



Clinical Picture of Recurrent Chemotherapy-Induced Neuropathic Pain in Young Children and Efficacy of Short Course of Pregabalin for the Secondary Prophylaxis

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Abstract

Background: Chemotherapy-Induced Neuropathic Pain (CINP) is one of the underestimated and/or undertreated complications of pediatric cancer practice due to lack of sufficient knowledge and pertinent pharmacological intervention.

Procedure: A retrospective review of the clinical charts of patients younger than three years of age treated for pediatric cancer in a single institute. We specifically analyzed the clinical pictures of recurrent CINP and verified the usefulness of the short course of Pregabalin (PGB) for prevention and treatment of recurrent CINP.

Results: Of the 14 children analyzed (mean age of 20 months), five patients (35.7 %) developed recurrent CINP. All the patients had been placed on at least one of the following neurotoxic chemotherapeutic agents: Vincristine Sulfate (VCR), Paclitaxel (PTX), or platinum compound. We found a strong temporal association between the drug exposure and the onset of related symptoms, such as bilateral buccal pain 3 days after VCR, migrating paresthesia 3 days after PTX, and acute back pain within a few hours after oxaliplatin. Previous platinum exposures and the presence of concurrent motor and/or autonomic symptoms (ataxic gait, hyporeflexia, excessive sweating, tachycardia, and constipation) were predictive of recurrent CINP. Secondary prophylaxis with short course of pregabalin was successful, but it is essential to optimize the dosage and/or duration depending on the patient basis.

Conclusions: An awareness of reagent specific clinical pictures together with target evaluation of concurrent motor and/or autonomic symptoms might be helpful to make an early diagnosis of CINP, especially in young children who are still unable to fully verbalize their complaints. A short course of PGB can be included as one of the secondary prophylaxes for recurrent CINP with tolerable safety profiles.



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Introduction

Chemotherapy-Induced Neuropathic Pain (CINP) is one of the underestimated and/or undertreated complications of pediatric cancer practice and severely interferes with the patients' Quality Of Life (QOL) [1,2]. To provide an individualized supportive measure during anticancer therapy, it is highly warranted to understand the agent-specific clinical manifestations and predisposing risk factors for developing CINP. Several assessment scales for peripheral neuropathy are available for school-aged population [3,4], but the clinical diagnosis of CINP is challenging in children due to their limited verbalization of their complaints. The epidemiological study showed that the diagnosis of Acute Lymphoblastic Leukemia (ALL) is peaked at two years of age [5], and it is therefore important to delineate the clinical pictures of the CINP especially in young children. To date, several pharmacological agents, such as tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, and antiepileptic drugs, are available for treatment of peripheral neuropathic pain [6], but there has been no established prophylactic intervention for CINP. In this report, we analyzed the clinical characteristics of recurrent CINP and verified a short course of prophylactic Pregabalin (PGB) for CINP in children younger than three years of age.

Patients and Methods

This is a retrospective review of the clinical charts of the patients younger than three years of age treated for pediatric cancer between July 2015 and March 2020 at Hyogo Prefectural Amagasaki General Medical Center. Patients with the following clinical conditions were excluded from this analysis: developmental delay, inherited genetic disorder, intracranial tumor, and epilepsy. The prescribed and cumulative doses of chemotherapy were within the standard range. The primary end point of this study was to delineate the clinical pictures of CINP of children younger than 3 years of age. The severity of peripheral neuropathy was serially scored according to the National Cancer Institute Common Toxicity Criteria, version 3.0. For patients with recurrent CINP, three patients received a short course of prophylactic PGB starting at least 3 days before the chemotherapy, and one patient was placed on PGB for the pre-existing CINP. In the light of lessening the side effects, we initially prescribed up to 0.75 mg/kg/dose of PGB at bedtime followed by gradual titration based on both its therapeutic benefit and side effect profile. Given the possible CYP3A4 mediated drug interaction between Vincristine Sulfate (VCR) and azole antifungal [7], the prophylactic fluconazole treatment was temporarily suspended in the presence of VCR-induced neuropathy. We obtained approval for this retrospective review from the institutional review board.

