# Vincristine (VCR)

Subjects: Oncology

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Vincristine (VCR) is a frequently used chemotherapeutic agent. However, it can lead to VCR-induced peripheral neuropathy (VIPN).

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## 1. Introduction

Vincristine (VCR) is a frequently-used chemotherapeutic agent in pediatric oncology since many decades[1][2]. VCR inhibits the mitotic spindle in the cell, thereby blocking cell division[3][4]. In the liver, it is metabolized into M1 by the cytochrome P450 (CYP) 3A enzymes[5]. A major adverse effect of VCR is neurotoxicity, which is characterized by autonomic and peripheral sensory-motor neuropathy and reported in 12–87% of VCR-exposed children[1][6][7][8]. Symptoms of VCR-induced peripheral neuropathy (VIPN) include paresthesia, muscle weakness, areflexia, pain, and diminished sensibility[9][10][11][12]. It usually starts after a few administrations and symptoms often reside several months after treatment cessation[1][2]. VIPN can lead to suboptimal treatment due to dose reductions or omissions of VCR[10][13]. VIPN is dose-dependent, with single administration doses exceeding 2.0 mg/m$^2$ leading to intolerable VIPN in children[14]. Children of older age or Caucasian ancestry seem more vulnerable. Furthermore, genetic predispositions and pharmacokinetics (PK) of VCR influence VIPN development[1][6][14][15][16][17][18][19][20][21]. Moreover, multiple studies have shown that concurrent azole antifungal and VCR treatment leads to more and severe VIPN in children, due to competitive interaction by the CYP enzyme[22][23][24]. This is clinically relevant, since azole antifungals are frequently used to prevent or treat invasive fungal infections in pediatric cancer[25]. Although VIPN is dose-limiting[1][14], prolongation of VCR administration showed that the single administration dose can be increased without leading to intolerable VIPN in children. In two studies using continuous VCR infusion up to five days, cumulative VCR doses of 4.0 mg/m$^2$ were well tolerated[26][27]. This could be due to lower peak-plasma concentrations that are related to longer lasting infusions, which seem associated with less VIPN[28]. Yet, multiple day VCR infusions are costly and cumbersome. Therefore, in clinical practice VCR is usually administered intravenously (iv) through a short-term push injection or infusion (up to 15 min). Sometimes it is administered through a one-hour infusion. Both push and one-hour administrations use standardized VCR doses of 1.5–2.0 mg/m$^2$ (maximum 2.0 mg) [29]. However, the effect of prolonging VCR infusion on VIPN using standardized dosing regimens, is unknown.

## 2. High Therapeutic Effectiveness of VCR

In the current study, in which 90 pediatric oncology patients were randomized to receive VCR administrations through iv push injections or one-hour infusions, overall VIPN did not differ between the two groups. However, when VCR was administered concurrently with azole antifungals, children in the one-hour group had a significantly lower total CTCAE score than those in the push group. When VIPN was assessed by ped-mTNS scores or by dichotomized outcomes (having VIPN or not), no significant differences were found between push administrations and one-hour infusions, irrespective of concurrent azole treatment, although a trend in the same direction as CTCAE results was shown.

VIPN is a debilitating toxicity with symptoms still present in adult survivors of childhood cancer[30]. Therefore, the overarching goal of this trial was to study an intervention possibly resulting in reduced VIPN during treatment of childhood cancer. To the best of our knowledge, this is the first RCT studying the effect of administration duration of VCR on VIPN, either in children or adults. During this trial we evaluated VIPN prospectively and longitudinally with repeated

measurements. At each hospital uniformly trained assessors evaluated VIPN using two different instruments (CTCAE and ped-mTNS) including standardized physical examination[31]. Especially the ped-mTNS has been systematically reviewed and is currently recommended for the assessment of VIPN in children[32].

Our results show that one-hour infusions result in lower total CTCAE scores when VCR is concurrently used with azole antifungals. In general, this concurrent treatment is associated with increased incidence and severity of VIPN [22][23][24]. In our study, estimated CTCAE score was 1.41 (95%CI: 1.19 to 1.64) for measurements without concurrent azole treatment and more than twice as high (2.87 (95%CI: 2.15 to 3.58)) for measurements with concurrent azole treatment ($p < 0.001$). However, when these scores of VIPN with concurrent azole antifungal use were evaluated for patients in each randomization group separately, estimated CTCAE score of patients in the one-hour group was 1.97 (95%CI: 0.92 to 3.01) vs. 3.64 (95%CI: 2.67 to 4.62) in the push group for measurements with concurrent azole treatment. These results show that concurrent treatment of azole antifungals and VCR has a smaller impact on VIPN when VCR is administered through one-hour infusions. This could also well be true for concurrent use with other strong CYP3A inhibitors, such as anti-retroviral drugs or carbamazepine.

