Role of Pregabalin in Treatment of Oxaliplatin-induced Sensory Neuropathy

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Abstract. *Background: Oxaliplatin use in gastrointestinal malignancies is limited by neurotoxicity. This study aimed to assess the efficacy of pregabalin (LYRICA®) in the treatment of oxaliplatin-induced neurotoxicity. Patients and Methods: A total of 23 gastrointestinal cancer patients with grade 2 and 3 oxaliplatin-induced sensory neuropathy were treated with pregabalin up to a target dose of 150mg orally (PO) three times a day (tid) based on benefit and tolerance. Neurological symptoms were serially evaluated. Results: The target dose of 150 mg tid provided the best benefit, but patients benefited even at lower doses. Onset of benefit was observed in 2-6 weeks. In the majority of patients (48%), neuropathy improved by 1 to 2 grades. Conclusion: Pregabalin significantly reduced the severity of oxaliplatin-induced sensory neuropathy. Being more potent than gabapentin, pregabalin achieved efficacy at lower doses and should lead to fewer dose-related side effects, although this remains to be established in a head-to-head trial.*

Oxaliplatin is a platinum derivative with proven antitumor activity in gastrointestinal cancers. Its structural difference from other platinum compounds in the form of a 1,2 diaminocyclohexane carrier ligand, allows formation of bulkier platinum-DNA adducts that inhibit DNA replication and transcription (1). Oxaliplatin in combination with 5-FU and leucovorin was approved as first-line, second-line as well as adjuvant therapy in advanced colorectal cancer, based on data showing longer median time to progression, better response rates and median survival (2-4). The most significant adverse effect associated with oxaliplatin is neurotoxicity, which can be acute and transient, or chronic cumulative sensory neuropathy.

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Key Words: Oxaliplatin, peripheral neuropathy, colon cancer, pregabalin, gabapentin.

The chronic sensory neuropathy is usually seen after cumulative doses of 780-850 mg/m^2 in approximately 10-15% of patients. Non-cold related dysesthesias/paresthesias can progress to fine sensory-motor discoordination and sensory ataxia. Approximately 6-12 months after cessation of oxaliplatin, neurotoxicities improve from grade 3 to 1 or less in the majority of patients. Symptomatic improvement correlates inversely with cumulative drug dose (2, 5, 6).

In contrast to chronic neuropathy, most patients experience an acute transient peripheral sensory neuropathy that occurs during or within a few hours of infusion, or within 1-2 days of administration. Patients develop paresthesias or dysesthesias in the distal extremities and perioral region, which are often triggered by exposure to cold. Few report a transient cold-induced sensation of shortness of breath or swallowing difficulty, known as pharyngolaryngeal dysesthesia. Acute motor toxicity can develop as well, although less commonly. Muscle spasms, fasciculations, and prolonged contractions can be very distressing for patients. These symptoms tend to resolve spontaneously within hours or days and often return on retreatment (7, 8).

The cumulative toxicity of oxaliplatin may be related to direct nerve toxicity as evidenced by morphological changes in the dorsal root ganglia of rats treated with cumulative intraperitoneal doses of oxaliplatin (9), although clinical neurophysiologic examinations and nerve biopsy studies have shown that patients displaying sensory symptoms have no signs or very mild signs of axonal degeneration (10). Acute oxaliplatin action on neurons involves an interaction with sodium channels located in the cell membrane (11, 12). Serial needle electromyography (EMG) and nerve conduction studies (NCS) performed pre- and post-administration during a phase I clinical study, revealed striking signs of reversible hyperexcitability caused by oxaliplatin in peripheral motor nerves (13). This effect on the excitability of sensory neurons has not been described with other platinum agents. Oxaliplatin affects voltage-gated sodium channels through its transformation into oxalate, which is a known intracellular calcium chelator that produces acute neurotoxic effects, such as with ethylene glycol poisoning (14). It is hypothesized that oxalate, released

intracellularly by oxaliplatin, chelates calcium producing an effect on inward sodium currents (15).