Results

Of the 23 patients, 9 patients (4 with Down syndrome, 1 with trisomy 18, 1 with leukodystrophy, 2 with intracranial tumor, and 1 with Dandy-Walker syndrome) were excluded from this analysis. The mean age of 14 patients was 18.9 months (median age, 20 months; range, 4-35), and 5 patients (35.7 %) developed recurrent CINP. All the patients received at least one of the following chemotherapeutic agents: VCR, paclitaxel (PTX), or platinum compound (Table 1). The affected patients developed a mean of 3.3 episodes of CINP (median, 2.0; range, 2-5). Four patients were placed on a short course of PGB for prevention and/or treatment of recurrent symptoms. The therapeutic effect was excellent with a complete resolution of the neuro-

pathic pain, and it also greatly relieved emotional distress of the guardians. Major adverse effects of PGB, such as dizziness, headache, somnolence, ataxia, and peripheral edema, were not remarkable as are commonly encountered with adult patients [8]. The clinical characteristics of these 5 patients with recurrent CINP were as follows.

Case 1: A 2-year and 6-month-old female patient had PRE-treatment Tumor EXTension III hepatoblastoma, and received two cycles of combination therapy of cisplatin 80 mg/m² on day 1 and terarubicin 30 mg/m² on days 1-2. As the clinical course was complicated with grade 2 nephrotoxicity and cardiotoxicity, the therapeutic regimen was changed to another combination therapy of VCR 1.5 mg/m² on day 1 and irinotecan 50 mg/m² on days 1-5 (VI therapy). Prior to the initiation of therapy, she developed grade 2 sensorimotor and autonomic neuropathy with ataxic gait, hyporeflexia, postural tachycardia, and constipation. On the third day of the first cycle of the therapy, she suddenly cried with buccal pain. Neither local inflammation nor periodontal disease was noted, and the diagnosis of CINP was obtained. She had no improvement with both acetaminophen and dexamethasone, but the pain symptoms resolved spontaneously within 2 days. We suspended the prophylactic fluconazole during the second cycle of the therapy, but we failed to prevent the recurrent CINP. Her guardian described the recurrent CINP as "It is truly like a storm which surely comes 3 days after VCR, and suddenly leaves. Bilateral buccal pain severely compromised her appetite". The therapeutic response to the VI therapy was excellent, and the residual tumor was completely resected thereafter. We decided to continue the same VI therapy for the post-operative chemotherapy with a short course of PGB prophylaxis. We started with 0.5 mg/kg/dose of PGB 3 days before the chemotherapy and finally escalated up to 3.0 mg/kg/day to gain the maximum analgesic effect at 3 days after the VCR exposure. We would like to note that the PGB prophylaxis dramatically suppressed the recurrent CINP and that the following clinical course was uneventful except for PGB-induced mild daytime sleepiness (Figure 1A).

Case 2: A 2-year and 4-month-old male patient had stage 4 sacrococcygeal germ cell tumor and developed motor palsy of the lower extremities, urinary retention, and rectal dysfunction due to spinal canal invasion of the tumor. He received 4 cycles of combination therapies of bleomycin 15 mg/m² on day 3, carboplatin (CBDCA) 600 mg/m² on day 2, and etoposide 120 mg/m² on days 1-3. Following normalization of serum tumor marker of alpha-fetoprotein, he received tumorectomy and coccygectomy to induce complete remission. He additionally received 2 cycles of the same chemotherapy regimen and was discharged without any neurological sequelae. Three months after the series of initial therapy, however, we found a locally relapsing tumor. He received complete tumor resection and was scheduled to receive postoperative combination chemotherapy. Prior to the initiation of the therapy, his medical condition was diagnosed as grade 2 sensorimotor and autonomic neuropathy with ataxic gait, hyporeflexia, and constipation. He received postoperative combination chemotherapy of PTX 135 mg/m² on day 1, ifosfamide 1800 mg/m² on days 1-5, and CBDCA 600 mg/m² on day 1. Three days after the first course of the therapy, he complained of migrating paresthesia continuing for the next 2 days. Neither non-steroidal anti-inflammatory drugs nor dexamethasone were effective for ameliorating the neuralgic pain. His guardian described the recurrent CINP as "He developed pain throughout his body, and he asked me to pat his back all night long. The pain gradually resolved within two days." We

therefore placed him on PGB prophylaxis of 2.0 mg/kg/day for the preceding 3 days before the initiation of the second cycle of therapy with excellent pain control. He was then scheduled to receive another combination therapy of gemcitabine 800 mg/m² and PTX 80 mg/m² on days 1 and 8 and Oxaliplatin (OX) 130 mg/m² on day 1. Although he received the same PGB prophylaxis for prevention of CINP, it was not enough to prevent acute back pain that developed a few hours after OX infusion. We started a short PGB prophylaxis for the preceding 5 days before OX infusion and escalated to 3 mg/kg/day with a satisfactory analgesic effect (Figure 1B).

