

Chemotherapy-induced neurotoxicity: the value of neuroprotective strategies

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a common major dose-limiting side effect of many chemotherapeutic agents, including platinum compounds, taxanes, vinca alkaloids, thalidomide and newer agents such as bortezomib. The incidence and degree of neuropathy depends on the type of cytotoxic drug, the duration of administration, cumulative dose and pre-existing peripheral neuropathy. Because of increasing survival rates of patients treated with neurotoxic agents, CIPN is accompanied by a significant decrease in the patient's quality of life among cancer survivors. Therefore, several neuroprotective strategies, including calcium/magnesium infusion, amifostine, glutathione, glutamine, acetyl-L-carnitine and erythropoietin as most promising, have been investigated to decrease the neurotoxicity without compromising anti-tumour efficacy. However, clinical evidence for the efficacy of these drugs is sparse. In this review we will give an outline of the neurotoxic effects of chemotherapeutic agents, their clinical manifestations and potential neuroprotective strategies.

KEYWORDS

Bortezomib, chemotherapy, cisplatin, neurotoxicity, oxaliplatin, paclitaxel

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is due to the inability of chemotherapeutic agents to differentiate between malignant and healthy cells.¹ CIPN is a common major dose-limiting side effect of anti-tumour treatment.^{2,5} As a result of this dose reduction, delay and withdrawal may lead to decreased chemotherapy efficacy

and survival.^{1,7} The incidence of CIPN varies from 30 to 40% of patients receiving chemotherapy and depends on the type of cytotoxic drug, the duration of administration, cumulative dose and pre-existing peripheral neuropathy.^{2,7} Symptoms are predominantly sensory, but the neurotoxicity also appears as a sensory-motor neuropathy and occasionally it will be accompanied by dysfunction of the autonomic nervous system.^{5,6} Although the peripheral nervous system has a high regenerating capacity, the cell body needs to be spared and a period of recovery is needed to achieve sufficient repair. In severe damage, CIPN is only partly reversible and sometimes even completely irreversible.^{4,5} Since survival of cancer increases, CIPN may significantly interfere with a patient's quality of life among cancer survivors.^{1,8} Despite multiple studies there is still no consensus on how to prevent CIPN. In this review we will give an outline of the neurotoxic effects of chemotherapeutic agents, their clinical manifestations and new developments in neuroprotective strategies.

NEUROTOXIC CHEMOTHERAPEUTIC AGENTS

Frequently used chemotherapeutic agents associated with neurotoxicity include platinum compounds, taxanes and vinca alkaloids (*table 1*).^{2,7} In addition, proteasome inhibitors, such as bortezomib, and treatment with thalidomide, are associated with CIPN.^{2,4,6}

Platinum compounds

The platinum compounds oxaliplatin and cisplatin are commonly associated with CIPN.^{2,3,9} The mechanism by which neuropathy is induced is unclear. Several trials have suggested that platinum compounds accumulate in the dorsal root ganglia and oxaliplatin also produces

Table 1. Chemotherapeutic agents causing peripheral neuropathy

Chemotherapeutic agents

Platinum compounds

Cisplatin

Oxaliplatin

Carboplatin

Taxanes

Paclitaxel

Docetaxel

Vinca alkaloids

Vincristine

Vinblastine

Vinorelbine

Other agents

Bortezomib

Thalidomide

Lenalidomide

axonal hyperexcitability and repetitive discharges due to changes in voltage-dependent Na⁺ channels.^{4,9-12} The neuropathy, due to cisplatin, is usually reversible and typically appears three to six months after treatment has started, and continues after discontinuation, which is called coasting.^{2,5,13} It is predominantly sensory and presents with paresthesias, loss of vibration sense and decreased tendon reflexes. In severe cases, patients develop sensory ataxia and Lhermitte's syndrome.¹⁴ Lhermitte's syndrome is a shock-like sensation of paresthesia radiating from the back to the feet during neck flexion. These clinical manifestations are accompanied by interference in activities of daily living in 6% of patients.^{2,5,13,14} Unlike cisplatin, oxaliplatin causes no nephrotoxicity and only mild haematological toxicity, but CIPN occurs in approximately 90% of patients.^{9,12,15} The neurotoxicity presents as two different types of neurotoxicity: firstly an acute, mainly cold-triggered neuropathy, and secondly, a chronic sensory neuropathy. Shortly after oxaliplatin infusion, the majority of patients develop distal paresthesias, dysesthesias and mild muscle contractions of the hands, feet and perioral region, which are characteristically reversible within a week.^{3,5,9-11} In addition, the symptoms associated with chronic neurotoxicity are mainly sensory and partly reversible in 80% of patients in four to six months. In 40% of patients, symptoms disappear completely in six to eight months.^{4,5,9}