The above data form the basis for using neuromodulatory agents in the management of acute and cumulative neurotoxicity from oxaliplatin. For example, it is known that divalent cations, like calcium, modify voltage-gated sodium channels (16). A retrospective study of 161 patients receiving varying regimens of oxaliplatin and 5-FU-LV showed that intravenous calcium gluconate and magnesium sulfate pre- and post-oxaliplatin infusion lowered grade 3 distal paresthesias, the acute symptoms of distal and perioral paresthesias, and patients recovered more rapidly from neuropathy. This took place without any bearing on treatment efficacy (17). A case has been reported of a patient in which oral calcium supplements were successful in treating his neurotoxicity and allowed him to receive high cumulative doses of oxaliplatin up to 2500 mg/m^2, of which 990 mg/m^2 with oral calcium only (18). Other small promising trials have included oral glutamine, acetyl L-carnitine, α-lipoic acid, gingko biloba extract, N-acetylcysteine, celecoxib, amifostine and glutathione infusions (19-27).

The acute hyperexcitability syndrome caused by oxaliplatin has also been treated with partial success with the use of anticonvulsant agents like carbamazepine and gabapentin. Carbamazepine decreases rapid repetitive firing of action potentials by enhancing sodium channel inactivation (28). Gabapentin and pregabalin are GABA analogs, which have a more tolerable side effect profile and are easier to administer than carbamazepine. They do not interact with $GABA_A$/$GABA_B$ or voltage-activated Na^+ channels. The site of action of both drugs is similar, the alpha2–delta (α2–δ) protein, an auxiliary subunit of voltage-gated calcium channels. There are several reports that the drugs reduce calcium current in neuronal cell body membranes. They subtly reduce the calcium-dependent release of synaptic neurotransmitters from neocortical tissues. Preclinical findings are consistent with a mechanism that involves reduction of abnormal neuronal excitability through reduced neurotransmitter release (29, 30).

Gabapentin has not proven very efficacious in the treatment of chemotherapy-induced and more specifically oxaliplatin-induced sensory neurotoxicity. While in a small pilot study of 15 patients treated with oxaliplatin, 5-FU and folinic acid as second-line treatment for advanced colorectal cancer, gabapentin was associated with resolution of neuropathic symptoms (31), other studies have not confirmed a role for gabapentin in ameliorating oxaliplatin-induced sensory neuropathy. For example, in a double-blind, placebo-controlled, crossover study of patients with chemotherapy-induced peripheral neuropathy, gabapentin did not significantly improve pain intensity or the ECOG toxicity rating for sensory neuropathy (32). Addition of gabapentin to a modified FOLFOX6 regimen caused no statistically significant difference in the severity of neurotoxicity compared to the cohort of patients treated with mFOLFOX alone (33).