Case 3: A 2-year and 1-month-old male patient received the Berlin-Frankfurt-Münster (BFM)-based induction therapy including weekly VCR (1.5 mg/m²/dose) for standard risk ALL. He developed grade 1 sensorimotor and autonomic neuropathy of hyporeflexia of both lower extremities, excessive sweating, and constipation after the first exposure of VCR. His guardians recognized the recurrent bilateral buccal pain peaking 3 days after weekly VCR infusion, but it was mostly underestimated by healthcare professionals due to the transient nature of the symptoms. These neuropathic symptoms resolved spontaneously during the continuation of the intensification therapy. Nine months after the induction therapy, he was scheduled to receive re-induction therapy with weekly VCR. He developed recurrent bilateral buccal pain and the diagnosis of recurrent CINP was obtained. His guardian described the recurrent CINP as, "During the induction therapy, we found the emergence of recurrent bilateral buccal pain 3 days after VCR, but the severity of neuropathic pain was generally mild in nature. But, during this time, it looks so painful and I become depressed with a **sense of helplessness**". We then prescribed prophylactic PGB of 1.5 mg/kg/day for the preceding 3 days before the initiation of VCR, and the following clinical course was uneventful except for mild daytime sleepiness (Figure 1C).

Case 4: A 2-year and 2-month-old male patient received induction therapy for standard risk ALL. He began to complain of neuropathic pain involving the left thumb after the second dose of VCR. The presence of the acral pain did not interfere with QOL, but the following therapy was rather complicated with the emergence of hyporeflexia, postural tachycardia, and excessive sweating. Neither immunocompromised infection nor heart failure was noted, and the diagnosis of grade 1 sensorimotor and autonomic neuropathy was obtained. All related symptoms once subsided spontaneously within 2 weeks, but he later developed resurgence of neuropathic pain and refused to walk even after the completion of the VCR treatment, namely coasting. Initial PGB prescription of 0.75 mg/kg/dose at bedtime was consistently inefficacious, but increased dosages of 0.75 mg/kg/dose three times a day (2.25 mg/kg/day) completely resolve the limb pain and allowed him to walk without discomfort (Figure 1D).

Case 5: A 2-year and 11-month-old male patient received induction therapy for standard risk ALL. He developed grade 1 hyporeflexia of the lower extremities and bilateral buccal pain peaking 3 days after the initial dose of VCR. His medical condition was diagnosed as VCR-induced sensorimotor neuropathy and neuropathic pain, and we discontinued the prophylactic fluconazole thereafter. The following weekly VCR was uneventful without recurrence of the CINP; however, we found persistent hyporeflexia without apparent motor symptoms. 5 months after the induction therapy, he received reinduction therapy with weekly VCR, and developed grade 2 constipation and grade 1 CINP involving buccal area, back, and lower extremities. The neuropathic pain resolved spontaneously within 2 weeks after VCR exposure, but the continuation of the following chemotherapy was hampered with the severe paralytic ileus and excessive sweating for 3 weeks thereafter.

Table 1: Chemotherapy-induced neuropathic symptoms and its related factors were highlighted with shadow.

