THE HONG KONG POLYTECHNIC UNIVERSITY

RESEARCH DEGREE PROPOSAL

1. **Name of Proposed Chief Supervisor (if applicable):**
   Prof. HO, Eva Ka Yan

2. **Project Title:**

   Cross-cultural adaptation and validation of the pediatric chemotherapy-induced neuropathy (P-CIN) for Chinese pediatric oncology patients: A methodological and descriptive study

3. **Project Objectives: (Purpose of proposed investigation)**
   This study aims to cross-culturally adapt and validate the original P-CIN for Chinese pediatric oncology patients.

4. **Scope and Background of Research:**
   (Please identify key issues/problems to be addressed)
   Chemotherapy-induced peripheral neuropathy (CIPN), one of the most common adverse effects of neurotoxic chemotherapeutic agents, has been defined as a single, or a combination of motor, sensory and autonomic impairments that results from the damage, inflammation, and degeneration of peripheral nerve fibers. CIPN is a marker of multiple serious consequences, including decreased physical activity, falling, pain, fatigue, sensory and motor deficits, poorer quality of life, mortality, and psychological distress. The development of CIPN may lead to dose reduction, interruption or cessation of the chemotherapy treatment, which can impact the treatment efficacy and decreasing their survival.[1] Clinical abnormalities attributable to CIPN including sensory and motor neuropathy, functional deficits and CIPN pain are common in pediatric oncology patients and can persist into adulthood. Systematic review has reported that CIPN incidence in pediatric patients varies from 2.8% to 100% depending on the assessment measures.[1] Therefore, it is crucial to accurately identify and assess CIPN at the earliest possible stage.

   The severity of CIPN may fluctuate during treatment courses, the overall trend tends to show increasing severity, even as dose intensity and treatment frequency may decrease over time. In addition, CIPN may last for months to several years after the end of anticancer chemotherapies.[2] Thus, early identification is imperative for the intervention implementation that can improve long term care and relieve disease burden. There is limited evidence to a feasible, simple and accurate assessment measure for pediatric CIPN and

numerous CIPN measures have been developed. According to our previous updated systematic review, the Total Neuropathy Score (TNS) variants including Pediatric-modified Total Neuropathy Score (Ped-mTNS) and Total Neuropathy Score-Pediatric Vincristine (TNS-PV), as an objective measure, is the most widely used assessment measure of CIPN. However, both have limitations associated with the pediatric oncology patients in clinical settings. The Ped-mTNS includes many physical examinations, such as light touch sensation, pin sensibility, vibration sensation, and strength and deep tendon reflexes. These measurements are not only the time-consuming and clinical space using for assessments but also induce discomforts associated with some testing procedures, e.g., pin prick. The TNS-PV is only for assessing CIPN severity in children taking Vincristine. In addition, a trained registered clinician performs these two measurements. Hence, the Ped-mTNS and TNS-PV maybe not feasible to be used widely in the clinical settings in China. Other pediatric CIPN assessment measures, the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group-Neurotoxicity (FACT-GOG-Ntx) only validated in pediatric patients with Hodgkin lymphoma and the Bruininks-Oseretsky Test of Motor Proficiency version 2 (BOT-2) only used to assess the motor skills in pediatric patietns with CIPN. Thus, these assessment measures cannot comprehensively evaluate the CIPN severity in pediatric oncology patients. Furthermore, the few existing pediatric CIPN measures are not well validated.

There is a critical need for pediatric CIPN measures. The Pediatric Chemotherapy-Induced Neuropathy (P-CIN), which includes the core elements of CIPN symptoms, was specially developed for assessing CIPN severity in pediatric patients. The P-CIN consists of 13 self-reported items using age-appropriate language and graphics without involving clinician examination, and it takes only a few minutes and can be completed by pediatric patients themselves or their parents' assistance. The P-CIN can be feasibly applied by pediatric oncology patients themselves or their parents in China where healthcare service space and service time lacking and short-staffing of pediatricians. In turn, the P-CIN helps in the early identification of CIPN in pediatric oncology patients and evaluate the effectiveness of an intervention.