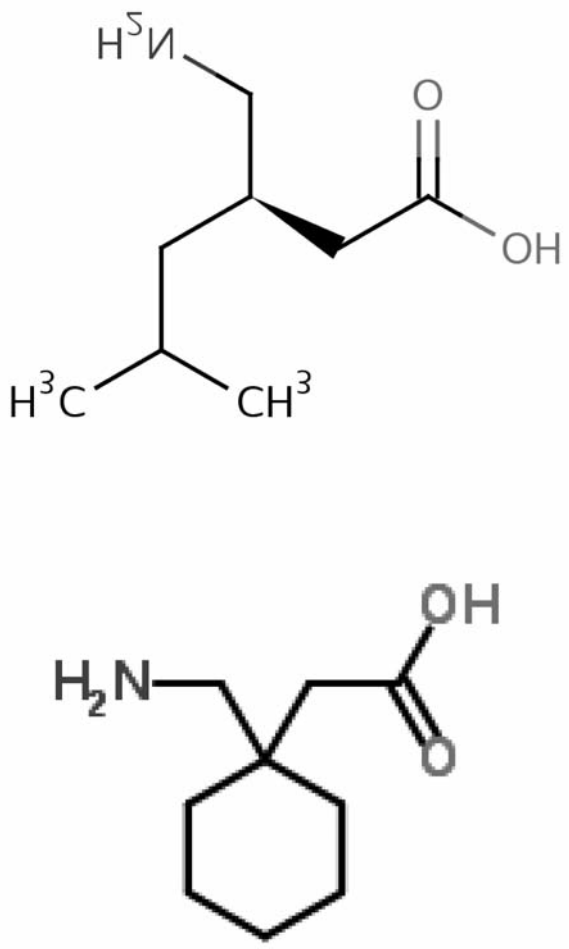

Figure 1. *Chemical structure of pregabalin: (S)-3-(aminomethyl)-5-methylhexanoic acid (top) and gabapentin (bottom). Adapted from Lyrica and Neurontin package inserts (50, 51).*

Pregabalin is a new antiepileptic drug approved in the U.S.A. and Europe as adjunctive therapy of partial seizures in adults. It has also been approved for treatment of pain from diabetic neuropathy and post-herpetic neuralgia, and is being considered for approval for treatment of anxiety disorders due to its anxiolytic effects (34, 35). Pregabalin is structurally related to the antiepileptic drug gabapentin (Figure 1), but unlike gabapentin, it is well absorbed (>90%), and its absorption is dose independent (36-38). There has been a case report of a patient undergoing chemotherapy with gemcitabine and oxaliplatin for pancreatic adenocarcinoma, who was treated with pregabalin for oxaliplatin-induced hyperexcitability syndrome. Pregabalin was prescribed at a dosage of 50 mg three times daily, and the patient developed dramatic improvement in her symptoms within 12 hours of taking pregabalin, and was almost asymptomatic within 72 hours (39).

Table I. *Grading of oxaliplatin-induced neurotoxicity (NCI-CTC v 3.0).*

Grade	Description
1	Mild paresthesia, dysesthesia of short duration, loss of deep tendon reflexes
2	Moderate paresthesia, dysesthesia persisting between cycles, mild or moderate objective sensory loss
3	Paresthesia/dysesthesia interfering with function, severe objective sensory loss
4	Permanent sensory loss that impairs function

Based on the above data, the present study aimed to assess the efficacy of pregabalin for treatment of neuropathic pain associated with oxaliplatin in a group of patients with gastrointestinal malignancies. The rate of pregabalin-induced side effects was investigated in the patient population in an effort to establish the best effective dose.

Patients and Methods

Patient population. From November 2006 to November 2008, a total of 23 patients with confirmed gastrointestinal cancers receiving oxaliplatin as part of the chemotherapy regimen were treated at Yale University Hospital with pregabalin. Patients with pre-existing neuropathy from diabetes mellitus, alcoholic disease, central nervous system diseases or neurotoxic chemotherapy were excluded from this study. Patients with grade 2 and 3 oxaliplatin-induced sensory neuropathy based on National Cancer Institute Common Toxicity Criteria (NCI-CTC) (Table I) were included.

Methods. Neurologic symptoms were serially evaluated before treatment initiation with pregabalin and every 2 weeks thereafter according to the abovementioned NCI-CTC scale (version 3.0), taking into account the intensity and duration of the symptoms. Interference with activities of daily living (ADL), including transient functional impairment in performing ADL such as manipulating buttons, opening jars and other measures of fine motor coordination were evaluated. Pregabalin was started at 50 mg by mouth (PO) three times a day (tid), and if tolerated, the dose was escalated by 50 mg increments until symptoms improved up to a maximum of 150 mg PO tid. The number of patients that achieved the maximum dose of 150 mg PO tid with benefit and tolerance was calculated, as well as the number of patients in whom the drug could not be escalated or had to be stopped secondary to no benefit or intolerance. The primary efficacy end point was objective improvement in sensory neuropathy in the pregabalin treated population. Response was calculated as a decrease in neuropathy by at least one grade according to the NCI-CTC scale. The data was tabulated to include number of patients with stable neuropathy, improved neuropathy, or no benefit. The rate of adverse non-hematological and hematological events was calculated and tabulated in order of highest incidence.