Patient characteristics				Reagents			Motor symptoms		Autonomic symptoms			Sensory symptoms	
Case	Sex	Age (mo)	Diagnosis	T	P	V	Repression of DTR	Drop foot	Constipation	Excessive sweating	Tachycardia	Neuropathic pain	PGB (mg/kg)
1	F	30	Hepatoblastoma	(-)	(+)	(+)	(+)	(-)	(+)	(-)	(+)	O	3
2	M	28	Germ cell tumor (sacral)	(+)	(+)	(-)	(+)	(-)	(+)	(-)	(-)	B	3
3	M	25	Acute lymphoblastic leukemia	(-)	(-)	(+)	(+)	(-)	(+)	(+)	(-)	O	1.5
4	M	26	Acute lymphoblastic leukemia	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(+)	L/E	2.25
5	F	35	Acute lymphoblastic leukemia	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(-)	O,B,L/E	(-)
6	M	4	Clear cell sarcoma of the kidney	(-)	(-)	(+)	(+)	(-)	(+)	(+)	(-)	(-)	(-)
7	F	4	Neuroblastoma Stage 4S	(-)	(+)	(+)	(-)	n.d	(-)	(+)	(+)	(-)	(-)
8	F	18	Acute lymphoblastic leukemia	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
9	M	8	Hepatic rhabdoid tumor	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
10	M	6	Neuroblastoma Stage 4	(-)	(+)	(-)	(-)	n.d	(-)	(-)	(-)	(-)	(-)
11	M	30	Neuroblastoma Stage 3	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
12	M	11	Germ cell tumor (mediastinum)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
13	F	20	Acute myeloid leukemia (M2)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
14	M	20	Acute myeloid leukemia (M6)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)

Abbreviations: T: Taxane; P: Platinum compound; V: Vincristine; n.d: not determined; PGB: Pregabalin; O: Orofacial; B: Back; L/E: Lower Extremity.

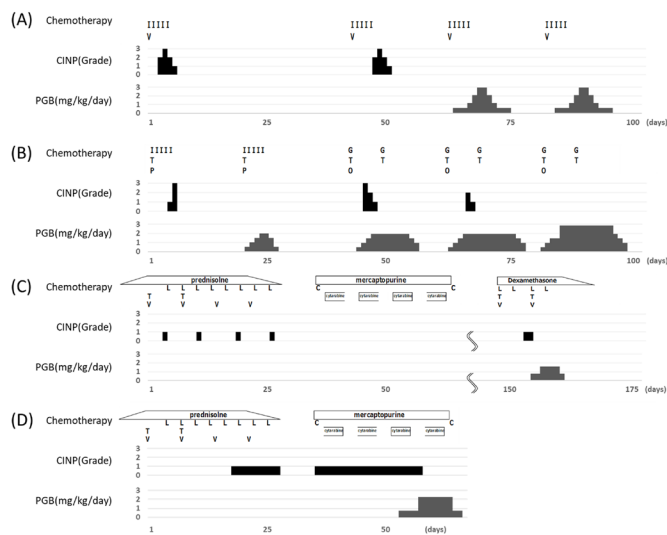


Figure 1: Clinical course of the 4 patients who received a short course PGB for recurrent chemotherapy-induced neuropathic pain. The upper, middle, and lower columns show the treatment schedule, the severity of CINP based on the National Cancer Institute Common Toxicity Criteria, version 3.0, and prescribed pregabalin (PGB) dosage, respectively. The x-axis shows the time after the initiation of the chemotherapy and day 0 indicates the first day of the first cycle of the therapy. **(A)** PGB was taken 3 days before and for 9 days after VCR exposure. We initially started 0.6 mg/kg/day of PGB at bedtime followed by dose escalation to 3.0 mg/kg/day peaking at 3 days after the VCR exposure. PGB completely prevented recurrent vincristine induced neuropathic pain (VINP), and the dosage was followed by gradual tapering thereafter. Abbreviations: I, irinotecan; V, vincristine. **(B)** Paclitaxel-induced migrating paresthesia was successfully controlled with 2.0 mg/kg/day of PGB, but careful dosing to 3.0 mg/kg/day and prolonged 5 days' incubation was required for the complete resolution of oxaliplatin-induced acute pain. Abbreviations: I, ifosfamide; P, carboplatin; T, paclitaxel; G, gemcitabine; O, oxaliplatin. **(C)** PGB was taken 3 days before and for 6 days after VCR exposure. 1.5 mg/kg/day of PGB was enough for VINP. Abbreviations: L, L-asparaginase; T, pirarubicin; V, vincristine. **(D)** Initial lower dose of 0.75mg/kg/dose PGB at bedtime was not enough for the ameliorating the neuropathic pain, but increased dosage of 2.25 mg/kg/d completely suppressed the symptoms.