Taxanes

The most important dose-limiting side effect of the taxanes, paclitaxel and docetaxel, is neurotoxicity.²⁻⁵ The underlying mechanism is not entirely understood. Preferentially large myelinated fibres, responsible for tactile sensation, vibration perception and proprioception,

are affected by paclitaxel.^{2,13} In 59 to 78% of patients a cumulative dose-dependent, painful sensory neuropathy sometimes occurs 24 to 72 hours after administration.¹³ The clinical manifestations are paresthesias, numbness, tingling and burning, hyperalgesia, and loss of tendon reflexes, vibration sensation and proprioception. Motor neuropathy is less common and includes a mild distal muscles weakness.^{2,4,5,13} The incidence of docetaxel-induced peripheral neuropathy is much lower than that of paclitaxel-induced peripheral neuropathy (1-9% versus 30%). The symptoms are similar, but they are usually mild and disappear spontaneously after discontinuation.^{5,13}

Vinca alkaloids

Neurotoxicity due to vinca alkaloids, with vincristine as the most neurotoxic, is usually reversible on discontinuation. Nevertheless, the recovery is slow and can last for months.^{3,13} Vincristine induces alterations in the cellular micro-tubuli structure, which leads to disruption of the axonal flow. This damage may cause a painful sensory neuropathy and autonomic dysfunction occurs in one third of the patients.^{2,3,5,13} In advanced stages, muscle weakness up to paralysis may appear.^{2,4,5,13} In patients with pre-existing hereditary neuropathy, administration of vincristine could lead to rapidly evolving paralysis similar to Guillain-Barré syndrome.^{2,4,5}

Other chemotherapeutic agents

Thalidomide-associated neurotoxicity appears in approximately 40% of patients, is also cumulative dose-dependent and is due to damage to the dorsal root ganglia.^{2,3,13,16} Clinically, it is characterised by paresthesias and a considerable loss of tactile and pain response.^{2,3,13} Bortezomib, a novel agent for the treatment of multiple myeloma, usually causes a painful sensory neuropathy with a sharp or burning pain of the feet and fingertips and in approximately 10% of patients also autonomic dysfunction.^{2,3,6,13,16} Motor neuropathy is not common with bortezomib and thalidomide.^{6,16,17} Symptoms are completely reversible in 60 to 75% of patients receiving bortezomib within a median follow-up of six months, versus 25% of patients receiving thalidomide.^{6,16,17}

NEUROPROTECTIVE STRATEGIES AND EVIDENCE

Neuroprotective agents aim to decrease the neurotoxicity associated with cytotoxic agents by providing protection for healthy tissue without compromising anti-tumour efficacy.^{1,7-14} Multiple strategies to prevent CIPN have been investigated (table 2). However, clinical evidence for the efficacy of these strategies is sparse. Because of the higher risk of CIPN developing in patients with pre-existing

