through the development of a target area under the curve (AUC) in

relation to exposures observed in children with cancer[24] and to the risk of VIPN.[25] The latter might not be applicable to Kenyan patients, as our findings suggest that the lower incidence of VIPN is the result of pharmacodynamics (PD) rather than PK. The use of a target AUC might not be sensible in Kenyan children until this is elucidated. A potential PD explanation could involve differences in vincristine transport. Li et al. highlighted the role of organic anion-transporting polypeptide 1B3 (OATP1B3), which was previously thought to only be hepatically expressed, in neuronal uptake of vincristine.[26] Inhibition of murine analog OATP1B2 protected mice from VIPN, while plasma vincristine concentrations or tumor efficacy were not affected. Lower activity of OATP1B3 in Kenyan patients might explain the lack of VIPN despite higher vincristine exposure.

The goal of the PK-guided dose escalation was to establish the proof of principle and subsequently follow-up with a clinical study. However, as this was not achieved in the majority of participants, the design of the clinical study will be adapted into a conventional dose-escalation study based on toxicity. OATP1B3 activity will be measured through biomarkers,[26,27] and a 24-hour PK sample will be collected. Response to treatment will be evaluated in a larger cohort. To characterize vincristine PK in Black children, a population PK model will be developed. A genomic analysis of participants will follow.

The strengths of this study were that VIPN was prospectively monitored with the CTCAE, and ped-mTNS measurement tool was more sensitive.[21,28] Vincristine concentrations were measured with a validated assay.[6] Missing samples were limited to one. Limitations are the lack of late PK samples. The nomogram in its current form is not applicable to the Kenyan population. There was considerable variation in vincristine blood concentrations, possibly related to diagnosis, nutritional status, and age.

In conclusion, Kenyan children with cancer have distinct vincristine PK and toxicity profiles compared to White children. Future research should focus on characterizing these differences so that the dosing regimen of vincristine can be tailored to Kenyan patients, and potentially to other Black patients as well.

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CONFLICT OF INTEREST STATEMENT

Gertjan Kaspers is an advisor to the board (no compensation) for World Child Cancer NL.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at Mendeley Data, doi: 10.17632/r4hgntw52m.1.[29]

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REFERENCES

1. van de Velde ME, Kaspers GL, Abbink FCH, Wilhelm AJ, Ket JCF, van den Berg MH. Vincristine-induced peripheral neuropathy in children with cancer: a systematic review. *Crit Rev Oncol Hematol*. 2017;114:114-130. doi:10.1016/j.critrevonc.2017.04.004
2. Triarico S, Romano A, Attinà G, et al. Vincristine-induced peripheral neuropathy (VIPN) in pediatric tumors: mechanisms, risk factors, strategies of prevention and treatment. *Int J Mol Sci*. 2021;22(8):4112.
3. Lew G, Chen Y, Lu X, et al. Outcomes after late bone marrow and very early central nervous system relapse of childhood B-acute lymphoblastic leukemia: a report from the Children's Oncology Group phase III study AALL0433. *Haematologica*. 2021;106(1):46-55. doi:10.3324/haematol.2019.237230
4. Skiles JL, Chiang C, Li CH, et al. CYP3A5 genotype and its impact on vincristine pharmacokinetics and development of neuropathy in Kenyan children with cancer. *Pediatr Blood Cancer*. 2018;65(3):e26854. doi:10.1002/pbc.26854
5. Uittenboogaard A, Njuguna F, Mostert S, et al. Outcomes of Wilms tumor treatment in western Kenya. *Pediatr Blood Cancer*. 2022;69(4):e29503. doi:10.1002/pbc.29503
6. Anghelescu DL, Faughnan LG, Jeha S, et al. Neuropathic pain during treatment for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2011;57(7):1147-1153. doi:10.1002/pbc.23039
7. Diouf B, Crews KR, Lew G, et al. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. *JAMA*. 2015;313(8):815-823. doi:10.1001/jama.2015.0894
8. Kishi S, Cheng C, French D, et al. Ancestry and pharmacogenetics of antileukemic drug toxicity. *Blood*. 2007;109(10):4151-4157. doi:10.1182/blood-2006-10-054528
9. Renbarger JL, McCammack KC, Rouse CE, Hall SD. Effect of race on vincristine-associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. *Pediatr Blood Cancer*. 2008;50(4):769-771. doi:10.1002/pbc.21435
10. Dennison JB, Jones DR, Renbarger JL, Hall SD. Effect of CYP3A5 expression on vincristine metabolism with human liver microsomes. *J Pharmacol Exp Ther*. 2007;321(2):553-563. doi:10.1124/jpet.106.118471
11. Arbitrio M, Scionti F, Di Martino MT, Pensabene L, Tassone P, Tagliaferri P. 1.26 - Pharmacogenetics/pharmacogenomics of drug-metabolizing enzymes and transporters. In: Kenakin T, ed. *Comprehensive Pharmacology*. Elsevier; 2022:657-697.
12. Kuehl P, Zhang J, Lin Y, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet*. 2001;27(4):383-391. doi:10.1038/86882
13. Roy J-N, Lajoie J, Zijenah LS, et al. CYP3A5 genetic polymorphisms in different ethnic populations. *Drug Metab Dispos*. 2005;33(7):884-887. doi:10.1124/dmd.105.003822
14. Egbelakin A, Ferguson MJ, MacGill EA, et al. Increased risk of vincristine neurotoxicity associated with low CYP3A5 expression genotype in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2011;56(3):361-367. doi:10.1002/pbc.22845
15. Lavoie Smith EM, Li L, Hutchinson RJ, et al. Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. *Cancer Nurs*. 2013;36(5):E49-E60. doi:10.1097/NCC.0b013e318299ad23
16. Lönnerholm G, Frost BM, Abrahamsson J, et al. Vincristine pharmacokinetics is related to clinical outcome in children with standard risk

