Oral Calcium Ameliorating Oxaliplatin-Induced Peripheral Neuropathy

Muhammad Wasif Saif, MD

University of Alabama at Birmingham, Birmingham, Alabama

KEY WORDS: oxaliplatin, neuropathy, colon cancer, calcium, magnesium

ABSTRACT

Oxaliplatin has become an integral part of the standard treatment for advanced colorectal cancer. While oxaliplatin has only mild hematologic and gastrointestinal side effects, its dose-limiting toxicity is a cumulative sensory neurotoxicity. Oxaliplatin causes a unique, but frequent, acute sensory neuropathy that is triggered or aggravated by exposure to cold but is rapidly reversible, without persistent impairment of sensory function. Various strategies have been proposed to prevent or treat oxaliplatin-induced neurotoxicity. One such strategy is the "Stop-and-Go" concept, which uses the reversibility of neurologic symptoms to aim at delivering higher cumulative oxaliplatin doses, as long as the therapy is still effective and the other is the administration of neuromodulatory agents (ie, calcium-magnesium infusions, carbamazepine, gabapentin, amifostine, alpha-lipoic acid, and glutathione) that could limit the neurotoxic effects of oxaliplatin. Among all of the agents, intravenous calcium and magnesium have shown the most promise in prophylaxis and treatment of oxaliplatin-induced neurotoxicity. We report a case of a patient, in which oral calcium supplements not only were successful in treating his neurotoxicity, but we also were able to administer a cumulative dose of 2500 mg/m^2 (990 mg/m^2 with oral calcium). Although the current recommendations for the management of the acute and cumulative neurotoxicity from oxaliplatin with the use of infusion of Ca/Mg remain valid, our case is the first report demonstrating the role of oral minerals in ameliorating neurotoxicity from oxaliplatin. Future studies to evaluate the role of oral Ca/Mg are warranted, since they could prove to be an effective, less expensive and more convenient way to treat and prevent oxaliplatin-associated toxicity.

INTRODUCTION

Oxaliplatin is a third generation platinum compound that differs both structurally and in its spectrum of activity from the related and widely used chemotherapeutic agents cisplatin and carboplatin. Platinum compounds exert their cytotoxic effects through the formation of DNA adducts that block both DNA replication and transcription, resulting in cell death in actively dividing cells, as well as through the induction of apoptosis. Unlike these *cis*-diamine platinums, oxaliplatin contains a 1,2 diaminocyclohexane carrier ligand. This structural alteration results in formation of bulkier platinum-DNA adducts that may be more difficult to repair, leading to increased inhibition of DNA synthesis and induction of apoptosis.[1]

Oxaliplatin combined with 5-fluorouracil (5FU) is now considered a standard treatment for metastatic colorectal cancer[2,3] and on November 4, 2004, the FDA approved oxaliplatin for injection for use in combination with infusional 5-fluorouracil/leucovorin (5-FU/LV) for adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor.[4] The combination of oxaliplatin with oral fluorouracil prodrugs, such as capecitabine,[5] is currently being evaluated. Its overall hematologic and gastrointestinal side effects profile is good, but neurotoxicity is a frequent dose-limiting toxicity. The peculiar acute neurotoxicity of oxaliplatin is manifested as a cold-related dysesthesia and sometimes accompanied by muscle contractions, which may occur shortly after drug administration. These clinical manifestations of this acute neurotoxicity differ greatly from cisplatin neurotoxicity and are not explained by morphological damage of the nerve,[4,6] and resemble those described in patients with congenital myotonia or tetany.[6,7] Therefore, it is hypothesized that oxaliplatin has a unique direct effect on nerve excitability. It is postulated that oxalate, one of the oxaliplatin metabolites, is responsible for the acute neurotoxic effects of oxaliplatin via Ca and/or Mg chelation;[8] which is based on the fact that oxalate is also responsible for the acute neurotoxic effects of ethylene glycol poisoning[8] and is a known chelator of both Ca and Mg. Based on this belief, the effectiveness of both Ca and Mg infusions has been evaluated in a retrospective cohort of 161 patients treated with oxaliplatin, 5-fluorouracil, and leucovorin for advanced colorectal cancer, with 3 regimens of oxaliplatin (85 mg/m^2 (every 2 weeks), 100 mg/m2 (every 2 weeks), 130mg/m^2 (every 3 weeks).[9] This study demonstrated that intravenous infusion of Ca/Mg seems to reduce the incidence and intensity of acute oxaliplatin-induced symptoms and might delay cumulative neuropathy, especially in 85 mg/m^2 oxaliplatin dosage.[9]

We describe a patient with advanced colon cancer, who was able to receive a cumulative dose of 2500 mg/m^2 of oxaliplatin with intravenous, and later oral calcium. This is the first case of oral calcium ameliorating neurotoxicity.

