# Pregabalin in Chemotherapy Induced Neuropathic Pain

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## ABSTRACT

Chemotherapeutic agents belonging to vinca alkaloids, taxanes, and antitubulins produce peripheral neuropathy for which there is no validated treatment. Pregabalin, a gamma-aminobutyric acid analog, is known to inhibit the α2δ subunit of the voltage-gated calcium channel. Earlier studies and case reports have shown pregabalin to be effective in treating neuropathic pain. We present a case series of patients with chemotherapy-induced peripheral neuropathy who were successfully treated with pregabalin with reduction in the hyperalgesia, allodynia, and improvement in the quality of life.

**Key words:** Cancer, Chemotherapy-induced peripheral neuropathy, Pregabalin

## INTRODUCTION

Peripheral neuropathy is a common, but a debilitating adverse effect of several classes of chemotherapeutic agents including vinca alkaloids, taxanes, and antitubulins.[1] The incidence of chemotherapy-induced peripheral neuropathy (CIPN) can vary from 3% to 7% with a single agent and rise up to 38% in patients who are on combination therapy.[2] The severity of neuropathy depends on the dose of the chemotherapeutic agent, duration of exposure, cumulative dose, concurrent use of other agents, and coexisting disease such as diabetes, Vitamin B12 deficiency, or alcoholism. CIPN pain is not only debilitating, but also may be the reason for stopping a lifesaving curative chemotherapy. Dysregulation in the calcium homeostasis in the dorsal nerve root ganglion and dorsal spinal cord has been implicated in the causation of neuropathic pain. Neuromodulators such as gabapentin and pregabalin inhibit the α2-δ subunit of the calcium channel in the neuronal cells thus reducing the neuropathic pain.[3] Between the two, pregabalin has been found to have a better efficacy and safety profile.[4]

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## CASE REPORTS

### Case 1

A 17-year-old boy diagnosed with early precursor T-cell, ALL and no other medical comorbidities completed his induction phase with vincristine, cytarabine, and cyclophosphamide in July 2015. In the beginning of August 2015, he was started on consolidation phase of chemotherapy with vincristine, daunorubicin, polyethylene glycol daunorubicin asparaginase, and prednisolone. Midway through the consolidation (after 2 cycles) phase, he developed tingling sensation in the plantar aspect and toes of his feet, which progressed to "pins and needles" sensation in 1 week. The pediatric oncology team abandoned his chemotherapy due to intolerable pain and admitted him for debilitating neuropathy. They started him on ultracet (tramadol 37.5 mg + paracetamol 325 mg) 4 times a day for pain. However, the boy did not have adequate pain control. He was referred to the department of pain



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and palliative medicine for pain management. The patient spent most time in bed and used a wheel chair to go to the toilet. On examination, the pain score was 7/10 (on Edmonton Symptom Assessment Scale). He had developed Grade III neuropathy (Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0). He was started on tablet pregabalin 75 mg at night and escalated his dose every 3rd day by 75 mg until pain was controlled. Ultracet was stopped. The boy had good pain control (Edmonton Symptom Assessment Scale - 1/10) on day 15 with no side effects. There was complete resolution of his neuropathy. He was able to walk to the bathroom without support and do his routine activities without any discomfort. There was complete resolution of the tingling sensation in the fingers. He was discharged with a plan of restarting his chemotherapy.

### Case 2

A 40-year-old lady who was diagnosed with primary peritoneal serous carcinoma and no other medical comorbidities was administered paclitaxel and carboplatin. While she was on chemotherapy, she developed mild burning sensation in the plantar aspects of forefoot and toes bilaterally. Within 1 month, this progressed to severe burning pain in the same regions. The pain was aggravated by walking, standing, and local application of pressure on the forefoot and toes. She also described symptoms suggestive of "walking on cotton-wool" sensation. These symptoms were severely disabling the patient. On examination, she was found to have Grade III peripheral neuropathy (NCI-CTC Version 3.0). She, however, had no motor neurological deficit. She was started on tablet pregabalin 75 mg at night, and the dose of pregabalin was increased by 75 mg every 3 days until resolution of pain. The patient responded to a dose of 375 mg of pregabalin without any of the known side effects of pregabalin (including drowsiness or giddiness). Her neuropathy improved from Grade III to Grade I. She was able to get back to doing her routine household work. In view of radiological progression of her disease, it was decided not to restart on chemotherapy. She followed up in outpatient department walking with minimal support. She, however, continues to have "walking on cotton-wool" sensation and occasional tingling sensation in her toes.