Results

Demographics. Of all 23 patients analyzed, 15 patients were receiving FOLFOX for the treatment of colorectal cancer, 2 patients were receiving Epirubicin/Oxaliplatin/Xeloda (EOX) for gastric cancer and 6 patients were receiving Gemcitabine/Oxaliplatin (GemOx) for the treatment of pancreatic cancer. The patient ages ranged from 50 to 71 years, 14 being males and 9 females.

Table II. *Effects of pregabalin on patient population.*

Drug effect	Drug dosage	Patients (number)	Patients (%)
With benefit	150 mg tid	5	22
	100 mg tid	8	35
	50 mg tid	2	9
	100 mg bid	1	4
Without benefit	100 mg tid	4	17
Stopped due to side effects	50 mg tid	3	13

Table III. *Pregabalin effect on neuropathy.*

Neuropathy	Patients (number)	Patients (%)
Grade 3 stable	0	0
Grade 3 → 2	3	13
Grade 3 → 1	2	9
Grade 2 stable	6	26
Grade 2 → 1	5	22
No benefit	4	17
Discontinued	3	13

Dose intensity of treatment. Pregabalin was started at 50 mg PO tid, and 5/23 patients (22%) were escalated to 150 mg PO tid with benefit and tolerance. Twelve patients (52%) were escalated to 100 mg tid, out of which 7 (58%) continued with benefit and tolerance. Four out of 12 (34%) stopped due to no benefit and one out of 12 (8%) due to weight gain. One patient out of 23 (4%) decided to follow an easier dosing schedule of 100 mg bid with benefit and tolerance. Five out of 23 (22%) could not be escalated above 50 mg tid, 2 of whom continued at this dose and 3 stopped due to CNS side effects (Table II).

Efficacy/response of treatment. Onset of benefit was observed in 2-6 weeks. Most patients continued pregabalin even beyond disease progression on oxaliplatin (15/21). Among those who

Table IV. *Side effects after pregabalin.*

Side effects	Patients (number)	Patients (%)
Non-hematological		
Dizziness	13	57
Headache	6	26
Somnolence	5	22
Ataxia	4	17
Dry mouth	4	17
Peripheral edema	3	13
Tremors	3	13
Constipation	2	9
Weight gain	2	9
Confusion	1	4
Vertigo	1	4
Diplopia	1	4
Muscle twitching	0	0
Hematological		
Thrombocytopenia	1	4

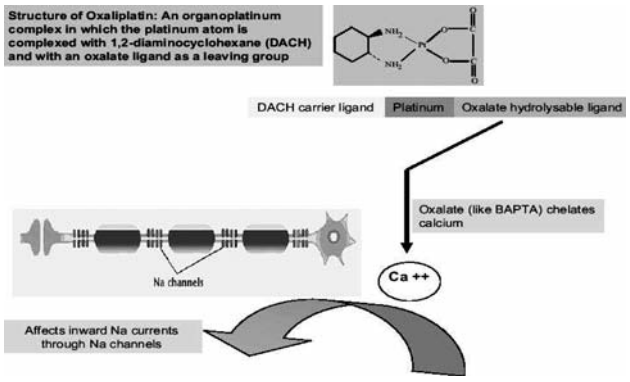

Figure 2. *Postulated mechanism underlying the pathogenesis of neurotoxicity caused by oxaliplatin. Na^+ channelopathy: the theory that an oxalate affects the sodium channels has been supported by several researchers. Oxalate is released intracellularly from oxaliplatin by bicarbonate ions. Oxalate and BAPTA, another calcium chelator, have produced effects on inward sodium currents in invertebrate models similar to those seen with oxaliplatin. BAPTA: 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid; DACH: 1,2-diaminocyclohexane (Adapted from reference 27).*