Abbreviations: L: L-asparaginase; T: pirarubicin; V: vincristine; C: Cyclophosphamide.

Discussion

In this report, we showed that 35.7 % of pediatric cancer patients younger than 3 years of age developed recurrent CINP, and the estimated rate was mostly comparable to those in the previous reports in children [9-11]. The pathognomonic impacts of individual and/or pharmacological risk factors of CINP are variable depending on chemotherapy regimen, study population, and assessment method applied [9-11]. Angheliescu *et al* showed that 38 % of patients who were uniformly treated with St. Jude Total XV protocol for ALL developed more than grade 2 VCR-induced neuropathic pain [9]. They showed that the white non-Hispanic race was an only strong risk factor, and there was no statistical significance between the severity and pharmacological variables. Lombardi *et al* reported that 34.9 % of hepatoblastoma patients developed VCR-induced neuropathic symptoms and also showed that prematurely born young children younger than 2 years of age are at risk to develop neurological complications, such as constipation, neuralgia, and cranial nerve palsy [11]. In this report, 2 patients (cases 1 and

2) who had been previously exposed to platinum reagent developed recurrent CINP following the first dose of VCR and PTX, respectively. This clinical observation might implicate that the previous medication had sensitized the peripheral nerve system to induce neurotoxic vulnerability, and further stressed the importance to include previous medication history as one of the risk variables of CINP.

Given the importance of early diagnosis of CINP, it is still one of the challenging subjects especially in young children [2,3]. In this study, we showed that concurrent neuropathic symptoms, such as ataxic gait, hyporeflexia, excessive sweating, postural tachycardia, and constipation are relatively common in the presence of CINP (Table 1). We also found a strong temporal association between the drug exposure and the onset of related symptoms, such as bilateral buccal pain 3 days after VCR, migrating paresthesia 3 days after PTX, and acute back pain within a few hours after oxaliplatin. These clinical findings suggest that the awareness of reagent specific clinical pictures together with target evaluation of concurrent neuropathic symptoms might be helpful to make an early diagnosis of CINP, especially in young children who are still unable to fully verbalize their complaints.

Several pharmacological approaches are already available for the management of CINP in adults [12], but a mere extrapolation from the adult practice might be unsatisfactory for young children, due to the different pharmacokinetics and side effect profiles. In this report, we showed that short-course PGB prophylaxis can be included as one of the therapeutic choices for the secondary prevention of recurrent CINP even in young children. PGB was originally synthesized as an adjuvant antiepileptic drug, but it was later found to bind strongly to the $\alpha 2\text{-}\delta 1$ subunit of the voltage gated calcium channel to reduce several types of peripheral neuropathic pain, such as diabetic peripheral neuropathy, fibromyalgia, and post-herpetic neuralgia. It is noteworthy that PGB has several advantages, such as higher bioavailability, rapid absorption, linear pharmacokinetics, and limited drug-drug interaction [13,14], and these unique pharmacological properties allowed us to develop a short-course PGB for the successful secondary prophylaxis of recurrent CINP.

This study has several limitations. First, due to the nature of retrospective study, we could not address whether the emergence of recurrent CINP is included as one of the risk variables of developing neurological late effects. Since roughly a half of childhood cancer survivors are prone to develop irreversible long-term sensory neuropathy¹, this issue should be worth to be investigated in the future. Second, **we had only 5 patients** with whom to discuss the clinical pictures of recurrent CINP. Still, we believe our clinical observation might be informative enough to address the clinical heterogeneity of CINP. Given that the spontaneous resolution of recurrent CINP could happen as was exemplified in case 5, we would like to propose that the indication of the pharmacological intervention should be confined to the recurrent cases with following particular clinical backgrounds, such as 1) previously medication with platinum compound, 2) persistence even after cessation ofazole antifungal agents, 3) considerable interference of QOL due to CINP related symptoms, and 4) suspected cases with concurrent autonomic and motor nerves symptoms. We believe that serial counseling coupled with short course intervention might identify the young patient who might be benefited from the supportive therapy, thereby improving the QOL during the anticancer therapy.

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Competing interests: The authors have no competing interests.

Author contributions: KK and HN designed the study; KK, HN, KT, AI, IU, and TM collected clinical data; KK. And TH wrote the manuscript; and all of the authors reviewed and approved the final manuscript.

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