CASE REPORT

A 62-year-old white male with metastatic colon cancer received oxaliplatin-based chemotherapy as a second line chemotherapy after unsuccessful treatment with bIFL (bolus 5-FU, irinotecan, and leucovorin). The patient received 8 cycles of FOLFOX-4 regimen (oxaliplatin/5FU/LV), initiated on November 25, 2002. He tolerated the treatment with only grade 1 neuropathy, which manifested as tingling, numbness, and paraesthesias in the lower extremity, and lasted for 3 to 4 days (Table 1). In March 2003, the patient moved to Wisconsin but decided to continue his treatment in Birmingham, Alabama. Therefore, due to responding disease and no significant toxicities, his regimen was changed to CAPOX (capecitabine with oxaliplatin) primarily because it was more convenient for the patient. The patient tolerated the first two cycles with minimal toxicity, but developed grade 2 neuropathy following cycle 2. An infusion of calcium and magnesium was added to cycle 3, but he continued to experience grade 2 neuropathy, hence, the dose of oxaliplatin was reduced to 110mg/m^2 in cycle 4 (June 2003, Table 1).

He received oxaliplatin at the reduced dose through September 2, 2003 without any complications or worsening of neuropathy. During cycle 8, he complained of a severe itch all over his body following the infusion of calcium and magnesium. The itch was so severe that intravenous benadryl, ranitidine,

Table 1. Patient's Dose and Administration of Oxaliplatin

Date of administration	Dose of oxaliplatin (mg/m^2)	Ca/Mg given (+)/not given (-)
11-25-02	85	-
12-19-02	85	-
12-30-02	85	-
1-13-03	85	-
1-27-03	85	-
2-10-03	85	-
2-24-03	85	-
3-10-03	85	-
3-24-03	130	-
4-14-03	130	-
5-20-03	130	+
6-09-03	110	+
6-30-03	110	+
7-21-03	110	+
8-11-03	110	+
9-02-03	110	+/-
9-29-03	110	-
10-20-03	110	-
11-10-03	110	-
12-01-03	110	-
12-22-03	110	-
1-12-04	110	-
2-02-04	110	-
2-16-04	110	-

diazepam, and decadron did not relieve it. The patient mentioned that previously, he had developed an itch every time he received the Ca/Mg infusion, but he did not mention it because it was not "bad" and he did not want to stop oxaliplatin, which continued to shrink his tumor. Post-oxaliplatin infusion of Ca/Mg was not given. He also thought his itch was caused by Mg and he refused to receive an infusion of Ca/Mg during cycle 9 of CAPOX on September 29, 2003. The patient also mentioned that when he went to Wisconsin and developed neuropathy described as numbness, lack of sensation on the feet and tips of fingers of both hands, he took a "pill" and "the new pill is really helping me". On the 29th of September, he felt 99% better (6 days later). I asked him to show me the "new pill", which was Rolaids (oral calcium supplement, over the counter). I asked the patient to maintain a diary of his symptoms and note whenever he took the oral calcium supplement (Table 2). The patient said that he had not developed any itch since infusions were stopped after the last cycle, and that oral calcium was helping him to ameliorate peripheral neuropathy. Due to his positive response to oral calcium, we tried oral magnesium (Mg Oxide 400mg PO x BID x 5 days starting on the evening of oxaliplatin administration), in addition to calcium starting with cycle 11 (November 10, 2003). The patient was able to continue oxaliplatin till February

Table 2. Dose of Oral Calcium and Outcome in Improvement of Neurotoxicity

DATE	TIME	AMOUNT OF ROLAIDS TAKEN	SYMPTOMS
9/30/03	PM	4	
10/1/03	AM	3	Noticed improvement in feet
10/1/03	PM	3	
10/2/03	8:30 AM	3	Reduced numbness considerably
10/2/03	2:30 PM	3	Numbness started to build up, Rolaids reversed
10/3/03	AM	3	Less severe numbness
10/4/03	9:00 AM	3	No numbness in Feet
10/4/03	7:00 PM	3	Numbness was returning
10/5/03	7:45 AM	3	Numbness improving
10/5/03	2:00 PM	3	
10/5/03	3:00 PM	2	
10/6/03		Took several	Both palms numb before taking rolaids
107/03	AM	3	Helping numbness
10/7/03	PM	3	Helping numbness
10/8/03		10 throughout day	Helping numbness
10/9/03	4:45 PM	3	Less numbness
10/10/03	AM	3	Helping numbness
10/11/03	4:00 PM	4	Hands were numb at this point
10/15/03			Numbness 50% better. Hardly peeling
10/20/03			Patient has an appointment

16, 2004 with a cumulative dose of 2500 mg/m^2 of oxaliplatin. He did not develop any severe diarrhea with Mg Oxide, which was probably counter balanced by the calcium. In March 2004, this regimen was stopped due to progressive disease. The patient is currently receiving erbitux and has no objective or subjective evidence of residual neuropathy.