Table 2. Trials for prevention of CIPN

Agent	Number of patients	Results	Design	Reference
Dosis	623	No difference in response rate with dose modification	RT; oxaliplatin	18
Modification	333	No difference in response rate with dose modification	RT; bortezomib	20
Amifostine	242	CIPN between two arms differ significantly after 6 cycles ($p=0.029$), with grade 0 CIN in 55% of amifostine arm vs (vs) 39% in the control arm. Grade 3-4 in 9 vs 15%	RCT open-label phase III trial; cisplatin	25
	187	CIPN grade 3-4 in 3.7% amifostine patients vs 7.2% ($p=0.02$) in control group	Multicentre randomised open label phase III trial; paclitaxel	26
	31	Not effective	Non randomised trial; case-control: paclitaxel/doxorubicin/cyclophosphamide	22
	90	No CIPN in 40% vs 49% of patients with amifostine (n.s.). Grade II 12 vs 2% and grade III 2% vs 1% in amifostine arm	RCT open phase II trial; paclitaxel/carboplatin	21
	71	Not effective	RCT placebo-controlled; double blind paclitaxel/carboplatin	23
Glutathione	52	Significantly less neuropathy after 8 cycles: 79% in placebo group vs 43% in the GSH group ($p=0.04$). Less grade 3-4 neuropathy in the GSH group ($p=0.003$)	RCT placebo-controlled; double blind, oxaliplatin	27
	27	No grade 3-4 CIN in the GSH group. Grade 2 in 50% in GSH arm vs 69% and grade 3 in 31% ($p=0.0037$) in the control arm	RCT placebo-controlled; oxaliplatin	28
	151	CIPN in 49% patients treated with cisplatin alone compared to 39% in the GSH arm ($p=0.22$)	RCT placebo-controlled; double blind, cisplatin	29
Ca/Mg infusion	161	69 of 161 patients received Ca/Mg. CIPN in 20% patients Ca/Mg vs 45% without Ca/Mg ($p=0.003$). Less grade 3 in Ca/Mg group (8 vs 20% $p=0.003$)	Retrospective study	31
	174	Initially worse response rate in Ca/Mg arm	RCT placebo-controlled; double blind; oxaliplatin	32
	102	Terminated after results CONCePT. Analysis with remaining data: CIN grade 2 or more in the Ca/Mg group compared to placebo (22% vs 41%; $p=0.038$)	RCT placebo-controlled; double blind; oxaliplatin	33
	144	Preanalysis in 52 patients: no difference in response rate (50% vs 53%; $p=0.45$). Neurotoxicity grade 3 was 5% vs 24% ($p<0.001$) between groups (blinding yet unbroken)	RCT placebo-controlled; double blind; oxaliplatin	34
	732	The incidence of all grade sensory neurotoxicity was 85% vs 92% in favour of the Ca/Mg arm ($p=0.02$). No significant difference in response rate	Retrospective study	35
Glutamine	86	Less grade 1 and 2 neuropathy and grade 3-4 neuropathy in the glutamine group after four cycles (5% vs 18%; $p=0.05$) and six cycles (12% vs 32%; $p=0.04$)	Open-label; oxaliplatin	36
	45	Less weakness (56 vs 25%; $p=0.04$) and interference with ADL (85 vs 27%; $p=0.001$) in the glutamine arm	Prospective cohort study; paclitaxel	37
	86	Less weakness ($p=0.02$), less loss of vibratory sensation ($p=0.04$) and less toe numbness ($p=0.004$) than controls	Case-control; paclitaxel	38
	43	Not effective	RCT placebo-controlled; double blind pilot study; paclitaxel	39
Vitamin E	37	CIPN in 3/16 (19%) of patients with vitamin E vs 10/16 (63%) of controls ($p=0.03$)	Randomised open-label; paclitaxel	40
	30	CIPN occurred in 3/14 (21%) of patients in vitamin E group vs 11/16 (69%) of the control group ($p=0.026$)	Randomised open-label; cisplatin	41
	41 (108)	Significant lower incidence of neuropathy in the vitamin E group (6%) than in the placebo group (42%)	Phase III; RCT placebo-controlled; cisplatin	42
	207	Not effective	Phase III; RCT placebo-controlled; double blind; multiple agents, mainly taxanes (108)	43
Erythropoietin	In vivo	EPO significantly reduced impaired sensory nerve conduction ($p<0.05$), increased thermal threshold	In vivo 62 rats; cisplatin	44
	In vivo	EPO significantly improved the thermal threshold (30%) ($p=0.05$), nerve conduction velocity by 10-12% ($p<0.05$) and intra epidermal nerve fibre density	In vivo 344 rats; docetaxel	45
Acetyl-L-carnityl	25	Patients received 1g ALC. The sensory neuropathy grade improved in 15 of 25 (60%), and motor neuropathy in 11 of 14 patients (79%). Total neuropathy score (TNS) improved in 23 (92%). Symptomatic improvement persisted in 12 of 13 evaluable patients at median 13 months after ALC	Experimental; phase I trial; cisplatin, paclitaxel	53

