Protection against oxaliplatin acute neurosensory toxicity by venlafaxine

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Venlafaxine (Effexor; Wyeth Lederlé) has previously shown therapeutic effects for the management of chronic and neuropathic pains. We report here the efficacy of venlafaxine upon acute neurosensory symptoms secondary to oxaliplatin toxicity. A dose of 50 mg of venlafaxine was given orally at the beginning of the oxaliplatin infusion. Patients did not experience any or very low paresthesias, even in the cold. As the results were very dramatic and reproducible, we propose that venlafaxine may be of use in the daily management of oxaliplatin-related neurosensory toxicity. *Anti-Cancer Drugs* 14:423–425 © 2003 Lippincott Williams & Wilkins.

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Introduction

The historical median survival of untreated patients with colorectal cancer metastatic to the liver is 4.5 months [1]. A major advance in the treatment of metastatic colorectal cancer (MCRC) in recent years has been the increase in efficiency of chemotherapy regimens [2–4]. Chemotherapy has prolonged, step by step, the median survival of MCRC patients up to 20 months [5]. Oxaliplatin is widely used in Europe for the treatment of MCRC and has recently been approved in the US. Neurotoxicity is dose-limiting and occurs in two distinct forms—an acute neurologic symptom complex that occurs within hours or days of therapy and a chronic, cumulative sensory neuropathy [6]. The most constant acute side-effect of oxaliplatin is a transient peripheral neuropathy manifesting as paresthesia and dysesthesia in the extremities and perioral area, triggered or enhanced by exposure to cold. These symptoms, often developing during oxaliplatin infusion, last between a few minutes and a few days. These special characteristics have motivated a specific grading scale, modified with increasing experience, and used for phase I and II clinical trials [7–9]. The chronic manifestations may also be exacerbated immediately following surgery [10]. Nevertheless, this neurotoxicity is slowly but consistently reversible upon treatment discontinuation [6]. Unfortunately, there is no active treatment for chemotherapy-induced neurosensory symptoms and patients have to live with it. Efforts to identify a successful neuroprotectant strategy would have a major impact on improving patient quality of life and the ability to deliver full doses of oxaliplatin. Venlafaxine (Effexor; Wyeth Lederlé) has previously shown therapeutic effects for the management of chronic and neuropathic pains, particularly in patients with diabetes mellitus [11]. We previously reported the activity of venlafaxine to improve paclitaxel-induced permanent neuropathy [12]. We report here the efficacy of venlafaxine upon acute neurosensory symptoms secondary to oxaliplatin toxicity. As the results were very dramatic and reproducible, we feel that venlafaxine may have rapid impact on the daily management of oxaliplatin-related neurosensory toxicity.

Method and results

A 33-year-old patient with metastatic colonic cancer was treated with 100 mg/m^2 of oxaliplatin as a 2-h infusion combined, as previously reported [4], with 5-fluorouracil (5-FU) and folinic acid. After 3 cycles of chemotherapy, he suffered of striking paresthesias of both hands from the end of the infusion up to 8 days. The symptoms were exacerbated by cold, fresh air, leading him to wear gloves. A dose of 50 mg of venlafaxine was given orally at the beginning of the fourth oxaliplatin infusion. At the end of the infusion, the patient did not have paresthesia any more, he could touch the metallic upright of the bed, the metal tree of the infusion and stopped wearing gloves when he left the hospital. At home, he was treated by 37.5 mg of venlafaxine hypochloride (Effexor LP) twice a day for 1 week. He did not have any neurosensory symptom in the cold.

Table 1 summarizes the results obtained in similar conditions in a small series of 10 patients treated with an oxaliplatin-containing chemotherapy. The chemotherapy regimen was either FOLFOX or GEMOX, administered as previously described [4,13]. When the patients experienced acute neurotoxicity at cycle 1, they were proposed a co-treatment with venlafaxine at initiation of

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Table 1 Acute neurosensory toxicity induced by oxaliplatin without (cycle 1) and with (cycle 2) venlafaxine co-treatment

	Cycle 1	Cycle 2
Patients	10	10
Chemotherapy regimen		
FOLFOX	8	8
GEMOX	2	2
Acute neurosensory manifestations		
acute paresthesias during infusion	2	0
painful paresthesias in the cold	9	2[a]
functional impairment	1	0

[a]The patients described an only partial improvement.

cycle 2. All the patients but one did not re-experience acute neurosensory symptoms under venlafaxine.

