Clinical activity of venlafaxine and topiramate against oxaliplatin-induced disabling permanent neuropathy

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Venlafaxine (Effexor; Wyeth Lederlé), a serotoninergic-like anti-depressant, and Topiramate (Epitomax; Jansen Cilag), a new anti-epileptic drug, share some evidence of clinical activity in the treatment of neuropathic pain. Several anti-cancer agents have neurosensory toxicity as limiting toxicity of their repeated administration. One of the most recent and the most widely used is oxaliplatin. No medication is presently known to be active against oxaliplatin permanent neurosensory toxicity. We observed that venlafaxine hydrochloride or low-dose topiramate could be active against the permanent neuropathy-related symptoms of oxaliplatin. Both agents allowed pain relief and a significant autonomy improvement. These preliminary results invite us to evaluate further venlafaxine hydrochloride and topiramate for the treatment of permanent anti-cancer chemotherapy-induced neuropathies. *Anti-Cancer Drugs* **16:587–591 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Anti-cancer chemotherapy is a common cause of peripheral nervous system disorders that manifest in a variety of clinical forms, the most prevalent being polynevritis. Peripheral neuropathy remains usually poorly symptomatic during therapy. However, the off-therapy worsening caused by cisplatin [1] or oxaliplatin may remain a problem. Functionally disabling toxic neuropathy may occur at standard doses in patients with pre-existing neuropathy [2]. The favorable toxicity profile of single-agent carboplatin led a group of trialists to propose carboplatin alone instead of carboplatin plus paclitaxel as a reasonable option as first-line chemotherapy for ovarian cancer [3], especially to avoid paclitaxel-related neurotoxicity.

Over the past two decades, our understanding of the pathophysiology of nerve injury has improved remarkably through the elucidation of the important roles of the polyol pathway of glucose metabolism, oxidative injury, vascular insufficiency and other mechanisms [4,5]. A large number of clinical treatment trials based upon this abundant scientific data have met with limited success.

Peripheral chemotherapy-induced neuropathy has a major impact on quality of life and may limit the amount of treatment patients can receive. Neurotoxic agents are used increasingly in oncologic practice, yet clinicians are often unaware of the protean manifestations of neuropathy and find its management troubling. Recent knowledge about the mechanisms of neuropathic disease and new treatments may help to minimize the impact of neuropathy in this vulnerable patient population.

Oxaliplatin (Eloxatin; Sanofi Aventis) is presently widely used for the treatment of metastatic colorectal cancer. Its addition to 5-fluorouracil (5-FU) increased both response rate and time to progression. Oxaliplatin is presently used as first-line therapy in metastatic colorectal cancer patients, as an alternative option to irinotecan. It is widely used in two-drug combinations in patients with metastatic colorectal cancer as first-line treatment [6] and more recently in the adjuvant setting [7]. Interestingly, oxaliplatin is being used as an alternative option to cisplatin in various cancers, such as ovarian cancer [8] and pancreatic cancer [9]. Similar perspectives are under clinical evaluation in bladder cancer and non-small cell lung cancer. Indeed, oxaliplatin is much better tolerated than cisplatin, both in terms of acute toxicity with significant impact upon daily life (acute vomiting, agueusia), social life (no ototoxicity) and no renal toxicity [10]. These tolerability improvements, even before the demonstration of equivalent efficacy indication per indication, led, in our experience, to a switch in the platinum used, especially in unfit patients. Hence, elderly patients and patients with severe co-morbidities take benefit from receiving a non-nephrotoxic and poorly hematotoxic agent. However, oxaliplatin long-term

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administration is limited by cumulative neurosensory toxicity [11].

Venlafaxine is an anti-depressant which inhibits re-uptake of both norepinephrine and serotonin. Venlafaxine has previously shown therapeutic effects for the management of chronic and neuropathic pains, especially in patients with diabetes mellitus. We already reported the efficacious use of venlafaxine for paclitaxel permanent disabling neurotoxicity [12]. Moreover, we found venlafaxine very active against the acute paresthesias induced by oxaliplatin [13]. Topiramate (Epitomax; Janssen-Cilag) is a new anti-convulsant drug which acts by blocking the spread of seizure activity [14]. Topiramate has also shown interesting effects for the treatment of neuropathic pains [15] and migraines [16,17]. We report here the first evidence of activity of venlafaxine and topiramate for the treatment of oxaliplatin cumulative and chronic neurosensory toxicity.

Case 1

A 82-year-old woman was treated for a peritoneal carcinomatosis from unknown primary revealed by a hypogastric tumor. A first-look surgery with omentectomy and biopsies revealed a metastatic mucinous adenocarcinoma. She underwent a chemotherapy using oxaliplatin at 85 mg/m^2 as a 2-h infusion of 130 mg combined with 5-FU and folinic acid (FOLFOX 4 regimen) [7].

She had a medical history including myelodysplasia, non-mellitus diabetes, angor and hypertension. She did not have any clinical diabetes complications or alcoholic intoxication, or underlying neuropathy.