Table 2. *Trials for prevention of CIPN*

Agent	Number of patients	Results	Design	Reference
ACTH/ ORG	55	Vibration perception was maintained in the intervention arm compared to the control arm	RCT placebo-controlled; double blind cisplatin	54
	220(196)	Not effective	RCT placebo-controlled; double blind cisplatin	55
RHuLIF	117	Not effective	RCT placebo-controlled; double blind paclitaxel/carboplatin	59
Anti-epileptica	36	Not effective	RCT; oxaliplatin	56
	13	Not effective	Phase I study; oxaliplatin	57
Nerve growth factors	62	Significant correlation between the decrease in circulating levels of NGF and the severity of CIPN ($r=-0.58$; $p<0.001$)	Observational study	58
Nimodipine	50	Not effective	RCT placebo-controlled; double blind	60
Ethosuximide	In vivo	Decrease of pain in rats	In vivo rats; paclitaxel	61

iRT = randomised trial; RCT = randomised controlled trial

neuropathy, alcohol abuse and poor nutritional state, prevention should begin by identifying those patients before starting chemotherapy.^{1,2,4,7}

Treatment modification

Since to date clinical evidence for the efficacy of neuroprotective agents is sparse (see below), alternative dosing regimens and early detection and the use of treatment modification schemes based on common toxicity criteria may be necessary to limit the amount of damage associated with neurotoxic chemotherapy. A neurologist can be helpful in establishing the exact grade of CIPN and sometimes in differentiating CIPN from other causes of neuropathy, since this may have important therapeutic consequences. Discontinuation and reintroduction of oxaliplatin administration in a stop-and-go strategy showed the same response rate with a lower incidence of CIPN in the OPTIMOX study.^{21,18} Nevertheless in general dose reduction may be associated with impaired overall and disease-free survival, especially in the adjuvant setting, so that it is necessary to carefully outweigh the benefits and level of toxicity of treatment. Dose-modification strategies based on common toxicity criteria have also been described and reported to be effective in thalidomide- and bortezomib-induced peripheral neuropathy.^{19,20} Therefore it seems an effective intervention in decreasing CIPN.

Amifostine

Amifostine serves as an antioxidant and binds to the metabolites of platinum compounds and alkylating agents, which protect normal tissue against the cytotoxic effects.^{1,14,21-24} In addition to a radioprotective role, it has been proposed as a potential neuroprotective agent.^{21,22}

The best evidence in cisplatin- and paclitaxel-induced neurotoxicity is shown in two randomised controlled trials.^{25,26} In both studies, patients were randomised to receive amifostine before administration or not. Although the primary study endpoint was the ability of amifostine to prevent haematological toxicity, neurotoxicity was studied as well. In cisplatin-receiving patients, the difference in neurotoxicity between the two treatment arms was statistically significant after six cycles.²⁵ In paclitaxel-receiving patients, amifostine appeared to be neuroprotective in grade 3 and 4 neuropathy.²⁶ Other studies demonstrated no significant difference in neurotoxicity.²¹⁻²³ All trials demonstrated hypotension as the major side effect and no difference in survival between groups.^{21-23,25,26} In conclusion, amifostine potentially reduces neurotoxicity. However, as neurotoxicity was not the primary endpoint of the studies, more trials are needed to investigate this drug. Besides, amifostine is accompanied by serious side effects, stressing the importance of more clinical evidence before standard use can be recommended.

Glutathione

Glutathione (GSH) is involved in detoxification and protection of tissue from oxidant injury and might prevent accumulation of platinum compounds in the dorsal root ganglia.^{1,4,7,27,28} Two small randomised placebo-controlled trials showed promising results on oxaliplatin-induced neurotoxicity, with significantly less grade 2 to 4 neuropathy in the GSH arm.^{27,28} Another larger trial with cisplatin showed a trend with less neuropathy in favour of GSH, although, the results were not statistically significant ($p=0.22$).²⁹ Furthermore, dropout rates were very high with only 39% versus 58% patients receiving six cycles in the

control and intervention arm, respectively. Nevertheless, the difference in discontinuation was significantly lower in the GSH arm.²⁹ No significant difference in tumour-response rate was found.²⁷⁻²⁹ These results provide evidence indicating that GSH might decrease CIPN. However, more studies are needed as dropout rates were high and long-term follow-up was lacking. Furthermore, the largest phase III trial demonstrated no significant results.