Since concurrent use of azole antifungals and VCR are generally avoided, alternative treatment for invasive fungal infections (IFI) must be used, such as echinocandins or (liposomal) amphotericin B. However, these agents have several disadvantages including high costs, iv administration only, and lack of evidence of superior efficacy over azole antifungals in children[33][34][35]. Therefore, in clinical practice IFI are frequently treated with azole antifungals irrespective of concurrent VCR treatment[36][37]. Although in clinical practice treatment with azole antifungals is sometimes discontinued 24 hours before VCR administration, this interval is too short, based on the half-life of azole antifungals, to have an impact on this drug-drug interaction[38]. It should be noted, that the absolute number of patients with concurrent VCR and azole treatment was small in our study ($n$ = 19, 21%). Therefore, future studies should be undertaken to replicate our results and indisputably confirm the favorable effect of one-hour infusions over push injections regarding VIPN development. Furthermore, due to low patient numbers, we were not able to study the effect of azole type, such as itraconazole, fluconazole, voriconazole, and posaconazole. This could very well be of importance as itraconazole is a stronger inhibitor of CYP3A4 than for instance fluconazole or voriconazole[39]. Finally, diagnostic indication for treatment with azole antifungals, such as prophylaxis or treatment of diagnosed mycoses, on the relation between administration method and VIPN should be considered as well in a future study.

Although VIPN is a serious toxicity, high therapeutic effectiveness of VCR is of utmost importance. Regarding administration method, it is not expected that one-hour infusions of VCR are associated with a worse therapeutic outcome than push injections. It might even be the contrary. In general, longer lasting infusions of chemotherapy may improve therapeutic efficacy of a drug with a short half-life and an action mechanism of the drug that is related to the cell cycle, both of which are true for VCR[26]. While it is conceivable, that one-hour infusions are too short to benefit from this cell-cycle dependence or prolonged half-life, it underlines the unlikeliness of lower therapeutic effectiveness of one-hour infusions of VCR. In our study we also did not find any differences regarding relapse or mortality between the two groups.

Our study had some limitations. First of all, we included a heterogeneous group of patients with multiple diseases, varying VCR dosing regimens and co-medications. These different co-medications could theoretically alter pharmacokinetics and thus VCR exposure and VIPN development. In order to further investigate the true effect of VCR administration duration on the development of VIPN, future studies including more uniform diagnostic study groups are needed. Furthermore, in treatment protocols for ALL and Hodgkin's lymphoma, the use of glucocorticoids is common practice[29][40]. Adverse effects of these agents could mimic symptoms of VIPN not attributed to VCR. However, we see a similar distribution of disease types in our two randomization groups, thereby ensuring similar distribution of co-medication. Secondly, the assessment of VIPN in children in general is difficult. Children of younger age are not able to verbally express their complaints. Therefore, for children aged <5 years VIPN assessment often relies on parent reports[31][41], which could introduce bias. The CTCAE lacks extensive physical examination, such as manual strength testing, vibration sense or assessment of sensibility, whereas the ped-mTNS cannot be used in younger children. As a consequence, both tools might not measure the same aspects of VIPN in the same population. Nevertheless, currently they represent the best available methods for VIPN assessment in children.

Furthermore, assessors of VIPN in this study, although frequently unaware of randomization status of the patients, were not strictly blinded to the randomization status. This could have introduced bias in the VIPN results reported.

Finally, VIPN is a multifactorial phenomenon, also influenced by PK of VCR and single nucleotide polymorphisms[1]. It would be beneficial to study the impact of administration duration on VIPN while also considering these factors. Data on VCR PK and SNP's were also collected as part of this trial, but analyses of these data was beyond the scope of this paper. Data of this trial regarding administration duration related to PK were published separately[42]. Potentially, infusion

of VCR in one-hour could lead to an increased risk of extravasation, which is dangerous in VCR treatment. However, in all our patients, VCR was administered using a central venous catheter, therefore, extravasation was not a potential risk factor.

