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CASE REPORT

Severe Vincristine-Induced Neuropathic Pain: A Case Report with Pharmacogenetic Analysis and Literature Review

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Abstract: Vincristine-induced peripheral neuropathy (VIPN) is a common adverse effect of vincristine (VCR) for which there is no preventative or curative treatment. Here, we report a case of a patient suffering from severe VCR-related neurotoxicity. To explore the possible causes of severe VIPN in this patient, a set of genes involved in VCR metabolism, transport or are related to the cytoskeleton, microtubules, and inherited neurological diseases gene polymorphisms were examined via pharmacogenetic analyses. The genotyping results revealed the presence of a complex pattern of polymorphisms in *CYP3A5, ABCC2, SYNE2, BAHD1, NPSR1, MTNR1B, CEP72*, miR-4481 and miR-3117. A comprehensive understanding of all the pharmacogenetic risk factors for VIPN may explain the occurrence of severe neurotoxicity in our patient. This case brings to light the potential importance of pharmacogenetic testing in clinical practice. It also exemplifies the importance of developing early-detection strategies to optimize treatment regimens through prior risk stratification while reducing adverse drug reactions and personalizing therapy.

Keywords: vincristine, peripheral neuropathy, pharmacogenetics, toxicity, polymorphisms, precision medicine

Introduction

Vincristine (VCR) is a crucial medication in combination chemotherapy regimens for the treatment of most pediatric cancers, such as acute lymphoblastic leukemia (ALL), lymphomas, rhabdomyosarcoma, neuroblastoma, and nephroblastoma.[1] The main side-effect of VCR is vincristine-induced peripheral neuropathy (VIPN) which causes peripheral and mostly symmetric sensory-motor neuropathy; these effects limit the dosage, delay treatment cycles, and even lead to discontinuation of chemotherapy.[2] Clinical symptoms of VIPN include neuropathic pain, numbness and tingling in the hands and feet, muscle weakness, areflexia, and altered gait, amongst others. Furthermore, it can cause autonomic nerve injury and impaired sight and hearing.[3] This debilitating feeling plagues approximately 30% of patients treated with VCR and severely reduces their quality of life.[4]

Multiple factors may alter the development and severity of VIPN, for example dose, age, gender, combination medicine and genetic variants.[3,5] Indeed, the role of genetics in VIPN has been well documented. Pharmacogenomics can detect associations between genetic variation and drug safety, avoiding adverse drug reactions and maximizing drug efficacy.[6] Single-nucleotide polymorphisms (SNPs) are the most common genetic variants. In the last decade, several SNPs associated with VIPN have been reported in pharmacogenomic studies through candidate gene studies[7–9] or population-based GWAS or EWAS (genome- or exome-wide association studies).[4,10] Variations in the expression or sensibility of VCR response-related proteins, such as drug metabolizing enzymes, transporters and therapeutic mechanisms are important sources of interindividual variability in drug response.

Here, we report a case of severe neuropathic pain after VCR chemotherapy in a patient with T-lymphoblastic lymphoma during the induction phase.