The original P-CIN was developed in 2021 and the first electronic CIPN patient reported outcome measure (PROM). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Chemotherapy-Induced Peripheral Neuropathy 20-item sub-scale (EORTC QLQ-CIPN20) served as a model when developing P-CIN specific items, and further validated in pediatric patients with CIPN in the United States. The P-CIN contains four items to rate CIPN subjective symptons - numbness and tingling in the hands and feet. If pediatric patients reported experiencing these symptoms, they were directed to answer four additional questions regarding painful numbness and tingling. Five items were used to quantify CIPN functional deficits experienced such as picking up a penny or heel-

walking. Evidence indicates that the P-CIN is reliable and valid in United States contect. However, there is a lack of measures for CIPN assessment in China after a systematic search and the P-CIN has never been validated for use with pediatric patients with CIPN in China. This lack of validated assessment measures preclude understanding the severity of the CIPN and hinders the development of appropriate interventions to promote CIPN symptoms managment. On the other hand, a culturally sensitive assessment is critical in defining, identifying, describing and understanding the signs and symptoms of CIPN[3] as the culture and language can impact the expression and interpretation of symptom characteristics.[4] For instance, in East Asia, terms like “burning” were never used, with patients may report “numbness”.[4, 5] Due to the aforementioned concerns, it may be not appropriate to apply the P-CIN to assess the CIPN severity of pediatric patients before cross-cultural adaptation and validation. It is essential that assessment measures are appropriately adapted and validated in a new cultural setting to ensure valid and reliable measures.

5. Research Methodology:

Study design

This methodological, descriptive study will be conducted in Shenzhen, Zhengzhou, Shanghai, mainland China, from November 2024 to April 2025. Pediatric oncology patients will be enrolled from inpatient ward in Shenzhen Children’s Hospital, Henan Cancer Hospital and Shanghai Children’s Medical Center.

This study will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data collection

Research team contacts with the dean of Nursing Department of each site. After approval, the name list of pediatric oncology patients receiving the neurotoxicity agents will be provided. Well-trained registered nurses will identify potentially eligible participants through checking the medical records and confirm the eligibility based on the inclusion and exclusion criteria. In addition, the registered nurse will approach these potential participants and ask all children and their parents who accompanied children for hospitalization in inpatient clinic or medical consultation in the outpatient clinic, and introduce the study. The information sheet including research purpose, procedures, confidentiality measures, and their rights as participants will be provided. All pediatric patients agree to participate the study will invite to sign an informed consent form with their legal guardian in accordance with the Declaration of Helsinki. We assure participants’ responses would remain confidential. After obtaining written consent, each child will be asked to complete the questionnaire independently. For those children who are unable to self-report, parents will

be asked to assist them in completing the questionnaire. To assess test-retest reliability, a sample of 50 children will be randomly selected to respond by phone to the P-CIN 2 weeks later.

Participants

Eligible participants are children 6 to 18 years of age[6] who (1) diagnosed with cancer, (2) had received or were currently receiving neurotoxic chemotherapy drugs (e.g., Vincristine, Cisplatin, Carboplatin, Oxaliplatin, Paclitaxel, Docetaxel, Ixabepilone, Bortezomib, Thalidomide), (3) children's, and parents' willingness to participate in the study voluntarily, (4) able to communicate, read, and write in Chinese without significant hearing and vision problems to ensure they understand our interview. The exclusion criteria are children who (1) diagnosis of a tumour involving the central nervous system (CNS) cancer, (2) diagnosis of relapsed cancer or secondary cancer, (3) in the terminal period, (4) plan to receive multiple cancer treatment (e.g., radiotherapy, immunotherapy), (5) suffering from other neuromuscular diseases (e.g., traumatic brain injury and cerebral palsy), (6) have a developmental deficit (e.g., Down's syndrome, other chromosomal disorders), (7) suffering from psychiatric diseases or using antipsychotic drugs, (8) severe cardiovascular system diseases and severe liver and kidney function abnormalities, (9) peripheral neuropathy symptoms caused by diabetes, genetic diseases, spinal cord injury, or alcoholism, (10) have other neuromuscular disorders (e.g., traumatic brain injury, cerebral palsy).

Sample size

Although there is no golden standard for the sample size calculation for validation study in nursing research, the recommended sample size for factor analyses is between 150 to 180.[7] In addition, the Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) must be conducted on different datasets.[8] We therefore determined to recruit 300 pediatric oncology patients in our validation study.