## References


1. van de Velde, M.E.; Kaspers, G.L.; Abbink, F.C.H.; Wilhelm, A.J.; Ket, J.C.F.; van den Berg, M.H. Vincristine-induced peripheral neuropathy in children with cancer: A systematic review. Crit. Rev. Oncol. Hematol. 2017, 114, 114–130.
2. Gidding, C.E.; Kellie, S.J.; Kamps, W.A.; De Graaf, S.S. Vincristine revisited. Crit. Rev. Oncol. Hematol. 1999, 29, 267–287.
3. Coccia, P.F.; Altman, J.; Bhatia, S.; Borinstein, S.C.; Flynn, J.; George, S.; Goldsby, R.; Hayashi, R.; Huang, M.S.; Johnson, R.H.; et al. Adolescent and young adult oncology clinical practice guidelines in oncology. JNCCN J. Natl. Compr. Cancer Netw. 2012, 10, 1112–1150.
4. Stryckmans, P.A.; Lurie, P.M.; Manaster, J.; Vamecq, G. Mode of action of chemotherapy in vivo on human acute leukemia--II. Vincristine. Eur. J. Cancer 1973, 9, 613–620.
5. Dennison, J.B.; Jones, D.R.; Renbarger, J.L.; Hall, S.D. Effect of CYP3A5 expression on vincristine metabolism with human liver microsomes. J. Pharmacol. Exp. Ther. 2007, 321, 553–563.
6. Anghelescu, D.L.; Faughnan, L.G.; Jeha, S.; Relling, M.V.; Hinds, P.S.; Sandlund, J.T.; Cheng, C.; Pei, D.; Hankins, G.; Pauley, J.L.; et al. Neuropathic pain during treatment for childhood acute lymphoblastic leukemia. Pediatr. Blood Cancer 2011, 57, 1147–1153.
7. Gutierrez-Camino, A.; Martin-Guerrero, I.; Lopez-Lopez, E.; Echebarria-Barona, A.; Zabalza, I.; Ruiz, I.; Guerra-Merino, I.; Garcia-Orad, A. Lack of association of the CEP72 rs924607 TT genotype with vincristine-related peripheral neuropathy during the early phase of pediatric acute lymphoblastic leukemia treatment in a Spanish population. Pharmacogenet. Genom. 2016, 26, 100–102.
8. Gilchrist, L.S.; Marais, L.; Tanner, L. Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children. Supportive Care Cancer 2014, 22, 359–366.
9. Gutierrez-Gutierrez, G.; Sereno, M.; Miralles, A.; Casado-Saenz, E.; Gutierrez-Rivas, E. Chemotherapy-induced peripheral neuropathy: Clinical features, diagnosis, prevention and treatment strategies. Clin. Transl. Oncol 2010, 12, 81–91.
10. Gomber, S.; Dewan, P.; Chhonker, D. Vincristine induced neurotoxicity in cancer patients. Indian J. Pediatrics 2010, 77, 97–100.
11. Windebank, A.J.; Grisold, W. Chemotherapy-induced neuropathy. J. Peripher. Nerv. Syst 2008, 13, 27–46.
12. Beijers, A.J.; Jongen, J.L.; Vreugdenhil, G. Chemotherapy-induced neurotoxicity: the value of neuroprotective strategies. Neth. J. Med. 2012, 70, 18–25.
13. Rosca, L.; Robert-Boire, V.; Delisle, J.F.; Samson, Y.; Perreault, S. Carboplatin and vincristine neurotoxicity in the treatment of pediatric low-grade gliomas. Pediatr. Blood Cancer 2018, 65, e27351.
14. Diouf, B.; Crews, K.R.; Lew, G.; Pei, D.; Cheng, C.; Bao, J.; Zheng, J.J.; Yang, W.; Fan, Y.; Wheeler, H.E.; et al. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. JAMA J. Am. Med Assoc. 2015, 313, 815–823.
15. Egbelakin, A.; Ferguson, M.J.; MacGill, E.A.; Lehmann, A.S.; Topletz, A.R.; Quinney, S.K.; Li, L.; McCammack, K.C.; Hall, S.D.; Renbarger, J.L. Increased risk of vincristine neurotoxicity associated with low CYP3A5 expression genotype in children with acute lymphoblastic leukemia. Pediatric Blood Cancer 2011, 56, 361–367.
16. Kishi, S.; Cheng, C.; French, D.; Pei, D.; Das, S.; Cook, E.H.; Hijiya, N.; Rizzari, C.; Rosner, G.L.; Frudakis, T.; et al. Ancestry and pharmacogenetics of antileukemic drug toxicity. Blood 2007, 109, 4151–4157.
17. Ceppi, F.; Langlois-Pelletier, C.; Gagné, V.; Rousseau, J.; Iolino, C.; Orenzo, S.D.; Evin, K.M.; Ijov, D.; Allan, S.E.; Ilverman, L.B.; et al. Polymorphisms of the vincristine pathway and response to treatment in children with childhood acute lymphoblastic leukemia. Pharmacogenomics 2014, 15, 1105–1116.
18. Abaji, R.; Ceppi, F.; Patel, S.; Gagne, V.; Xu, C.J.; Spinella, J.F.; Colombini, A.; Parasole, R.; Buldini, B.; Basso, G.; et al. Genetic risk factors for VIPN in childhood acute lymphoblastic leukemia patients identified using whole-exome sequencing. Pharmacogenomics 2018, 19, 1181–1193.
19. Lopez-Lopez, E.; Gutierrez-Camino, A.; Astigarraga, I.; Navajas, A.; Echebarria-Barona, A.; Garcia-Miguel, P.; Garcia de Andoin, N.; Lobo, C.; Guerra-Merino, I.; Martin-Guerrero, I.; et al. Vincristine pharmacokinetics pathway and