After the eighth cycle, she developed a neurosensory toxicity with few paresthesias in the fingers of both hands. She mainly described hypoesthesias of the last phalanx of the fingers. Oxaliplatin was interrupted after the 10th cycle because of major functional impairments: she could not grip thin things such as plates and spoons, she could not button her clothes, and she could not write anymore. We decided to start a treatment with venlafaxine hydrochloride (Effexor XR). The initial dose and schedule were 37.5 mg once a day. She reported a very quick recovery of the use of her fingers and a minor reduction of the paresthesias. Since the initial dose was well tolerated, 3 days later the dose was increased up to 37.5 mg twice daily. The symptoms improved and the functional impairment disappeared in daily life. Residual paresthesias still persisted after a 6-month follow-up.

Case 2

A 53-year-old man was treated for a rectal adenocarcinoma with synchronous lung and liver metastases. He received a chemotherapy combining a 2-h infusion of 85 mg/m^2 oxaliplatin and infusional 5-FU, according to the FOLFOX4 regimen, repeated every 2 weeks. He did not have any underlying neuropathy and had no identified co-morbidity at risk for neuropathy such as ethylism or diabetes mellitus. He received nine cycles.

A bowel obstruction occurred leading to a palliative colostomy. While the patient reported mild paresthesias in both hands after nine cycles, he noticed an acute aggravation following surgery, as previously described [18]: he presented a painful neuropathy in both legs, starting in the feet and ascending in the legs. The pain was exacerbated by contact with the ground and by walking. The patient became so disabled that he could not stand up and was immobilized in bed. A treatment with venlafaxine hydrochloride was initiated and increased to 37.5 mg twice daily, 3 days later. After 2 weeks of treatment, no symptom improvement was noticed and venlafaxine was interrupted. A treatment with topiramate (Epitomax) was started using the initial dose of 25 mg in the evening. After 1 week, the dose was increased to 50 mg in the evening, and 1 week later to 25 mg in the morning and 50 mg the evening for a further 3 days. Finally, the dose was increased up to 50 mg twice a day for the following days. The patient noticed the beginning of pain relief. With treatment continuation, within 1 week, symptom relief allowed the patient to stand up and walk. He did not mention any residual pain in the legs. However, some residual paresthesias persisted in the extremities. The effect was sustained during the month of follow-up.

Discussion

We report here two patients with severe disabling oxaliplatin-induced neuropathy who greatly benefited from either venlafaxine or low-dose topiramate. We initially detected the potential interest of venlafaxine for the treatment of permanent paclitaxel-induced neuropathy [8]. More recently, we noticed a reproducible activity of venlafaxine for the treatment of acute oxaliplatin-induced neuropathies [11]. Here, we focused our efforts to palliate the symptoms related to oxaliplatin-induced permanent neuropathy. We observed that venlafaxine hydrochloride may be helpful in this setting (Case 1). Moreover, in the case of venlafaxine-resistant neurologic symptoms, we described the efficacy of another agent, topiramate.

Neurotoxicity is the dose-limiting toxicity of oxaliplatin. Acute neurotoxicity is characterized by the rapid onset of cold-induced distal dysesthesia and/or paresthesia. Sensory symptoms may also be 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 persistent sensory peripheral neuropathy may also develop with prolonged treatment, eventually causing superficial and

deep sensory loss, sensory ataxia, and functional impairment. The similarity of the acute symptoms induced by oxaliplatin with those caused by several drugs or toxins acting on neuronal or muscular ion channels suggests that these symptoms may result from a specific interaction of oxaliplatin with ion channels located in the cellular membrane [19].

Oxaliplatin-induced neuropathic pain may be perpetuated by various mechanisms, with pathophysiologic targets (and possible treatments). The exacerbation of oxaliplatin neurotoxicity after surgery observed in Case 2 is presently well elucidated. The patient presented here a typical increase of the sensitive symptoms following surgery. The persistence of high concentrations of intra-erythrocytic oxaliplatin at the time of surgery and the perioperative lysis may account for this phenomenon, as we previously described [18].

Tricyclic anti-depressants, gabapentin and opioids can act through functional reduction of inhibitory interneuron activity and impaired descending nociceptive inhibition, but were not found effective.

Recent data indicate that oxaliplatin may act on specific isoforms of the voltage-gated sodium (Na^+) channel to increase the excitability of sensory neurons, an action inhibited by the Na^+ channel-blocker carbamazepine. This contention is supported by recent clinical findings indicating that pharmacologic blockade of Na^+ channels may prevent and/or repress the acute neurotoxicity of oxaliplatin. Grolleau *et al.* [20] reported an inhibitory effect of oxaliplatin on voltage-gated sodium (VGS) current. The activation of the VGS current controls the rising phase of the action potential in the dorsal unpaired median neurons. Oxaliplatin reduced the spike amplitude by altering VGS channels; the current inhibition is progressive during the first 10 min after establishment of the whole-cell patch-clamp configuration. The intracellular inhibition of the peak sodium current amplitude is oxaliplatin dose dependent. Interestingly, oxaliplatin induced a lower effect on the fully inactivated inward sodium current.

We previously described the pragmatic choice of introducing venlafaxine, due to a possible action upon sodium channels [13]. Topiramate may also be a good candidate to interact with these channels.