continued (15), duration of therapy was 4 weeks-24 months. In 3/23 patients (13%) receiving pregabalin, oxaliplatin-induced neuropathy improved from grade 3 to grade 2. In 2/23 patients (9%), neuropathy improved from grade 3 to grade 1. In 6/23 patients (26%), neuropathy improved from grade 2 to grade 1. No patients remained at grade 3. Five out of 23 patients (22%) remained stable at grade 2. As mentioned above 4/23 patients (17%) stopped the drug due to no benefit. Three out of 23 (13%) patients stopped the drug due to CNS side effects, and 1/23 due to weight gain (4%). The best benefit derived from pregabalin was observed at a dose of 150 mg tid, followed by 100 mg tid (Table III).

Safety. The most common non-hematological toxicities of pregabalin were dizziness (57%), headache (26%), somnolence (22%), dry mouth (17%), ataxia (17%), tremor (13%), peripheral edema (13%), weight gain (13%), blurred vision (13%), constipation (9%), diplopia (4%), confusion (4%), vertigo (4%) and muscle twitching (0%) (Table IV). The only hematological toxicity observed was grade 1 thrombocytopenia, but an effect from chemotherapy could not be excluded.

Discussion

Akin to gabapentin, pregabalin is a GABA analog with a more tolerable side effect profile, and it does not interact with $GABA_A$ /$GABA_B$ or voltage-activated Na^+ channels. The preclinical findings are consistent with a mechanism that involves reduction of abnormal neuronal excitability through reduced neurotransmitter release (29, 30) and the present clinical study underlined the need for evaluating the role of pregabalin in ameliorating oxaliplatin-induced neuropathy.

Neurotoxicity is the most frequent dose-limiting toxicity of oxaliplatin. Acute sensory neurotoxicity manifests itself as rapid onset of cold-induced distal dysesthesia and/or paresthesia, sometimes accompanied by cold-dependent muscular contractions of the extremities or the jaw. The symptoms, often occurring during or shortly after infusion, are usually transient and mild. A cumulative sensory peripheral neuropathy may also develop with prolonged treatment with oxaliplatin, eventually causing superficial and deep sensory loss, sensory ataxia and functional impairment (27).

The acute sensory neuropathy seen with oxaliplatin is described in the literature as 'channelopathy'. This is based on the similarities that oxaliplatin-induced neuropathy shares with hereditary myotonias and certain toxin exposures (14, 15). After an action potential has been elicited in a sensory neuron, the fast depolarizing current is dependent upon sodium influx through voltage-gated ion channels. The action potential is terminated through sodium channel inactivation coupled with repolarization by an efflux of potassium ions (Figure 2). Disorders of these nerve ion channels are characterized by an increase or decrease in the excitability of a neuron. Hyperexcitability of peripheral axons is seen in neuromyotonia, which is a rare syndrome characterized by muscle stiffness, slowed muscle relaxation, and paresthesias. Neuromyotonia symptoms are aggravated by repetitive activation and cold. The condition can be idiopathic, autoimmune mediated, or a side effect of drugs and toxins (40-42). Autoantibodies to K^+ channels as well as a mutation in a voltage-gated sodium channel have been implicated in

neuromyotonia (43-45). The acute electrophysiologic findings post-oxaliplatin administration are the same as those seen in neuromyotonia (27).

The current recommendations for the management of the acute and cumulative neurotoxicity from oxaliplatin include education about exposure to cold, dose modification, 'stop and go', and use of neuromodulatory agents, in particular, intravenous calcium and magnesium infusion (24). However, the role of anticonvulsants and other agents remained to be fully elucidated.