CIPN measurements

Pediatric chemotherapy-induced peripheral neuropathy (P-CIN)

It was originally developed for children ≥ 6 years old who had received or were receiving neurotoxic chemotherapy and reported peripheral neuropathy to quantify numbness and tingling in the hands and feet and the functional deficits in the past two to three days[6]. The P-CIN comprises 13 items, with eight items to rate CIPN symptoms in the hands and feet and five items to rate the difficulty of performing functional tasks, e.g., standing on one leg and closing eyes for 15 seconds[6]. Each item is rated using a 6-point faces scale. The total score ranges from 0 to 65 with higher scores indicating more severe CIPN[6].

Clinician diagnosis of pediatric CIPN

In our previous systematic review of assessment measures for CIPN among pediatric oncology patients(reference), it was concluded that the method of choice for assessing pediatric CIPN was combination of subjective and objective assessment measures. The diagnosis of pediatric CIPN in our study was established solely if the abnormal Nerve Conduction Studies (NCS) criteria, NCI-CTCAE score ≥ 2, and clinical consultation (including the chemotherapeutic drugs used, cumulative doses, and clinical characteristics and time course of neuropathy symptoms) of CIPN symptoms were simultaneously observed based on the consensus of pediatric neurologists in the three hospitals.

(1) NCS criteria:

For the NCS, the motor responses of median and ulnar nerves in the bilateral upper limb and the fibular and tibial nerves in the bilateral lower limb and the sensory responses of median and ulnar nerves in the bilateral upper limb and sural and medial plantar nerves in the bilateral lower limb were recorded. Nerve conduction parameters recorded included distal motor latency (DML), peak to peak sensory nerve action potential amplitude, motor nerve conduction velocity (MNCV), and sensory nerve conduction velocity (SNCV). Pediatric individuals who are at least 4 years old are deemed to have achieved the NCS reference ranges typically seen in adults.[14] The reference values for each nerve were according to reference limits of NCS parameters for Chinese subjects from Fong et al. as follows:

Table 1 Reference lists of NCS parameters for Chinese subjects and range in all subjects

Parameters	Reference limits Chinese	Range all subjects
Motor		
Median		
DML (ms)	4.1	2.5-4.3
Amplitude (mV)	7.3	7.0-17.9
MNCV (m/s)	52	50-65
Ulnar		
DML (ms)	3.0	2.0-3.1
Amplitude (mV)	6.4	6.3-15.6
MNCV (m/s)	53	52-68
Fibular		
DML (ms)	4.2	2.6-4.4
Amplitude (mV)	3.3	2.4-10.9
MNCV (m/s)	43	42-58
Tibial		
DML (ms)	3.9	2.4-4.3

Amplitude (mV)	7.5	5.1-26.7
MNCV (m/s)	41	38-57
Sensory		
Median		
Amplitude (mV)	7	5-34
SNCV (m/s)	48	45-67
Ulnar		
Amplitude (mV)	6	2-22
SNCV (m/s)	48	46-66
Sural		
Amplitude (mV)	6	2-34
SNCV (m/s)	42	38-61
Medial plantar		
Amplitude (mV)	3	2-37
SNCV (m/s)	40	26-36

NCS parameters including distal latencies, amplitudes, and velocities were considered abnormal, if values were more than 2.0 standard deviation of the normal reference values. In our study, the pediatric neurologist considered CIPN as the presence of abnormal NCS parameters in two or more nerves.

(2) National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0

The CTCAE (version 5.0) consists of over 330 items scoring adverse events (AE) due to cancer treatment divided into 26 different categories. Grade refers to the severity of the adverse events. Possible grades range from grade 1 (Mild, asymptomatic or mild symptoms, clinical or diagnostic observations only), grade 2 (Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)), grade 3 (Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL), grade 4 (Life-threatening consequences; urgent intervention indicated) to grade 5 (Death related to AE). The NCI-CTCAE items used for the assessment of CIPN are peripheral sensory neuropathy, peripheral motor neuropathy, constipation, diarrhea, and neuralgia due to the sensory, motor and autonomic symptoms of pediatric CIPN[15]. The maximum CTCAE sum score of these 5 items is 22. Participants with a total score of 2 or higher are considered to have CIPN[16, 17].