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Presentation of Case

On January 21, a 10-year-old Chinese boy had numbness of the lips and face accompanied by obvious pain, which was improved after oral administration of ibuprofen. Since his tumor was primary in the neck and mediastinum and required vigilance for central invasion, the lymphoblastic lymphoma was deemed to be stage IV. According to Chinese Children Cancer Group-lymphoblastic lymphoma-2016 (CCCG-LBL-2016) treatment protocols, he began remission induction therapy with VCR, daunorubicin, prednisone, PEG-aspargase and triple it (methotrexate, cytarabine, and dexamethasone, intrathecally). The patient's height and weight were 145 cm and 54 kg on admission, respectively. Thus, he received 2 mg (maximum dose, but < 1.5 mg/m^2) VCR once daily on Days 1, 8, 15, and 22 of induction chemotherapy. In the following days, the child was given recombinant human granulocyte stimulating factor (rhG-CSF) injection to increase the number of neutrophils and voriconazole was used to prevent fungal infection. Three days after receiving the fourth dose of VCR, on February 15, the patient reported mild abdominal pain at night, which was relieved spontaneously. Examination of serum or urine amylase and color ultrasounds of hepatobiliary, pancreatic, and splenic tissues showed no significant abnormality. On the afternoon of February 17, the child cried and complained of pain in both legs, which was scored as 9 using the visual analogue scale (VAS). At night, it developed into systemic pain, mainly in the back, lower limbs and shoulders, which was paroxysmal and not relieved after his parents gave ibuprofen sustained-release capsules orally (dose unknown), with a VAS score of 8. After subsequent oral administration of compound paracetamol tablets (dose unknown) given by parents, the VAS score was 5. The physician considered peripheral neuralgia caused by rhG-CSF-stimulated myeloproliferation and/or VCR, so the patient was given an analgesic pump for intravenous analgesia after consultation with the anesthesiologist on February 18, and on the next day the VAS score decreased to 0. The patient then proceeded with sequential chemotherapy. On February 29, the patient reported transient abdominal pain, which was not severe and was relieved spontaneously. After this adverse event, no similar symptoms occurred during the following chemotherapy courses until the patient received the next dose of VCR.

Four months later, the patient was admitted to the hospital for reinduction chemotherapy with dexamethasone, VCR, epirubicin, PEG-aspargase and triple it (methotrexate, cytarabine, and dexamethasone, intrathecally). At this admission, the patient's height did not increase, but his weight dropped to 44 kg. He received VCR 1.95 mg (1.51 mg/m^2) on July 3, the first day of reinduction chemotherapy. After two days, the child reported pain around the gingiva and soft tissue at night which was accompanied by facial pain and headache when the pain was severe. On examination, significant local tenderness of the gingiva was noted, but there was no significant redness, swelling, suppuration, or dental caries, with a VAS score of 5. The patient's symptoms did not decrease after oral administration of cefathiamidine and metronidazole for anti-infection, and the VAS score did not change. Therefore, the doctor gave the child compound paracetamol tablets (450 mg) for pain relief. Then the toothache was gradually relieved, and the VAS score decreased to 2 on July 8. However, on July 9, the patient began to experience back pain, which was suspected to be caused by drug toxicity of VCR, and the VAS score was 2. On July 10, while receiving the second dose of 1.95 mg (1.51 mg/m^2) VCR, the patient was given mecobalamin to nourish the nerves, but in the following days the back pain persisted. On July 14, the patient received two intravenous bolus doses of tramadol hydrochloride, 50 mg and 100 mg, respectively, owing to body aches, especially in the back. By the night of July 16, the child had systemic pain and shortness of breath when the pain was severe with a VAS score of 3, and the doctor decided to treat him with an analgesic pump for pain relief; then, the VAS score decreased to 1. Since the patient did not appear to tolerate the neurotoxicity of VCR, the VCR in the regimen was replaced with vindesine to continue chemotherapy. On July 22, the systemic pain was improved, but the patient began to experience abdominal pain and urine trypsinogen was positive. Pancreatitis was considered, and chemotherapy was suspended until August 10, during which several episodes of abdominal pain occurred. On August 11, the patient's condition was improved, and chemotherapy was continued in sequence. Notably, the patient still had occasional back pain for more than twenty days from July 24 to August 13. The chronology of chemotherapy medications and adverse effects is shown in Figure 1.

Materials and Methods

To investigate the genetic basis of severe neuropathic pain, we summarized genes that identified by pharmacogenetic studies as responsible for the large interindividual differences in VIPN. Since there were no pharmacogenetic studies on T-lymphoblastic lymphoma with VCR in the database, we searched PubMed with a combination of the keywords "pharmacogenetic" AND "vincristine". Of those genes, two SNPs in metabolism-associated genes (CYP3A4 and CYP3A5),[9] five