neurotoxicity during early phases of treatment in pediatric acute lymphoblastic leukemia. Pharmacogenomics 2016, 17, 10.

20. Aplenc, R.; Glatfelter, W.; Han, P.; Rappaport, E.; La, M.; Cnaan, A.; Blackwood, M.A.; Lange, B.; Rebbeck, T. CYP3A genotypes and treatment response in paediatric acute lymphoblastic leukaemia. Br. J. Haematol. 2003, 122, 240–244.
21. Renbarger, J.L.; McCammack, K.C.; Rouse, C.E.; Hall, S.D. Effect of race on vincristine-associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. Pediatr. Blood Cancer 2008, 50, 769–771.
22. Van Schie, R.M.; Bruggemann, R.J.; Hoogerbrugge, P.M.; Te Loo, D.M. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J. Antimicrob. Chemother. 2011, 66, 1853–1856.
23. Moriyama, B.; Henning, S.A.; Leung, J.; Falade-Nwulia, O.; Jarosinski, P.; Penzak, S.R.; Walsh, T.J. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. Mycoses 2012, 55, 290–297.
24. Baxter, C.G.; Marshall, A.; Roberts, M.; Felton, T.W.; Denning, D.W. Peripheral neuropathy in patients on long-term triazole antifungal therapy. J. Antimicrob. Chemother. 2011, 66, 2136–2139.
25. Science, M.; Robinson, P.D.; MacDonald, T.; Rassekh, S.R.; Dupuis, L.L.; Sung, L. Guideline for primary antifungal prophylaxis for pediatric patients with cancer or hematopoietic stem cell transplant recipients. Pediatr. Blood Cancer 2014, 61, 393–400.
26. Kellie, S.J.; Koopmans, P.; Earl, J.; Nath, C.; Roebuck, D.; Uges, D.R.A.; De Graaf, S.S.N. Increasing the dosage of vincristine: A clinical and pharmacokinetic study of continuous-infusion vincristine in children with central nervous system tumors. Cancer 2004, 100, 2637–2643.
27. Pinkerton, C.R.; McDermott, B.; Philip, T.; Biron, P.; Ardiet, C.; Vandenberg, H.; Brunat-Mentigny, M. Continuous vincristine infusion as part of a high dose chemoradiotherapy regimen: Drug kinetics and toxicity. Cancer Chemother. Pharmacol. 1988, 22, 271–274.
28. Gidding, C.E.; Fock, J.M.; Begeer, J.H.; Koopmans, P.; Meeuwsen-de Boer, G.J.; Kamps, W.A.; Uges, D.R.A.; De Graaf, S.S.N. Vincristine disposition and neurotoxicity in children. In Proceedings of the Annual Meeting-American Society of Clinical Oncology, Los Angeles, CA, USA, 16–19 May 1998. Abstract N22-2068-ASCO 1998. 16-5-1998.
29. DCOG Protocol ALL-11 (2013): Treatment Study Protocol of the Dutch Childhood Oncology Group for Children and Adolescents (1–19 year) with Newly Diagnosed Acute Lymphoblastic Leukemia. Version 4.0. Available online: https://www.skion.nl/workspace/uploads/Onderzoeksprotocol-ALL11-version-4-3-september-2014.pdf (accessed on 5 October 2020).
30. Varedi, M.; Lu, L.; Howell, C.R.; Partin, R.E.; Hudson, M.M.; Pui, C.H.; Krull, K.R.; Robison, L.L.; Ness, K.K.; McKenna, R.F. Peripheral Neuropathy, Sensory Processing, and Balance in Survivors of Acute Lymphoblastic Leukemia. J. Clin. Oncol. 2018, 36, 2315–2322.