Wong-baker FACES Pain Rating scale

This scale combines pictures and numbers to enable the user to rate pain which demonstrates six faces with increasing degree of pain from left to right, where each face is rated on a scale of 10 in which 0 indicated no hurt, 2 indicated hurts a little, 4 indicated hurts little more, 6 indicated hurts, even more, 8 indicated hurts a whole lot, 10 indicated hurts worst[18]. It can be used for children over the age of 3, and for adults[18]. This scale has adequate psychometric properties and it is easy and quick to[19] and it has been validated among Chinese children with acute fever[20].

Chinese version of the Pediatric Quality of Life Inventory (PedsQL) Cancer Module

The PedsQL Cancer Module will be used to assess the participants' QoL. This scale contains 27 items grouping into eight subscales including (1) pain and hurt, (2) nausea, (3) procedural anxiety, (4) treatment anxiety, (5) worry, (6) cognitive problems, (7) perceived physical appearance, and (8) communication. There are parallel and identical versions for pediatric patients (young child: 5-7 years old, child: 8-12 years old, and adolescent: 13-18 years old) and parents (toddler: 2-4 years old plus the above three age groups). The participants rated how frequently a particular problem occurred in the past month, using a three-point Likert scale (0 = Never, 2 = Sometimes, 4 = Almost always) for children 5-7 years old and a five-point Likert scale (0 = Never, 1=Almost never, 2=sometimes, 3=often, 4 = Almost always) for children of 8-18 years old and for the parents of patients of all ages. Each item score will be reversely scored and then linearly transformed into 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). The scale is the average of the total item scores. Higher scores represent better quality of life (QoL). The psychometric properties of the Chinese version of the scale have been well-examined[21]. This scale has been demonstrated as a valid and reliable tool in assessing QoL for Hong Kong Chinese adolescent with cancer[21].

Psychometric evaluation

Reliability assessment

Reliability refers to the ability of a instrument to determine that a measurement yields reproducible and consistent results. Three important reliability criteria are: internal consistency, and stability. **Internal consistency** shows if all subparts of an instrument measure the same characteristic. Cronbach's alpha coefficient and the corrected item-total correlation will be used to assess internal consistency of the P-CIN. **Stability** estimates the consistency of measurement repetition and can be performed using test-retest method. The time span between measurements will influence the interpretation of test-retest reliability; therefore, the time span from 10 to 14 days is considered adequate for the test and retest. A group of 50 children will be randomly selected for the achievement of statistical significance for an alpha value is 0.05 and with a power of 0.90.[22] The intraclass correlation coefficient (ICC) is one of the most used tests to estimate continuous variables stability, as it takes into

account the measurement errors.

Validity assessment

Validity refers to an instrument measures exactly what it proposes to measure. Validity can be assessed in different forms such as content validity, convergent validity, criterion validity, and construct validity. **Content validity** can be defined as the extent to which an assessment tool accurately and fully reflects the concept being measured. The Delphi technique will be used to establish the content validity of the P-CIN. We will obtain the opinions of 10 experts through a structured questionnaires delivered two iterations until consensus will be reached. **Convergent validity** is the degree to which scores on a measure associate with scores on other measures that are intended assess similar constructs. Pain level, self-reported quality of life are CIPN-related concepts that have been identify pediatric oncology patients with CIPN risk[15]. Therefore, convergent validity will be explored using well-established CIPN-related measurements, namely, (1) the Wong-baker FACES pain rating scale to assess levels of pain; and (2) the Pediatric Quality of Life Inventory (PedsQL) Cancer Module to determine level of quality of life with the help of the Spearman's correlation coefficient (r). **Criterion validity** is the relation between the score of a certain instrument and some external criterion. This criterion has to be a widely accepted measure, with the same characteristics of the assessment tool. Criterion validity will be evaluated using the pediatric neurologists' CIPN diagnosis as a reference criterion. Spearman's correlation coefficient (r) will be calculated to evaluate the correlations between the P-CIN and the CIPN diagnosis. Using diagnostic testing to determine the presence or absence of the CIPN is essential. The ROC curve aims to find an optimal cut-off value with the best CIPN diagnostic performance. Additionally, the ROC curve is utilized to evaluate the overall diagnostic performance of a test and to compare multiple diagnostic tests.[23] The area under the curve (AUC) will be used to measure the accuracy of diagnostic test. Generally, an AUC ≥ 0.8 is considered acceptable. Youden statistic (calculated as sensitivity + specificity - 1) was used to determine the optimal cut-off value.[24] The point at which this value is maximized is determined as the optimal cut-off value.[24]