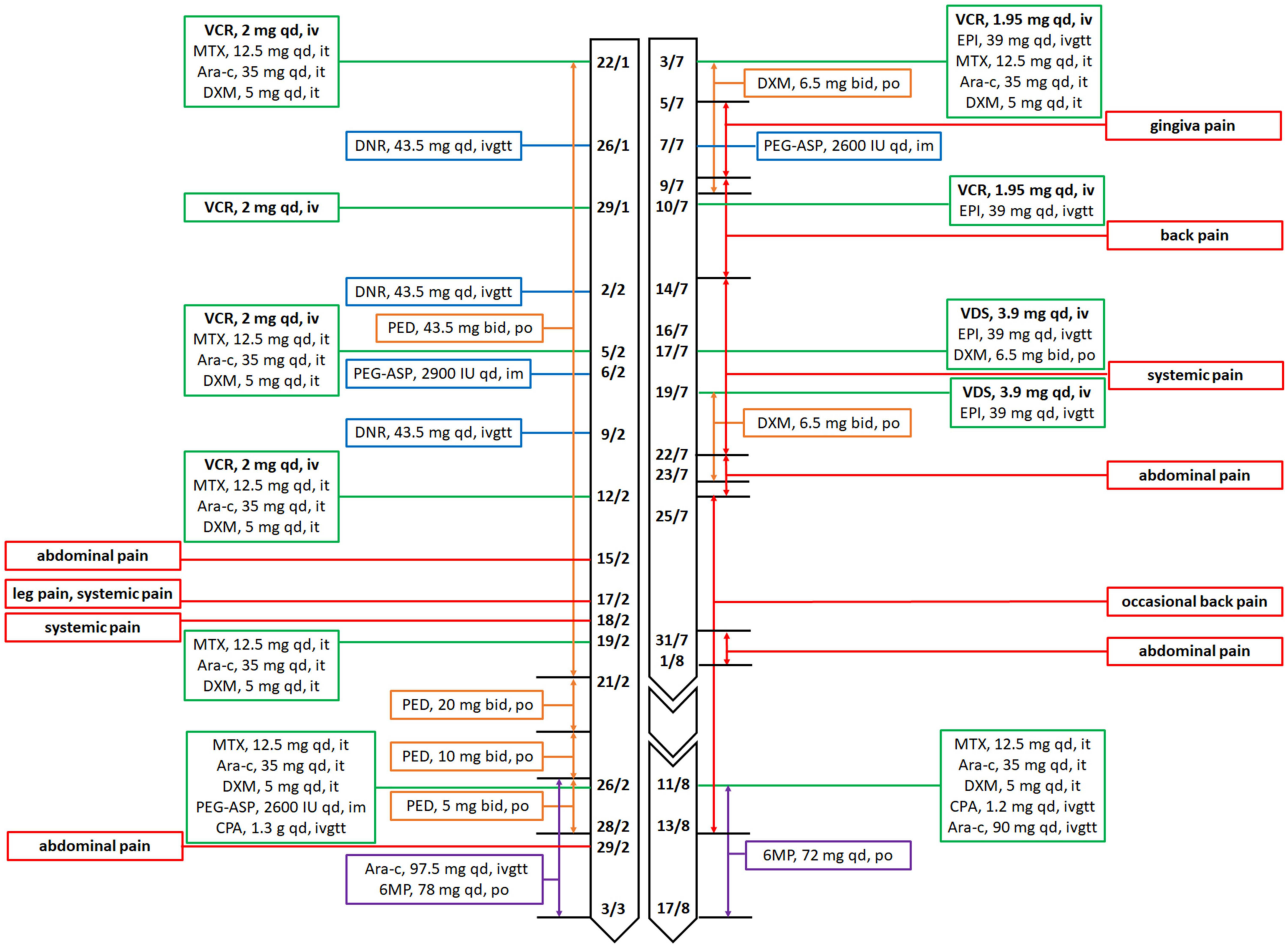

Figure 1 Chronology of Chemotherapy Medications and Adverse Effects.
Abbreviations: VCR, vincristine; MTX, methotrexate; Ara-c, cytarabine; DXM, dexamethasone; DNR, daunorubicin; PED, prednisone; PEG-ASP, PEG-aspargase; CPA, cyclophosphamide; 6MP, mercaptopurine; EPI, epirubicin; VDS, vindesine; qd, once a day; bid, twice a day; iv, intravenous injection; it, intrathecal injection; ivgtt, intravenous drip; po, oral adminstration; im, intramuscular injection.