31. Gilchrist, L.S.; Tanner, L. The pediatric-modified total neuropathy score: A reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. Supportive Care Cancer 2013, 21, 847–856.
32. Smolik, S.; Arland, L.; Hensley, M.A.; Schissel, D.; Shepperd, B.; Thomas, K.; Rodgers, C. Assessment Tools for Peripheral Neuropathy in Pediatric Oncology: A Systematic Review From the Children's Oncology Group. J. Pediatr. Oncol. Nurs. 2018, 35, 267–275.
33. Leverger, G.; Timsit, J.F.; Milpied, N.; Gachot, B. Use of Micafungin for the Prevention and Treatment of Invasive Fungal Infections in Everyday Pediatric Care in France: Results of the MYRIADE Study. Pediatr. Infect Dis. J. 2019, 38, 716–721.
34. Bochennek, K.; Balan, A.; Muller-Scholden, L.; Becker, M.; Farowski, F.; Muller, C.; Groll, A.H.; Lehrnbecher, T. Micafungin twice weekly as antifungal prophylaxis in paediatric patients at high risk for invasive fungal disease. J. Antimicrob Chemother. 2015, 70, 1527–1530.
35. Lee, C.H.; Lin, J.C.; Ho, C.L.; Sun, M.; Yen, W.T.; Lin, C. Efficacy and safety of micafungin versus extensive azoles in the prevention and treatment of invasive fungal infections for neutropenia patients with hematological malignancies: A meta-analysis of randomized controlled trials. PLoS ONE 2017, 12, e0180050.
36. Fisher, B.T.; Zaoutis, T.; Dvorak, C.C.; Nieder, M.; Zerr, D.; Wingard, J.R.; Callahan, C.; Villaluna, D.; Chen, L.; Dang, H.; et al. Effect of Caspofungin vs Fluconazole Prophylaxis on Invasive Fungal Disease among Children and Young Adults with Acute Myeloid Leukemia: A Randomized Clinical Trial. JAMA 2019, 322, 1673–1681.
37. Papachristou, S.; Iosifidis, E.; Roilides, E. Invasive Aspergillosis in Pediatric Leukemia Patients: Prevention and Treatment. J. Fungi. 2019, 5, 14.
38. Saad, A.H.; DePestel, D.D.; Carver, P.L. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy 2006, 26, 1730–1744.

39. Pana, Z.D.; Roilides, E. Risk of azole-enhanced vincristine neurotoxicity in pediatric patients with hematological malignancies: old problem—New dilemma. Pediatr. Blood Cancer 2011, 57, 30–35.
40. The EuroNet-PHL-C2 Protocol (2016) Second International Inter-Group Study for Classical Hodgkin's Lymphoma in Children and Adolescents. Version 3.0. Available online: https://clinicaltrials.gov/ct2/show/NCT02684708 (accessed on 5 October 2020).
41. Lavoie Smith, E.M.; Li, L.; Hutchinson, R.J.; Ho, R.; Burnette, W.B.; Wells, E.; Bridges, C.; Renbarger, J. Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. Cancer Nurs. 2013, 36, E49–E60.
42. Van de Velde, M.E.; Panetta, J.C.; Wilhelm, A.J.; van den Berg, M.H.; van der Sluis, I.M.; van den Bos, C.; Abbink, F.C.H.; van den Heuvel-Eibrink, M.M.; Segers, H.; Chantrain, C.; et al. Population Pharmacokinetics of Vincristine Related to Infusion Duration and Peripheral Neuropathy in Pediatric Oncology Patients. Cancers 2020, 12, 1789.