Factor analysis

Factor analysis is valuable for evaluating sampling adequacy, internal consistency, factor rotation, factor identification, item retention, and other analytical processes. Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) are two common techniques used in scale adaptation studies. EFA will be conducted to determine the number of underling latent factors and the structure of items. Following the execution of the EFA, a measurement model will be applied to examine CFA using three critical results: parameter estimates, fit indices, and modification indices. In our study, the sample will be randomly

split into two halves (half for EFA and half for CFA).

EFA will be performed by using the SPSS software, version 29.0 for Mac (SPSS Inc., Chicago, IL, United States). Suitability of the matrix for conducting the EFA will test using the Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity. The KMO sampling adequacy test will be deemed adequate if the value was greater than 0.6. A significant level of *P*-value < 0.05 of Bartlett's Test of Sphericity indicates EFA can be performed. The number of factors that should be retained in the model was determined using eigenvalues and scree-plot. All factors with eigenvalues above one was retained according to the Kaiser's criteria. In addition, factors corresponding to data points lying above the point of inflexion of the scree-plot were also retained. Principal component analysis will be performed to conduct an additional factor analysis, which helps determine the loadings for every factor selected. Analyze the factor composition and the factor loading of each item on the corresponding factor, and delete items with factor loading < 0.50. Cumulative variance contribution rate be above 50%. We will apply the varimax type of rotation. In addition, varimax rotation will be chosen since it minimizes factor complexity while, at the same time, maximizing the variance of factor loadings.

Following the execution of the EFA, CFA will be accomplished using IBM SPSS Amos, version 29.0. CFA will be used to establish and validate the constrcut validity of the P-CIN. Maximum Likelihood was used as the estimation method. To evaluate the goodness of fit, the following statistical measures will be utilized: ratio of chi-square and degrees of freedom (χ^2/df), root mean square residual (RMR), standardized root mean square residual (SRMR), goodness of fit index (GFI), comparative fit index (CFI), root mean square error of approximation (RMSEA).

Feasibility

Feasibility means percentage of children who completed the P-CIN independently. In this study, we use the item 'Did the children need assistance by a parent or other adults to complete the survey?' to evaluate the feasibility.

Data analysis

The IBM Statistical Package for the Social Sciences (SPSS, version 29.0, NY, USA) will be performed to conduct all statistical analyses. For demographic data, continuous variables are represented by mean (standard deviations), while categorical variables are shown as frequencies (percentages). For the psychometric data, Cronbach's alpha coefficient and corrected item-total correlation will be used to assess **internal consistency** of the P-CIN. Cronbach's alpha value higher than 0.70 is acceptable with the interpretation as follows: below 0.70 = poor; between 0.70 and 0.79 = fair; between 0.80 and 0.89 = good; and above 0.90 = excellent.[25] Values for corrected item-total correlation can be explained as follows: values between 0 and 0.19 indicate that the item is not discriminating well, 0.2-0.39 indicate