Calcium and magnesium infusion

Calcium and magnesium (Ca/Mg) have been proposed as neuroprotective agents by increasing extracellular calcium concentration.^{4,7,30} First a retrospective study demonstrated significantly less neurotoxicity with prophylactic calcium 1 g and magnesium 1 g infusion before and after oxaliplatin, compared with a historic control group ($p=0.003$) without compromising anti-tumour effect.³¹ However, three years later the CONcept trial was terminated because of a presumed lower tumour-response rate in the Ca/Mg arm, although a critical appraisal after discontinuation of this study could not confirm these findings.^{7,32} A concomitant study of the North Central Cancer Treatment Group (NCCTG) was terminated because of the suspected effect on anti-tumour response.^{32,33} Remaining data of the prematurely aborted NCCTG study demonstrated a significantly lower incidence of grade 2 or more neurotoxicity in the Ca/Mg group.³³ Nevertheless, long-term follow-up data are lacking and the planned number of patients was not achieved. In response to these trials, early analyses of the Neuroxa study have been revealed and a large retrospective study has been performed.^{34,35} They both confirmed the neuroprotective results from Ca/Mg infusion without compromising response rate.^{34,35} All studies used the same dosage of Ca/Mg as the first retrospective study. Correlation of clinical effects with alterations in plasma levels could not be determined, as the plasma Ca and Mg levels were either not observed or not reported in these studies. Thus, although concerns about the safety of Ca/Mg infusions are valid, clinical trials did not demonstrate convincing differences in tumour-response rates in the Ca/Mg infusion arms compared with placebo, while there are data supporting a neuroprotective effect of Ca/Mg infusion in oxaliplatin-induced neuropathy.³²⁻³⁵ Ideally, regarding the contradictory results from the presented studies, the effect of Ca/Mg on CIPN and tumour growth should be confirmed in larger randomised controlled trials.

Glutamine

Glutamine, a non-essential amino acid stored in skeletal muscle (75%) and liver (25%), is another investigated agent to prevent neurotoxicity.^{4,36,37} During long periods of stress, such as malignancy, glutamine depletion develops

with negative impact on tissue functions.^{4,7,36,37} Two pilot studies suggested glutamine (10 g three times a day for four days) as a neuroprotective agent without interfering with chemotherapy response.^{37,38} Accordingly, a randomised trial with colorectal patients reported significantly less CIPN and interference with ADL in the glutamine arm (15 g twice a day for seven consecutive days) compared with control.³⁶ However, there were no differences in electrophysiological examination between groups.³⁶ Furthermore, a randomised pilot study revealed no difference in the use of glutamate 500 mg.³⁹ Since plasma glutamine levels were not assessed in any of these studies, no correlation with altered glutamine plasma levels could be determined. These results suggest that glutamine may reduce CIPN; however, results are inconsistent and need to be confirmed in large randomised, placebo-controlled trials.

Vitamin E

Many studies have examined the role of antioxidants such as vitamin E, vitamin C and alpha-lipoic acid. The best evidence is reported concerning vitamin E.^{2,4,7,40,41} Two small studies investigated the role of vitamin E in preventing CIPN due to cisplatin or paclitaxel.^{40,41} In both studies, the incidence of neurotoxicity was approximately 20% versus 68% ($p=0.03$) in the vitamin E arm compared with the control arm, respectively.^{40,41} In 2010, a phase III study showed a significantly lower incidence of neuropathy in the vitamin E group. However, only 41 out of 108 patients, with 17 in the vitamin E group, were eligible for analysis and no intention-to-treat analysis was preformed.⁴² Another large trial reported no difference in neuropathy.⁴³ In conclusion, there is no convincing evidence that vitamin E is beneficial in the prevention of CIPN and we do not recommend its use. Studies were of poor quality and populations were small. Besides, the largest phase III trial reported no difference in neurotoxicity in the vitamin E group compared with placebo.⁴³

Erythropoietin

Erythropoietin (EPO), used in the treatment of haematological toxicity for its effect on erythropoiesis, has also been demonstrated to have neurotrophic activity and receptors in nerve axons, Schwann cells and dorsal root ganglia which protect cells from injury and apoptosis.^{44,48} After injury, these receptors are over-expressed and the basis for therapeutic use. EPO has been shown to prevent cisplatin and docetaxel-induced neurotoxicity without compromising chemotherapeutic activity and increasing tumour growth in animal studies.^{44,46,49} These results are very promising, especially because of its concomitant use against haematological toxicity. Therefore, the neuroprotective effect of EPO should be confirmed in clinical trials.