## DISCUSSION

Certain chemotherapeutic agents belonging to vinca alkaloids, taxanes, and antitubulins class produce adverse effects such as sensory and motor neuropathy, laryngeal neuropathy, and sensory ataxia, which can significantly affect patient's quality of life. Multiple mechanisms have been hypothesized in the causation of CIPN, which include myelinopathy, axonopathy, intraepidermal nerve fiber loss, and mitotoxicity.[5] CIPN occurs in the "glove and stocking" distribution and occasionally perioral paresthesia is experienced with certain chemotherapeutic agents.[6] Sensory symptoms that are commonly reported include paresthesia, dysesthesia, allodynia, hyperalgesia, hypoalgesia, or pain that is burning, shooting, or electric-shock-like.[6] Painful symptoms may persist well-beyond discontinuation of treatment (so called "coasting"), resulting in a condition as painful or more painful than the original cancer.[7] CIPN pain among other sensory symptoms has presently no standard protocol and the current approach is to stop the chemotherapeutic agent until the neuropathy resolves, in some conditions abandon the chemotherapy regimen and use a lower dose or alternative chemotherapeutic agent. This might significantly impact the survival of the patients.

Multiple approaches have been discussed to either prevent or treat chemotherapy-induced neuropathic pain. In a study, calcium gluconate and magnesium sulfate (Ca/Mg) infusions, prior and after oxaliplatin treatment, seemed active against acute symptoms; however, the trial had to be interrupted as there was lower tumor response rate in this group.[8,9] Antidepressants and anticonvulsants are the standard modalities of treatment for neuropathic pain.

Duloxetine and venlafaxine are known to significantly reduce pain and paresthesia,[10,11] but other antidepressants such as amitriptyline and nortriptyline failed to show any effect.[12] Antidepressant drugs can produce serious adverse effects which might limit the dose escalation, especially in elderly.[13] These drugs significantly interact with other drugs concomitantly administered in cancer treatment resulting in serious adverse reactions.[14]

Neuromodulators such as gabapentin and pregabalin are gamma-aminobutyric acid analogs, which interact with the α2-δ subunit of the voltage-gated calcium channels, found to be effective in neuropathic pain.[3,4] Cancer chemotherapeutic agents cause increased expression of sodium channel, α2-δ1 subunit of the calcium channel (also activated by opening of sodium channel and N-methyl-D-aspartate [NMDA] receptor activation), and NMDA receptors at the dorsal nerve root ganglion and dorsal horn cells. Activation of these receptors leads to influx of extracellular calcium and leakage of the mitochondrial calcium. This rise in the intracytoplasmic

calcium leads to neuronal cell death through generation of toxic oxygen radicals and triggering of apoptosis.[5] Gabapentin and pregabalin reduce the calcium-dependent neurotransmitters in the neuronal membrane, thus inhibiting the neuronal excitability.[15,16] Pregabalin, in contrast to gabapentin, has a higher bioavailability (90% vs. 33–66%), rapid absorption (peak: 1 h) with plasma concentration increasing linearly with increasing dose, which justifies its equivalent efficacy at a lower dose and lower risk of adverse effect.[17,18] Also as pregabalin is not known to have drug-drug interaction, it can be safely co-administered with chemotherapeutic agents.[14] Our patients showed reduction in the hyperalgesia and allodynia and improvement in the quality of life. The common side effects include dizziness and somnolence, which is known to resolve with continued treatment,[19] followed by dry mouth, peripheral edema, blurred vision, weight gain, abnormal thinking, myoclonus, asterixis, and gynecomastia.[4,20,21] Pregabalin was well-tolerated by our patients with none of these side effects.

## CONCLUSION

Chemotherapy-induced neuropathic pain though an uncommon side effect has significant impact on the quality of life of the patients. The current approach of reducing the dose of chemotherapy or stopping the medication can significantly affect the survival of the patients. Pregabalin has successfully treated neuropathic pain in our patients. There is, thus, a need to explore the use of neuromodulators such as pregabalin in the management of chemotherapy-induced neuropathic pain.

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### Conflicts of interest

There are no conflicts of interest.

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