good discrimination, 0.4 and above indicate very good discrimination. Good internal consistency reliability is indicated by a Cronbach's alpha coefficient ≥0.70 and item-total score correlations ranging from 0.30 to 0.70. The intraclass correlation coefficient (ICC) will be used to evaluate the **test-retest reliability**. For the results interpretation, minimum ICC values of 0.70 are considered satisfactory, values above 0.8 or 0.9 are often regarded as a sign of good or excellent test-retest reliability.[26] Concerning for the **content validity**, a scale with excellent content validity should be composed of I-CVIs of 0.78 or higher and UA -CVI/Ave-CVI of 0.8 and 0.9 or higher, respectively. Spearman's correlation coefficient (r) will be performed to evaluate **convergent validity**. The correlation values for convergent validity are classified as follows: r=0, no correlation; r=0.10-0.29 (–0.10 to –0.29), negligible correlation; r=0.30-0.49 (–0.30 to –0.49), low positive (negative) correlation; r=0.50-0.69 (–0.50 to –0.69), moderate positive (negative) correlation; r=0.70-0.89 (–0.70 to –0.89), high positive (negative) correlation; r=0.90-1.00 (–0.90 to –1.00), very high positive (negative) correlation.[27] Spearman's correlation coefficients equal to 0.70 or over are desirable. To determine **criterion validity**, Spearman's correlation coefficient will be used. Concerning the effectiveness diagnostic test, receiver operating characteristic (**ROC**) curve analysis will be performed. The interpretation of the **AUC** as follows: fail ($0.5 \leq AUC < 0.6$), poor ($0.6 \leq AUC < 0.7$), fair ($0.7 \leq AUC < 0.8$), good ($0.8 \leq AUC < 0.9$), excellent ($0.9 \leq AUC$). **Youden's Index** will be used to calculate the optimal cut-off value. Concerning the CFA, χ^2/df for value lower than 5 the fit is acceptable. RMR and SRMR: the lower the values, the better the fit. GFI and CFI values over 0.90 are considered a good fit (with a maximum value equal to 1). Reference value for the RMSEA between 0.05 to 0.08 mean the adjustment is good. Factor loading values above or close to 0.70 are better to explain the structure. As for the clinical feasibility, the P-CIN will be considered a practical tool for implementation in clinical practice settings if 80% or more of the children completed the questionnaire independently.

Ethical considerations

This study will not involve any invasive procedure, thus the chance of imposing physical harms on subjects is minimal. If the there is any adverse effects that happens during the data collection, the registered nurses will immediately stop and ask the participants whether they would like to continue or terminate the study. With parental consent, we will pass their contact to the head nurses of pediatric oncology ward (our co-investigators). They will further assess the psychological well-being of the participants. If necessary, they will refer these participants to relevant medical personnel, e.g. doctors, clinical psychologists and/or social workers to follow-up.

References

1. Johnston W, Erdmann F, Newton R, Steliarova-Foucher E, Schüz J, Roman E: Childhood cancer: Estimating regional and global incidence. *Cancer epidemiology* 2021, 71:101662.
2. Beijers AJM, Vreugdenhil G, Oerlemans S, Eurelings M, Minnema MC, Eeltink CM, van de Poll-Franse LV, Mols F: Chemotherapy-induced neuropathy in multiple myeloma: influence on quality of life and development of a questionnaire to compose common toxicity criteria grading for use in daily clinical practice. *Supportive Care in Cancer* 2016, 24(6):2411-2420.
3. Purser M, McMillan H, Johnston D: Chemotherapy-Induced Peripheral Neuropathy among Pediatric Oncology Patients. *Pediatric Blood & Cancer* 2013, 60:S50-S51.
4. Kandula T, Park SB, Cohn RJ, Krishnan AV, Farrar MA: Pediatric chemotherapy induced peripheral neuropathy: A systematic review of current knowledge. *Cancer Treat Rev* 2016, 50:118-128.
5. Bjornard KL, Gilchrist LS, Inaba H, Diouf B, Hockenberry MJ, Kadan-Lottick NS, Bowers DC, Dolan ME, Ullrich NJ, Evans WE, Ness KK: Peripheral neuropathy in children and adolescents treated for cancer. *The Lancet Child & Adolescent Health* 2018, 2(10):744-754.
6. Smith E M L , Kuisell C , Cho Y ,et al.Characteristics and patterns of pediatric chemotherapy-induced peripheral neuropathy: A systematic review[J].Cancer Treatment and Research Communications, 2021:100420. DOI:10.1016/j.ctarc.2021.100420.
7. E.M. Lavoie Smith, L. Li, C. Chiang, et al., Patterns and severity of vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia, J. Peripher. Nerv. Syst. 20 (2015) 37–46.
8. L. Gilchrist, L. Tanner, Chemotherapy-induced peripheral neuropathy in non-cns cancers: comparison between diagnostic groups, Pediatr. Blood Canc. 61 (2014) S393.
9. A.J. Lombardi, M.E. Sutton, G.M. Tiao, J.I. Geller, Vincristine-associated neurological morbidity in the treatment of hepatoblastoma, J. Pediatr. Hematol. Oncol. 37 (2015) e258–e263.
10. Salat K, Furgala-Wojas A, Salat R: The Microglial Activation Inhibitor Minocycline, Used Alone and in Combination with Duloxetine, Attenuates Pain Caused by Oxaliplatin in Mice. *Molecules* 2021, 26(12).
11. Triarico S, Romano A, Attina G, Capozza MA, Maurizi P, Mastrangelo S, Ruggiero A: Vincristine-Induced Peripheral Neuropathy (VIPN) in Pediatric Tumors: Mechanisms, Risk Factors, Strategies of Prevention and Treatment. *Int J Mol Sci* 2021, 22(8).
12. Uittenboogaard A, Neutel CLG, Ket JCF, Njuguna F, Huitema ADR, Kaspers GJL, van de Velde ME: Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy in Children with Cancer: A Systematic Review and Meta-Analysis. *Cancers (Basel)* 2022, 14(3).
13. Lazzerini M, Martelossi S, Magazzu G, Pellegrino S, Lucanto MC, Barabino A, Calvi A, Arrigo S, Lionetti P, Lorusso M *et al*: Effect of Thalidomide on Clinical Remission in Children and Adolescents with Ulcerative Colitis Refractory to Other Immunosuppressives: Pilot Randomized Clinical Trial. *Inflamm Bowel Dis* 2015, 21(8):1739-1749.
14. L. Rosca, V. Robert-Boire, J.-.F. Delisle, et al., Carboplatin and vincristine neurotoxicity in the treatment of pediatric low-grade gliomas, Pediatr. Blood Canc. 65 (2018) e27351.
15. Lin, M.J.; Paul, M.R.; Kuo, D.J. Severe neuropathic pain with concomitant administration of Vincristine and Posaconazole. J. Pediatr. Pharmacol. Ther. 2018, 23, 417–420
16. S. Dudeja, S. Gupta, S. Sharma, et al., Incidence of vincristine induced neurotoxicity in children with acute lymphoblastic leukemia and its correlation with nutritional deficiencies, Pediatr. Hematol. Oncol. 36 (2019) 344–351.
17. P. Jain, S. Gulati, R. Seth, S. Bakhshi, G.S. Toteja, R.M. Pandey, Vincristine-induced