SNPs in transporter-associated genes (ATP-binding cassette transporter (ABCB1, ABCC1, ABCC2),[8] solute carrier family 5 member 7 (SLC5A7)[11]), six SNPs in cytoskeleton-associated genes (centrosomal protein 72 (CEP72),[4] spectrin repeat containing nuclear envelope protein 2 (SYNE2), mitochondrial ribosomal proteins 47 (MRPL47),[10] capping actin protein gelsolin (CAPG), actin gamma 1 (ACTG1)[7]), six SNPs in genes detected by GWAS or EWAS (transmembrane protein 215 (TMEM215), melatonin receptor 1B (MTNR1B), Ewing's tumor-associated antigen 1 (ETAA1), NADH: ubiquinone oxidoreductase complex assembly factor (NDUFAF6),[4] bromo adjacent homology domain containing 1 (BAHD1),[10] alpha tocopherol transfer protein (TTPA)[11]) and two SNPs in miRNA genes (miR–3117 and miR-4481[12]) were reported to be significantly associated with VIPN. In addition, seven SNPs in the neuropeptide S receptor 1 (NPSR1) gene were implicated with recurrent abdominal pain.[13] The polymorphisms of above-mentioned genes were examined. The study was performed in accordance with the Helsinki Declaration and the study protocol was approved by the Children's Hospital of Nanjing Medical University ethics committee (Protocol number 202206117–1).

According to the manufacturer's instructions, DNA was extracted from the patient's peripheral blood using a DNA extraction kit (BioTeke Corporation, Wuxi, China) and stored at −80 °C. Twenty-eight, relative SNPs were genotyped by direct automated DNA sequencing on an ABI 3730 analyzer after polymerase chain reaction (Applied). The primers used are listed in Supplementary Table S1.

Results

Sequence analysis revealed the presence of a complex pattern of polymorphisms: *CYP3A5* rs776746 GG, *ABCC2* rs12826 GG, *SYNE2* rs2781377 AA, *BAHD1* rs3803357 AA, *NPSR1* rs887020 AG, miR-4481 rs7896283 GG, miR-3117-3p rs12402181 GA, *MTNR1B* rs12786200 CT, and *CEP72* rs924607 CT (Table 1). Taken together, the genetic

Table 1 Patient's Genotype Results Associated with VIPN and ALFA Allele Frequency

Gene	SNP	Risk Genotype	Patient's Genotype	Interpretation	ALFA Allele Frequency*
CYP3A5	rs776746	GG (A>G)	GG	CYP3A5*3/*3 (CYP3A5 nonexpresser) ↑ risk and severity of VIPN	Caucasion: T/C=0.070032/0.929968
					African: T/C=0.69646/0.30354
					Asian: T/C=0.287/0.713
ABCC2	rs12826	GG	GG	↑ neurotoxicity	Caucasion: C/T=0.628557/0.371443
					African: C/T=0.8487/0.1513
					Asian: C/T=0.795/0.205
SYNE2	rs2781377	AA (G>A)	AA	↑ risk of VIPN	Caucasion: G/A=0.930333/0.069667
					African: G/A=0.8720/0.1280
					Asian: G/A=0.9032/0.0968
miR-4481	rs7896283	CC (T>C)	CC	↑ risk of VIPN	Caucasion: A/G=0.50419/0.49581
					African: A/G=0.6483/0.3517
					Asian: A/G=0.580/0.420
miR-3117	rs12402181	GG (G>A)	GA	Low-risk genotype	Caucasion: G/A=0.84586/0.15414
					African: G/A=0.6368/0.3632
					Asian: G/A=0.723/0.277
MTNR1B	rs12786200	TT (C>T)	CT	May ↑ the severity of VIPN	Caucasion: C/T=0.77462/0.22538
					African: C/T=0.7809/0.2191
					Asian: C/T=0.705/0.295
CEP72	rs924607	TT (C>T)	CT	Low-risk genotype	Caucasion: C/T=0.57101/0.42899
					African: C/T=0.8869/0.1131
					Asian: C/T=0.77/0.23
BAHD1	rs3803357	CC (C>A)	AA	↓ VIPN severity grade	Caucasion: C/A=0.502364/0.497636
					African: C/A=0.2455/0.7545
					Asian: C/A=0.1824/0.8176
NPSR1	rs887020	GG (A>G)	AG	↑ risk of abdominal pain in children	Caucasion: A/G=0.457305/0.542695
					African: A/G=0.8191/0.1809
					Asian: A/G=0.185/0.815