A single randomized, double-blind, placebo-controlled trial was performed to assess the efficacy of glutathione in the prevention of oxaliplatin-induced neurotoxicity. Fifty-two patients were randomized to receive a 1500 mg/m^2 glutathione infusion over 15 minutes or normal saline before oxaliplatin infusion. Oxaliplatin was administered on a bimonthly regimen. The median cumulative dose of oxaliplatin did not differ amongst the two arms. The glutathione group showed significantly less grade 2 or higher neurotoxicity after 8 cycles of chemotherapy (58% *vs*. 10%). The response rates were similar between the glutathione and placebo groups (26.9% *vs*. 23.1%), suggesting that glutathione does not change the efficacy of oxaliplatin (46).

In a small German study, 40 patients refractory to 5-FU were treated with oxaliplatin, 5-FU, and folinic acid as a second-line therapy. Ten patients were additionally treated with carbamazepine maintaining serum levels of 3-6 mg/l. The patients in the carbamazepine group were able to receive significantly higher cumulative doses of oxaliplatin (722 mg/m^2 *vs*. 510 mg/m^2; p=0.02). No neuropathy higher than grade 1 occurred in the carbamazepine group compared with 30% in the control group (47). In contrast, carbamazepine therapy administered to 12 patients in a phase I study designed to establish the maximum tolerated dose of capecitabine given with oxaliplatin, did not alter clinical symptoms or electromyographic abnormalities of axonal hyperexcitability (13).

In another double-blind, placebo-controlled phase III trial, 115 patients with chemotherapy-induced peripheral neuropathy (for ≥1 month, with average pain rating of ≥4/10 or Eastern Cooperative Oncology Group [ECOG] sensory neuropathy ≥1/3) were randomized to either: gabapentin (target dose=900 mg tid) for 6 weeks then crossover to placebo for 6 weeks (n=57), or treatment in the reverse order (n=58). A 2-week washout occurred between crossover treatments. The co-primary endpoints were the average daily pain numerical analogue intensity rating (0=no pain to 10=worst pain imaginable) and the ECOG toxicity rating for sensory neuropathy (0=none to 3=severe). The results of the study showed that gabapentin did not significantly improve the co-primary endpoints of pain intensity (–0.5 *vs*. –1.0 change from baseline to week 6 for patients on gabapentin and placebo respectively, p=0.18) or the ECOG toxicity rating for sensory neuropathy (–0.2 *vs*. –0.1 for gabapentin and placebo respectively, p=0.38). Patients on gabapentin reported significantly more nystagmus (p=0.009) and dizziness (p=0.02). Therefore, the study was not able to confirm the benefit of the use of gabapentin in ameliorating peripheral neuropathy (32).

Pregabalin, in contrast to gabapentin, has a rapid absorption (peak 1h) and plasma concentration increases linearly with increasing dose (48). The higher bioavailability and rapid absorption allow for much lower doses to be used to achieve an equianalgesic effect to gabapentin (38). There are no head-to-head studies comparing the side effects of pregabalin *vs*. gabapentin, but because lower dosages can be used, it is likely that pregabalin will be associated with fewer dose-related adverse events. Pregabalin is well-tolerated, with dizziness and somnolence being the most frequently reported adverse events, followed by dry mouth, peripheral edema, blurred vision, weight gain, abnormal thinking, and case reports of myoclonus, asterixis, and gynecomastia (34, 35, 49). In our study the best benefit with pregabalin was achieved at a dose of 150 mg tid, but patients experienced significant symptomatic relief even at lower doses of 50mg tid. Importantly, no patients remained at neuropathy grade 3, and in others neuropathy was reduced by 1-2 grades. Side effect profile in our study population was similar to that described in the literature, with dizziness, headache, and somnolence being the most common.

In summary, pregabalin significantly reduced the severity of oxaliplatin-induced neuropathy. Larger placebo-controlled trials assessing the safety and efficacy of oral pregabalin are warranted in patients treated with oxaliplatin.

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Received April 11, 2010
Revised May 14, 2010
Accepted May 20, 2010