neuropathy in childhood all (acute lymphoblastic leukemia) survivors: prevalence and electrophysiological characteristics, J. Child Neurol. 29 (2014) 932–937.
18. S. Gomber, P. Dewan, D. Chhonker, Vincristine induced neurotoxicity in cancer patients, Ind. J. Pediatr. 77 (2010) 97–100.
19. T.J. ajdyk, F.A. Boyle, K.S. Foran, et al., Obesity as a potential risk factor for vincristine-induced peripheral neuropathy, J. Pediatr. Hematol. Oncol. 42 (2020) e637–e640, https://doi.org/10.1097/MPH.0000000000001604.
20. Kandula T, Farrar MA, Kiernan MC, et al. Neurophysiological and clinical outcomes in chemotherapy-induced neuropathy in cancer. Clin Neurophysiol 2017; 128: 1166–75.
21. F. Brigo, R. Balter, P. Marradi, et al., Vincristine-related neuropathy versus acute inflammatory demyelinating polyradiculoneuropathy in children with acute lymphoblastic leukemia, J. Child Neurol. 27 (2012) 867–874.
22. H. Courtemanche, A. Magot, Y. Ollivier, et al., Vincristine-induced neuropathy: atypical electrophysiological patterns in children, Muscl. Nerv. 52 (2015) 981–985.
23. S. Gomber, P. Dewan, D. Chhonker, Vincristine induced neurotoxicity in cancer patients, Ind. J. Pediatr. 77 (2010) 97–100.
24. H. Kayiliog˘lu, U. Kocak, D. Kan Karaer, et al., Association of cyp3a5 expression and vincristine neurotoxicity in pediatric malignancies in turkish population, J. Pediatr. Hematol. Oncol. 39 (2017) 458–462.
25. E.M.L. Smith, L. Li, R.J. Hutchinson, et al., Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia, Canc. Nurs. 36 (2013) E49–E60.
26. F. Brigo, R. Balter, P. Marradi, et al., Vincristine-related neuropathy versus acute inflammatory demyelinating polyradiculoneuropathy in children with acute lymphoblastic leukemia, J. Child Neurol. 27 (2012) 867–874.
27. C.G. Tay, V.W.M. Lee, L.C. Ong, K.J. Goh, H. Ariffin, C.Y. Fong, Vincristine-induced peripheral neuropathy in survivors of childhood acute lymphoblastic leukaemia, Pediatr. Blood Canc. 64 (2017) e26471.
28. S. Lieber, M. Blankenburg, K. Apel, G. Hirschfeld, P. Herna´iz Driever, T Reindl, Small-fiber neuropathy and pain sensitization in survivors of pediatric acute lymphoblastic leukemia, Eur. J. Paediatr. Neurol. 22 (2018) 457–469.
29. McCrary, J. MattGoldstein, DavidBoyle, FrancesCox, KeithGrimison, PeterKiernan, Matthew C.Krishnan, et al., Optimal clinical assessment strategies for chemotherapy-induced peripheral neuropathy (CIPN): a systematic review and Delphi survey[J].Supportive care in cancer. 2017, 25(11).
30. Cheng H L , Molassiotis A .Longitudinal validation and comparison of the Chinese version of the European Organization for Research and Treatment of Cancer Quality of Life - Chemotherapy - Induced Peripheral Neuropathy Questionnaire (EORTC QLQ - CIPN20) and the Functional Assessment of Cancer - Gynecologic Oncology Group - Neurotoxicity subscale (FACT/GOG - Ntx)[J].Asia - Pacific Journal of Clinical Oncology, 2019, 15.
31. Klafke N, Bossert J, Kröger B, Neuberger P, et al., Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy (CIPN) with Non-Pharmacological Interventions: Clinical Recommendations from a Systematic Scoping Review and an Expert Consensus Process. Med Sci (Basel). 2023 Jan 30;11(1):15.
32. Tamburin S, Park SB, Schenone A, et al. Rehabilitation, exercise, and related non-pharmacological interventions for chemotherapy-induced peripheral neurotoxicity: systematic review and evidence-based recommendations. Crit Rev Oncol Hematol. 2022;171, 103575. https://doi.org/10.1016/j.critrevonc.2021.103575.
33. Toth MJ, Voigt TB, Tourville TW, Prior SM, Guigni BA, Schlosberg AV, Smith IB, Forest TJ, Kaufman PA, Wood ME, Rehman H, Dittus K. Effect of neuromuscular electrical stimulation on skeletal muscle size and function in patients with breast cancer receiving chemotherapy. J Appl Physiol (1985). 2020 Jun 1;128(6):1654-1665. doi: 10.1152/japplphysiol.00203.2020. Epub 2020 May 7.