Also of note, during the entire period of treatment, he continued to work full days at work and gardened outdoors at home. He denied any fatigue, anorexia, nausea, vomiting, diarrhea, mucositis, cough, or abdominal pain; his only persistent problem was grade 1 to grade 2 neuropathy.

DISCUSSION

Neurotoxicity is the principal and dose-limiting toxicity of oxaliplatin, with two distinct subtypes: acute and cumulative.[2,3] An acute neurosensory toxicity, which develops shortly after infusion of oxaliplatin, presents as paresthesias and dysesthesias of the hands, feet, and perioral region; jaw tightness; and unusual pharyngo-laryngo-dysesthesias. The pharyngo-laryngo-dysesthesias/syndrome is characterized by a loss of sensation of breathing without any objective evidence of respiratory distress but may rarely involve laryngospasm.[10] Acute neurotoxicity may be triggered or exacerbated by exposure to cold. These symptoms occur within hours of exposure and are usually reversible over the following hours or days, and they may increase in both duration and severity with repeated administration of oxaliplatin. Cumulative neuropathy is manifested as a persistent sensory peripheral neuropathy that may develop with prolonged treatment, eventually causing

superficial and deep sensory loss, sensory ataxia, and functional impairment. Development of sensory neuropathy is correlated with the cumulative dose of oxaliplatin. On cessation of drug, the chronic neurotoxicities improve in the majority of patients within 4 to 6 months and will completely resolve in approximately 40% of patients within 6 to 8 months.[11] The likelihood of symptomatic improvement on discontinuation of oxaliplatin correlates inversely with cumulative dose.

The differences in symptom onset and clinical spectrum suggest a different mechanism for the acute and chronic forms of oxaliplatin-associated neurotoxicity. Studies have shown patients with acute sensory symptoms display little or no axonal degeneration, suggesting a specific effect of oxaliplatin on sensory neurons and/or motor neurons or muscle cells that is not observed with other platinum agents. The similarity of acute symptoms induced by oxaliplatin with those caused by several drugs or toxins acting on neuronal or muscular ion channels suggest that these symptoms may result from a specific interaction of oxaliplatin with ion channels located in the cellular membrane. 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.[12-15] There is no indication at this time that a common cellular mechanism induces both the acute and the cumulative neurotoxicity of oxaliplatin.

Various strategies have been proposed to prevent or treat oxaliplatin-induced neurotoxicity. The "Stop-and-Go" concept uses the reversibility of neurologic symptoms to aim at delivering higher cumulative oxaliplatin doses as long as the therapy is still effective, such as OPTIMOX trial.[16]

Calcium and magnesium possess the ability to modify the properties of the voltage-gated sodium channels. In particular, increasing extracellu1ar calcium concentration has a hyperpolarizing effect on the cell membrane. Kinetic analyses show that increasing calcium concentrations increases the probability of sodium channel closing. In a state of extended refractory period like that observed in the presence of oxaliplatin, increasing extracellular calcium concentration should facilitate sodium channel closing and reduce the oxaliplatin hyperstimulatory effect. These results provided the rationale for using calcium and magnesium supplementation in patients with severe acute neurotoxicity symptoms. Gamelin L et al[9] recently reported a retrospective study of 161 patients treated with oxaliplatin with 5-fluorouracil and leucovorin for advanced colorectal cancer, with 3 regimens of oxaliplatin (85 mg/m2/2 weeks, 100 mg/m2/2 weeks, 130 mg/m2/3 weeks). Ninety-six patients received infusions of Ca gluconate (1 g) and Mg sulfate (1 g) before and after oxaliplatin (Ca/Mg group) and 65 did not. Only 4% of patients withdrew for neurotoxicity in the Ca/Mg group versus 31% in the control group ($P = 0.000003$). The tumor response rate was similar in both groups. The percentage of patients with grade 3 distal paresthesia was lower in Ca/Mg group (7 versus 26%, $P = 0.001$). Acute symptoms such as distal and lingual paresthesia were much less frequent and severe ($P = 10(-7)$), and pseudolaryngospasm was never reported in Ca/Mg group. At the end of the treatment, 20% of patients in Ca/Mg group had neuropathy versus 45% ($P = 0.003$) in the

control group. Patients with grade 2 and 3 neuropathy at the end of the treatment, in the 85 mg/m^2 oxaliplatin group, recovered significantly more rapidly from neuropathy than patients who were not receiving Ca/Mg. No comparison exists at present between this approach and other alternatives such as carbamazepine, glutathione, □lipoïc acid, or amifostine.[17-20] The efficacy of such neuromodulatory agents is not established and they can generate toxic side effects and interfere with oxaliplatin efficacy.