Note: *ALFA allele frequency data are from www.ncbi.nlm.nih.gov.

profile may be related to the pharmacokinetics and pharmacodynamics of VCR, thus explaining the observed VIPN. The results of all genotypes of the patient are shown in Supplementary Table S2.

Discussion

The present case report describes a pediatric patient with T-lymphocytic lymphoma whose complex pattern of genetic polymorphisms may be the cause of severe neuropathic pain.

VCR pharmacokinetics showed large interpatient variability in the pediatric population.[14] The genotypes of enzymes involved in VCR metabolism may affect the pharmacokinetic process of VCR. CYP3A family of enzymes is responsible for the metabolism of VCR. In fact, a link between genetic variants in CYP3A enzymes and drug toxicity has been established.[15] Of note, CYP3A5 showed higher selective oxidation and 9- to 14-fold intrinsic clearance of VCR than CYP3A4, which was mainly manifested by a higher catalytic formation of primary metabolites (M1).[16,17] Furthermore, the M1 plasma concentration was indicated to be negatively correlated with the severity of neuropathy. The *CYP3A5*1* allele is required for the production of a functional enzyme. The *CYP3A5*3* allele has a SNP in intron 3, resulting in a premature stop codon and no active CYP3A5 enzyme.[18] Therefore, the polymorphic expression of *CYP3A5* may be an important factor in the individual differences in VCR disposal and toxicity. Subjects with at least one *CYP3A5*1* allele are called CYP3A5 expressers. In contrast, people with *CYP3A5*3/*3* genotypes are considered CYP3A5 nonexpressers. The predicted intrinsic clearance of VCR was 5-fold higher in CYP3A5 expressers than nonexpressers.[16] Compared with CYP3A5 expressers, CYP3A5 nonexpressers metabolize VCR slower (higher [VCR]/[M1] ratios) and experience more severe VIPN.[9,15,19,20] However, contradictory results regarding the relationship between the *CYP3A5* genotype and VCR-related neurotoxicity have been reported.[7,21] In addition, a meta-analysis supported the point that CYP3A5 expression status was not a significant risk factor for the development of VIPN. The authors argued that considering the heterogeneity of the study population, treatment regimens, assessment methods, definitions of VIPN, and interpretation of the results are limited.[1] The concentration time curve (AUC) of CYP3A5 nonexpressers was significantly higher than that of expressers.[9] There is a statistically considerable association between AUC and the degree of neurotoxicity.[22] To explore the relationship between drug exposure and VIPN, the potential of therapeutic drug monitoring (TDM) has therefore been highlighted. In the present case, the patient has the *CYP3A5*3/*3* genotype and is a nonexpresser of this enzyme, which may lead to decreased metabolism of VCR and increased risk of drug exposure and VIPN.