34. Yan D, Vassar R. Neuromuscular electrical stimulation for motor recovery in pediatric neurological conditions: a scoping review. Dev Med Child Neurol. 2021 Dec;63(12):1394-1401. doi: 10.1111/dmcn.14974.
35. Wang TS, Wang SF, Song WD, Tang ZC, Wei W, Wang GK. Neuromuscular electrical stimulation for cancer pain in children with osteosarcoma: A protocol of systematic review. Medicine (Baltimore). 2020 Jul 24;99(30):e21311.
36. Kimura T, Kaneko F, Iwamoto E, Saitoh S, Yamada T. Neuromuscular electrical stimulation increases serum brain-derived neurotrophic factor in humans. Exp Brain Res. 2019 Jan;237(1):47-56. doi: 10.1007/s00221-018-5396-y. Epub 2018 Oct 10. PMID: 30306243.
37. Kandula T, Farrar MA, Cohn RJ, Carey KA, Johnston K, Kiernan MC, Krishnan AV, Park SB. Changes in long term peripheral nerve biophysical properties in childhood cancer survivors following neurotoxic chemotherapy. Clin Neurophysiol. 2020 Apr;131(4):783-790. doi: 10.1016/j.clinph.2019.12.411.
38. Wang J, Jacobs S, Dewalt DA, Stern E, Gross H, Hinds PS. A Longitudinal Study of PROMIS Pediatric Symptom Clusters in Children Undergoing Chemotherapy. J Pain Symptom Manage. 2018 Feb;55(2):359-367.
39. Streckmann, F., Kneis, S., Leifert, J.A., Baumann, F.T., Kleber, M., Ihorst, G., et al., 2014. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. Ann. Oncol. 25, 493–499.