Our clinical observation (Case 2) suggests that topiramate titration should be performed gradually, so as not to neglect cases responsive to low doses. The potential benefit of topiramate titration was previously underlined for the treatment of essential tremor [21]. Topiramate at low doses proved to be an effective therapeutic approach to reduce headache frequency in patients with chronic migraine [11] and analgesic overuse [22].

No side-effects were observed and improvement was sustained during the follow-up period. Nevertheless, topiramate use requires a careful follow-up since evidence of potential side-effects is emerging [23]. Topiramate was associated with an increased frequency of anorexia, depression, diarrhea, ecchymosis, nausea, taste perversion, thinking abnormalities, weight loss and abnormal blood clotting (pulmonary embolism and deep venous thrombosis) [24].

Topiramate induces less pharmacokinetic interactions with other drugs than other anti-epileptic agents [25]. Topiramate, a sulfamate fructopyranose derivative, might antagonize alcohol's rewarding effects associated with abuse liability by inhibiting mesocorticolimbic dopamine release via the contemporaneous facilitation of γ-aminobutyric acid activity and inhibition of glutamate function [26].

Both excitatory and inhibitory chemical neurotransmission can be modulated by the topiramate. Relatively low topiramate concentrations inhibited the transient and persistent sodium current fractions [27]. The drug-inhibitory effect increased with the duration of membrane depolarization. Topiramate seems also to promote neurite outgrowth in cell cultures [28] and to prevent motor neuron degeneration in culture models [29], suggesting topiramate could act as a neuroprotectant. Topiramate, as well as gabapentin, or spinal cord stimulation, may act on central sensitization and increased central excitability. The treatment choices should be aimed at remodulating, normalizing, disrupting or preventing the progression of abnormalities in pain processing. As the oxaliplatin neuropathy seems to be related to the VGS channel, to use a sodium channel blocker appears to be a valuable option. Topiramate has been reported to interact with various ion channel types, including AMPA/kainate receptors. In whole-cell voltage-clamp recordings from principal neurons of the rat basolateral amygdala, topiramate at low concentrations (IC_{50}, approximately 0.5 μM) selectively inhibited pharmacologically isolated excitatory synaptic currents mediated by kainate receptors containing the GluR5 subunit [30].

Several neuromodulatory agents such as calcium–magnesium infusions, anti-epileptic drugs like carbamazepine or gabapentin, amifostine, α-lipoic acid and glutathione have been undergoing clinical evaluation for the prophylaxis and symptomatic treatment of oxaliplatin-induced neurotoxicity. Several compounds have been tested in the clinical setting for the preventive or palliative treatment of chemotherapy-induced neuropathies. Amifostine (WR-2721) failed to prevent or improve clinically significant (grade 2 or higher) neurotoxicity associated with cisplatin and 3-h paclitaxel chemotherapy [31]. Acetyl-L-carnitine (ALC) is a natural occurring compound with a neuroprotective activity in several experimental paradigms, and its

protective role on cisplatin and paclitaxel-induced neuropathy has been tested [32]. A co-treatment with ALC was able to significantly reduce the neurotoxicity of both cisplatin and paclitaxel in rat models, and this effect was correlated with a modulation of the plasma levels of nerve growth factor in the cisplatin-treated animals. Moreover, experiments in different tumor systems indicated the lack of interference of ALC in the anti-tumor effects of cisplatin and paclitaxel. Glutamine deficiency may impact on normal tissue tolerance to anti-tumor treatment, and may lead to dose reductions and compromised treatment outcome. The role of glutamine in the prevention of chemotherapy and radiation-induced toxicity is evolving. Glutamine supplementation might reduce the incidence of neurologic complications of cancer therapy.

Because of a very specific semiology, the physician may anticipate the installation of the neuropathy of oxaliplatin and schedule treatment interruption. Nevertheless, given the benefit:risk ratio, on a case by case basis, patients may receive more cycles while already having permanent symptoms. More importantly, even after treatment interruption, the neuropathy may be exacerbated either spontaneously or in case of surgery. As a consequence, we may predict that the management of oxaliplatin-induced permanent neuropathy will become a more and more prevalent clinical problem in the coming years. Oxaliplatin has become an integral part of various chemotherapy protocols; in particular, in advanced colorectal cancer. Various strategies have been proposed to prevent or treat oxaliplatin-induced neurotoxicity. The 'Stop-and-Go' approach uses the reversibility of neurologic symptoms to aim at delivering higher cumulative oxaliplatin doses as long as the therapy is still effective in chronic cancer patients.

Although there is no demonstration that a common cellular mechanism induces both the acute and the cumulative neurotoxicity of oxaliplatin, controlled clinical trials are currently underway to establish the value of Na^+ channel blockade against both acute and cumulative oxaliplatin neurotoxicities. We are presently undertaking an ongoing placebo-controlled phase III clinical trial to evaluate the potential interest of venlafaxine for oxaliplatin acute neurotoxicity. Further studies are needed to define the role of venlafaxine and topiramate in chemotherapy-induced permanent neurosensory toxicity.

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