Discussion

These observations report for the first time reproducible evidence of complete protection against acute oxaliplatin-induced paresthesia. Combining oxaliplatin-based chemotherapy and surgical resection of metastases has become a prevalent therapeutic strategy to improve long-term survival in MCRC [2,4,7,8,14]. Two phase III randomized trials have shown that the addition of oxaliplatin to 5-FU and leucovorin regimen results in a significantly higher response rate [4,15]. Multiple oxaliplatin-based chemotherapy regimens are under prospective evaluation in MCRC patients [for review, see 16]. In 5-FU-refractory cancer patients, the addition of oxaliplatin and CPT-11 has suggested promising results [7,8]. Three-agent regimens might allow more rapid and more complete responses [17], and ongoing trials are evaluating the potential interest of the association of the three active cytotoxic agents as first-line treatment. Oxaliplatin is an active agent not only for metastatic colorectal cancer, but also in numerous other malignant diseases [13,18–21]. Because of its excellent tolerability, oxaliplatin is of particular interest in the growing population of 'unfit' patients, suffering from either cachexia, alteration of performance status or severe chronic co-morbidities, a frequent situation in diseases such as pancreatic, gastric or non-small cell lung cancers [13,20,21].

However, peripheral sensory neuropathy with predominantly hyperpathic symptoms induced by cold is the most severe and dose-limiting toxicity resulting from oxaliplatin therapy. The typical neurotoxicity of oxaliplatin has been linked to the axonal and dorsal root ganglia neurons accumulation of di-chloro-DACH platinum, a biotransformation product of DACH platinum compounds [22]. Biotransformation products such as $Pt(dach)Cl_2$ and its hydrolysis products are more neurotoxic than the parent drugs oxaliplatin and ormaplatin [23]. Oxaliplatin alters sodium channel kinetics on sensory neurons. This effect could be antagonized *in vitro* by a sodium channel blocker, carbamazepine. Within the clinical concentration range (40–500 μM), oxaliplatin applied intracellularly decreased the amplitude of the voltage-gated sodium current resulting in a reduction of half the amplitude of the action potential. In contrast, two other platinum derivatives, cisplatin and carboplatin, were ineffective at reducing the sodium current amplitude [24].

No treatment has demonstrated activity for the treatment of severe chemotherapy-induced neuropathies. Tricyclic antidepressants, analgesics and anticonvulsant agents, such as clonazepam, are helpful in the management of neuropathic pain, and provide approximately the same mild benefit. Several treatments have been evaluated for the treatment of oxaliplatin-induced neuropathy. The acute neurotoxicity seen with oxaliplatin is characterized by peripheral nerve hyperexcitability and the findings are similar to the clinical manifestations of neuromyotonia. Carbamazepine, which provides symptomatic relief in acquired neuromyotonia, was not able to prevent acute neurosensory symptoms [25]. Glutathione is an antioxidant agent interfering with the cellular metabolism of platinum derivatives, which might have a protective effect against oxaliplatin toxicity. A randomized, double-blind, placebo-controlled trial assessed the efficacy of glutathione (GSH) in the prevention of oxaliplatin-induced cumulative neurotoxicity. Fifty-two patients treated with a bimonthly oxaliplatin-based regimen were randomized to receive GSH (1500 mg/m^2) over a 15-min infusion period before oxaliplatin or normal saline solution. The neurophysiologic investigations (sural sensory nerve conduction) showed a statistically significant reduction of the values in the placebo arm, but not in the GSH arm [26].

Venlafaxine is an antidepressant, a serotonin and norepinephrine reuptake inhibitor (SNRI), which does not bind to muscarinic-cholinergic, histaminic or α_1-adrenergic receptors, resulting in less adverse effects than tricyclic antidepressants. A randomized study compared the effect of venlafaxine versus placebo in 244 patients with painful diabetic neuropathy. Venlafaxine was significantly ($p < 0.05$) more active than placebo on pain relief [27]. Interestingly, venlafaxine prevents the thermal hyperalgesia associated with experimental neuropathy in rats [28]. Moreover, venlafaxine was recently found, at therapeutically relevant concentrations, to block sodium channels in guinea pig ventricular myocytes [29]. Whether venlafaxine also blocks neuronal sodium channels has not yet been tested [30]. Based on the mechanism of action of venlafaxine and on the physiopathology of oxaliplatin neurotoxicity, we expected venlafaxine to be also active against oxaliplatin-induced acute neurosensory symptoms. Our results are encouraging. We also have preliminary evidence of activity of venlafaxine for the symptomatic treatment of the cumulative oxaliplatin-induced neurotoxicity. These

results need to prospectively evaluate the efficacy of venlafaxine in oxaliplatin-induced neuropathies.

Conclusion

Venlafaxine treatment may improve the quality of life of advanced cancer patients treated with oxaliplatin who experience severe acute neuropathy. Our observations provide evidence that venlafaxine is a promising drug for the prevention of oxaliplatin-induced acute neurosensory symptoms. Further studies are warranted to define more precisely the mechanism of the protection by venlafaxine. A randomized phase II study is underway to confirm these results in a larger population of patients treated with oxaliplatin.

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