acute lymphoblastic leukemia. *Br J Haematol*. 2008;142(4):616-621. doi:10.1111/j.1365-2141.2008.07235.x
17. European Pharmacopoeia (Ph. Eur.) 11th Edition. Council of Europe; 2023.
18. Van der Heijden LT, Nijstad AL, Uittenboogaard A, et al. Development of a therapeutic drug monitoring strategy for the optimization of vincristine treatment in pediatric oncology populations in Africa. *Ther Drug Monit*. 2023;45:354-363. doi:10.1097/ftd.0000000000001090
19. van der Heijden LT, Gebretensae A, Thijssen B, et al. A highly sensitive bioanalytical method for the quantification of vinblastine, vincristine, vinorelbine and 4-O-deacetylvinorelbine in human plasma using LC-MS/MS. *J Pharm Biomed Anal*. 2022;215:114772. doi:10.1016/j.jpba.2022.114772
20. National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) version 5. National Institutes of Health. Accessed May 29, 2024. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5×11.pdf
21. Gilchrist LS, Tanner L. The pediatric-modified total neuropathy score: a reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. *Support Care in Cancer*. 2013;21(3):847-856. doi:10.1007/s00520-012-1591-8
22. RStudio Team. RStudio: integrated development for R. RStudio, PBC; 2020.
23. Israels T, Damen CWN, Cole M, et al. Malnourished Malawian patients presenting with large Wilms tumours have a decreased vincristine clearance rate. *Eur J Cancer*. 2010;46(10):1841-1847. doi:10.1016/j.ejca.2010.03.002
24. Barnett S, Hellmann F, Parke E, et al. Vincristine dosing, drug exposure and therapeutic drug monitoring in neonate and infant cancer patients. *Eur J Cancer*. 2022;164:127-136. doi:10.1016/j.ejca.2021.09.014
25. Centanni M, van de Velde ME, Uittenboogaard A, et al. Model-informed precision dosing to reduce vincristine-induced peripheral neuropathy in pediatric patients: a pharmacokinetic and pharmacodynamic modeling and simulation analysis. *Clin Pharmacokinet*. 2024;63(2):197-209. doi:10.1007/s40262-023-01336-1
26. Li Y, Drabison T, Nepal M, et al. Targeting a xenobiotic transporter to ameliorate vincristine-induced sensory neuropathy. *JCI Insight*. 2023;8(14):e164646. doi:10.1172/jci.insight.164646
27. Li Y, Jin Y, Taheri H, et al. A metabolomics approach for predicting OATP1B-type transporter-mediated drug-drug interaction liabilities. *Pharmaceutics*. 2022;14(9):1933. doi:10.3390/pharmaceutics14091933
28. Mora E, Smith EML, Donohoe C, Hertz DL. Vincristine-induced peripheral neuropathy in pediatric cancer patients. *Am J Cancer Res*. 2016;6(11):2416-2430.
29. Uittenboogaard A. A pharmacokinetically guided dose-escalation feasibility study of vincristine in Kenyan children with cancer (CHAPATI study). Mendeley Data, V1; 2024. doi:10.17632/r4hgntw52m.1

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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