VCR transport and clearance are mainly contributed by the ABC family, which consists of transmembrane proteins that mediate VCR efflux across cell membranes. Several SNPs of ABCB1, ABCC1 and ABCC2 were found to be significantly correlated with VIPN.[7,8] ABCC1 is responsible for transporting VCR into the blood whereas ABCB1 and ABCC2 play a critical role in the biliary elimination of VCR.[8] In this case, we found that the patient carried the wild-type homozygote in *ABCC2* 12826 GG after analyzing the SNPs in the above related genes. A retrospective study suggested that the GG genotype was most strongly associated with an increase in neurotoxicity, which remained statistically significant after false discovery rate (FDR) correction. The minor allele showed a dominant protective effect.[8] The function of ABCC2 (also known as multidrug-resistance protein 2, MRP2) has been shown to be related to VCR resistance or sensitivity in several cell line studies.[23,24] rs12826 is a downstream SNP with a predicted role at the transcriptional regulation level. This SNP may affect the general expression or function of ABCC2 in some way, resulting in changes in VCR clearance. However, the absence of mutation carriers may be accompanied by an accumulation of VCR in cells, leading to increased intracellular concentrations, thus explaining the association with neurotoxicity.

The cellular cytoskeleton-associated gene *SYNE2*, which encodes the Nesprin-2 protein, interacts with the nuclear lamina and plays a critical role in neuronal migration and neural development.[25,26] Abaji et al identified that the AA allele of rs2781377 in the *SYNE2* gene had an increased risk of high-grade VIPN by combining whole-exome sequencing (WES) and an exome-wide association study (EWAS) strategy.[10]

Accumulated evidence has shown that microRNAs (miRNAs) mediate posttranscriptional regulation involved in drug pharmacokinetics and pharmacodynamics directly or indirectly[27] Gutierrez-Camino et al observed that CC alleles of rs7896283 CC/miR-4481 increased the risk of VCR-induced neurotoxicity by 2.6-fold ($p = 0.017$). In contrast, only the AA alleles of rs12402181/miR-3117 significantly decreased the risk of grade 1–4 neurotoxicity ($p = 0.00042$).[12] It is

worth noting that the pathway enrichment analysis revealed that rs7896283 in miR-4481 may be significantly related to the nervous system.[12] Genetic variants in miR-4481 could alter miRNA levels and consequently, decrease the expression of genes involved in peripheral nerve regeneration and leading to an increase in peripheral neuropathy.

CEP72 gene is involved in the formation of microtubules and has been shown to be associated with VCR sensitivity. Diouf et al took a genome-wide approach and revealed that patients carrying the TT allele in *CEP72* rs924607 had a higher incidence of VIPN than CC/CT patients,[4] which was confirmed by two subsequent studies.[11,28] Therefore, the CT genotype in this case cannot explain the observed neurotoxicity. Furthermore, genetic variants in *MTNR1B* rs12786200 may be correlated with the severity of VIPN based on the univariate, meta-analytic p-values from a North American cohort in this study.[4]

Interestingly, among the detected SNPs, a C to A polymorphism in the *BAHD1* gene was identified as protective against high-grade VIPN. The CA/AA genotypes of rs3803357 were associated with a lower incidence of toxicity of VCR.[10] BAHD1 is a heterochromatinization factor that may lead to neuropsychiatric disorders due to abnormal epigenetic features,[29] which in itself, is linked to sensory and autonomic neuropathy.

Neuropeptide S receptor 1 (NPSR1) is a G protein-coupled receptor (GPCR) that is expressed in various regions of the brain and enteroendocrine cells in the gut and regulates several, physiological processes, including inflammation and pain.[30] Considering the frequent occurrence of abdominal pain in our patient, seven SNPs in *NPSR1* associated with recurrent abdominal pain[13] were genotyped. *NPSR1* polymorphisms may modulate abdominal pain by impacting its expression.

Conclusions

In conclusion, the severe VIPN developed in this patient might be associated with a complex pattern of polymorphisms. This case highlights the potential importance of pharmacogenetic testing in clinical practice. Unfortunately, there are no widely accepted genetic biomarkers. Therefore, further investigations in this field are needed to identify high-risk patients. Comprehensive risk assessments of pharmacogenomic factors may allow a safer, personalized approach to VCR-based chemotherapy in children.

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Disclosure

Gui-Zhou Li, Jia-Yi Long, and Qing-Yan Yang are visiting graduate students from China Pharmaceutical University. The authors declare no conflict of interest.

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