Acetyl-L-carnitine

Also acetyl-L-carnitine (ALC) was shown to reduce neuropathy in animal studies, with beneficial effect of ALC administration in rats receiving oxaliplatin.⁵⁰⁻⁵² A clinical study included 25 patients who developed neuropathy due to paclitaxel or cisplatin. After discontinuation of chemotherapy, they received ALC 1 g for eight weeks. Sensory neuropathy and motor neuropathy decreased in 60 and 79% respectively. Furthermore, a significant improvement in sensory action potential occurred.⁵³ These results should also be confirmed in randomised trials.

Other agents

Numerous other agents have been studied for their potential effectiveness in reducing chemotherapy-induced neurotoxicity, including ORG 2766,^{54,55} antiepileptic agents such as carbamazepine and oxcarbazepine^{56,57}, nerve growth factor,⁵⁸ recombinant human leukaemia inhibitory factor (rhuLIF),⁵⁹ nimodipine⁶⁰ and ethosuximide.⁶¹ Ethosuximide has been demonstrated to decrease pain induced by paclitaxel in rats.⁶¹ However, other agents showed no evidence of neuroprotection and/or were only investigated in very small studies of poor quality.^{54-57,59,60}

SYMPTOMATIC TREATMENT OF ESTABLISHED CIPN

Neuropathic pain is a frequent problem in many chemotherapy-induced neuropathies. Recommendations on treatment of neuropathic pain in cancer patients are usually based on studies concerning 'benign' neuropathic pain, such as painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia.⁶² Although chemotherapy-induced pain may be very different from benign neuropathic pain, almost no randomised controlled studies exist for this specific condition.^{63,64}

Dutch guidelines on neuropathic pain in cancer patients recommend treatment with the antiepileptic agents gabapentin or pregabalin, or tricyclic antidepressants (TCAs).⁶⁵ However, TCAs are accompanied by many adverse effects and a phase III trial did not report any difference between gabapentin compared with placebo in chemotherapy-induced neuropathic pain specifically.^{64,66,67} Recently, the antidepressant venlafaxine, a serotonin and a norepinephrine reuptake inhibitor (SNRI), has been investigated in preventing acute oxaliplatin-induced neurotoxicity and demonstrated a significant relief of acute neurotoxicity (31% versus 5%; $p=0.03$) and, as secondary endpoint, less grade 3 toxicity after three months (0% versus 33%, $p=0.03$).^{67,68}

CONCLUSIONS AND RECOMMENDATIONS

The overall and progression-free survival in cancer patients was shown to be increased after the introduction of treatment with oxaliplatin, taxanes and bortezomib. Therefore, quality of life plays an increasingly important role among cancer survivors. CIPN is one of the major dose-limiting toxicities associated with these agents. Treatment of CIPN remains difficult, especially because recommendations on treatment of neuropathic pain in cancer patients are usually based on studies concerning 'benign' neuropathic pain. Therefore, we should focus on prevention. Several neuroprotective strategies, including Ca/Mg infusion, amifostine, GSH, glutamine, acetyl-L-carnitine and erythropoietin as most promising, have been investigated.^{21-23,25-29,44-53,69} Particularly erythropoietin is a hopeful approach to reduce CIPN because of the concomitant effect on haematological toxicity and effect on the quality of life. In addition, it has a toxicity profile itself. However, clinical evidence for standard use is insufficient. Therefore, alternative dosing regimens, early detection, and the use of treatment modification schemes based on common toxicity criteria may be necessary to limit the amount of damage associated with neurotoxic chemotherapy.

In summary, clinical evidence for the efficacy of these drugs is sparse. Consequently, no explicit recommendations on neuroprotective strategies can be given yet except for the importance of identifying high-risk patients before starting chemotherapy. In the future, trials concerning neuroprotective agents should continue. Meanwhile, alternative dosing regimens, early detection and treatment modification schemes are necessary to limit CIPN.

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