Calcium and magnesium infusions are nontoxic and well-tolerated, except for the itch side effect in our case study patient. Neurotoxic effects are experienced by a large number of patients; whereas the cumulative effects are experienced by a smaller number of patients and are potentially reversible, even adequate management of the former may render oxaliplatin therapy highly tolerable. But now with the addition of targeted therapy, such as avastin, to oxaliplatin, it is expected to have longer time to treatment failure, measures to allow patients to receive higher cumulative doses of oxaliplatin are prudent. Whereas the current recommendations for the use of Cal/Mg infusion for the management of the acute and cumulative neurotoxicity from oxaliplatin remain valid, data suggest that oral supplements need to be explored in this setting. Larger prospective studies to explore the role of these minerals in oral form should be considered. If oral calcium and/or magnesium can be effective in ameliorating neurotoxicity induced by oxaliplatin, then it can lead to a less expensive and more convenient way to treat and prevent this toxicity.

REFERENCES

1. Raymond E, Chaney SG, Taama A, et al. Oxaliplatin: A review of preclinical and clinical studies. *Ann Oncol*. 1998;9:1053-1071.
2. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol.* 2000;18:2938-2947.
3. de Gramont A, Vignoud J, Tournigand C, et al. Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer.* 1997;33:214-219.
4. de Gramont A, Boni C, Navarro M, Tabernero J. Oxaliplatin/5FU/ LV in adjuvant colon cancer: safety results of the international randomized MOSAIC trial. *Proc Am Soc Clin Oncol.* 2002;21:132a.
5. Cassidy J, Tabernero J, Twelves C, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. *J Clin Oncol*. 2004;22:2084-2091.
6. Wilson RH, Lehky T, Thomas RR, Quinn MG, Floeter MK, Grem JL. Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol.* 2002;20:1767-1774.
7. Cannon SC. Ion-channel defects and aberrant excitability. In myotonia and periodic paralysis. *Trends Neurosci*. 1996;19:3-10.
8. Jacobsen D, Mc Martin KE. Methanol and ethylene glycol poisonings. Mechanisms of toxicity, clinical course, diagnosis and treatment. *Med Toxicol.* 1986;1:309-334.
9. Gamelin L, Boisdron-Celle M, Delva R, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res*. 2004;10:4055-4061.
10. Extra JM, Marty M, Brienza S, Misset JL. Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol.* 1998;25:13-22.
11. Brienza S, Vignoud J, Itzhaki M, et al. Oxaliplatin (L-OHP): Global safety in 682 patients. *Proc Am Soc Clin Oncol.* 1995;14:209. Abstract 513.
12. Adelsberger H, Quasthoff S, Grosskreutz J, Lepier A, Eckel F, Lersch C. The chemotherapeutic oxaliplatin alters voltage-gated Na (+) channel kinetics on rat sensory neurons. *Eur J Pharmacol*. 2000;406:25-32.
13. Grolleau F, Gamelin L, Boisdron-Celle M, Lapied B, Pelhate M, Gamelin E. A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neural voltage-gated sodium channels. *J Neurophysiol.* 2001;85:2293-2297.
14. Sirois JE, Atchison WD. Effects of mercurial on ligand-and voltage-gated in channels: a review. *Neurotoxicology*. 1996;17:63-84.

15. Rizzo M, Kocsis JD, Waxman SG. Mechanisms of paresthesiae, dysesthesiae, and hyperesthesiae: role of Na^+ channel heterogeneity. *Eur Neurol.* 1996;36:3-12.

16. Andre T, Figer A, Cervantes A, et al. FOLFOX7 compared to FOLFOX4. Preliminary results of the randomized optimox study. *Proc Am Soc Clin Oncol.* 2003;22:253. Abstract 1016.

17. Eckel F, Schmelz R, Adelsberger H, Erdmann J, Quasthoff S, Lersch C. Prevention of oxaliplatin-induced neuropathy by carbamazepine. A pilot study. *Dtsch Med Wochenschr*. 2002;127:78-82.

18. Cascinu S, Catalano V, Cordella L, et al Neuroprotective effects of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol.* 2002;20:3478-3483.

19. Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Scheithauer W. Subcutaneous administration of amifostine: a promising therapeutic option in patients with oxaliplatin-related peripheral sensitive neuropathy. *Ann Oncol.* 2000;12:421-422.

20. Gedlicka C, Sheithauer W, Schull B, Kornek GV. Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. *J Clin Oncol.* 2002;20(15):3359-3361.