Successful desensitization to oxaliplatin with incorporation of calcium gluconate and magnesium sulfate

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Since the results of the MOSAIC trial demonstrated an improved disease-free survival in stage III colorectal patients treated with oxaliplatin combined with 5-fluorouracil and folinic acid when they were compared with those treated with 5-fluorouracil and folinic acid alone, the addition of this organoplatin to 5-fluorouracil and folinic acid has become first-line adjuvant treatment for stage III colorectal cancer. Unfortunately, there is a small population of patients who develop grade III/IV hypersensitivity reactions to oxaliplatin which, until recently, have interfered with further treatment with oxaliplatin-containing regimens. Successful oxaliplatin desensitization protocols for patients having severe oxaliplatin hypersensitivity reactions have been reported. However, none of these protocols, have incorporated magnesium and calcium salts. Retrospective data has suggested that pretreating colorectal cancer patients with magnesium sulfate and calcium gluconate before the administration of oxaliplatin may reduce the incidence of neurotoxicities induced by this drug. Therefore, we modified a previously published oxaliplatin-desensitization protocol by incorporating intravenous calcium gluconate and magnesium sulfate, and report a patient with stage IIIc colorectal cancer and prior severe hypersensitivity reactions to oxaliplatin who underwent successful oxaliplatin desensitization using this protocol. *Anti-Cancer Drugs* 18:721–724 © 2007 Lippincott Williams & Wilkins.

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Introduction

Oxaliplatin (Eloxatin; Sanofi-Aventis, Bridgewater, New Jersey, USA) is a novel third-generation organoplatinum indicated in combination with 5-fluorouracil (5-FU) and folinic acid (FA) as first-line treatment of progressive colorectal cancer and as adjuvant treatment for stage III colorectal cancer [1–3]. Although oxaliplatin can be safely administered in the outpatient setting, hypersensitivity reactions (HSR) developing during or shortly after the infusion of this drug have been reported [3–12]. HSR can occur with other chemotherapy drugs including asparaginase, procarbazine, doxorubicin, 6-mercaptopurine, the other platinum agents, cisplatin and carboplatin, as well as taxanes and epipodophyllotoxins [4].

Mild HSR to oxaliplatin including flushing, dyspnea, tachycardia, fever, pruritis, rash, vomiting, headache, burning sensation, dizziness and edema occur in approximately 12–16% of patients [5–12]. Severe (defined as grade III/IV) HSR to oxaliplatin are reported to occur in less than 1% of patients [7–12] and, until recently, was considered a contraindication for further treatments with this drug. To overcome these severe HSR, oxaliplatin desensitization protocols using 10-fold serial dilutions of oxaliplatin have been published [3–6]. However, no one has reported incorporating either calcium or magnesium salts in the desensitization protocol.

We present a patient with stage IIIc colorectal cancer and prior severe HSR to oxaliplatin who successfully underwent oxaliplatin desensitization with a protocol containing calcium and magnesium salts. Since then, she has been able to receive nine cycles of mFOLFOX-6 at our institution without developing a severe HSR.

Case report

A 40-year-old woman with a previous history of irritable bowel syndrome presented to our clinic for a second opinion regarding the management of her recently diagnosed stage IIIc adenocarcinoma of the sigmoid colon.

The patient had noted chronic intermittent constipation and diarrhea originally attributed to worsening irritable bowel syndrome. She subsequently developed small-calibur stools, worsening fatigue and pallor, and intermittent episodes of bright red blood per rectum. A colonoscopy revealed a three-quarter circumferential sigmoid colonic mass at 18–22 cm. Biopsy of this mass confirmed an adenocarcinoma. A baseline staging

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computed tomography of the chest, abdomen and pelvis was negative for metastatic disease. The patient underwent a hemicolectomy and pathology revealed a poorly differentiated adenocarcinoma with lymphovascular invasion. Six out of seventeen resected lymph nodes contained adenocarcinoma and the primary tumor extended to the serosa. Staging was consistent with a T3N2M0 or stage IIIc adenocarcinoma [13]. Postoperative carcinoembryonic antigen was less than 0.5 μg/l.

Approximately 6 weeks before coming to our clinic for evaluation, the patient was offered adjuvant chemotherapy and she received 4 out of 6 weeks of one cycle of the FLOX regimen, which consists of weekly boluses of 5-FU (500 mg/m^2), folinic acid (500 mg/m^2) per the Roswell Park regimen [14] with oxaliplatin (85 mg/m^2) infusion administered on alternating weeks. She received palonosetron (0.25 mg) for premedication during this chemotherapy regimen. During the first oxaliplatin infusion she complained of severe nausea and vomiting followed by a headache for 24 h and striking loss of vision of her right eye due to the development of bright spots in the visual field of that eye and severe photophobia. Given that the symptoms resolved in 24 h, no further workup or treatment was offered. She subsequently received the second week of chemotherapy consisting of 5-FU and FA without complications. The second dose of oxaliplatin was administered over an extended 3 h interval because of the patient's prior oxaliplatin HSR. Unfortunately, she developed severe, crushing chest pain, and headaches in addition to recurrence of the right visual impairment and photophobia described above. She received diphenydramine (50 mg) and hydrocortisone (100 mg) in the chemotherapy infusion suite, and was subsequently taken to the emergency room for further evaluation. Cardiopulmonary evaluation was unremarkable, and her symptoms resolved with intravenous support and monitoring in the emergency room. She subsequently received her fourth week of chemotherapy with 5-FU and FA without recurrence of the above symptoms.

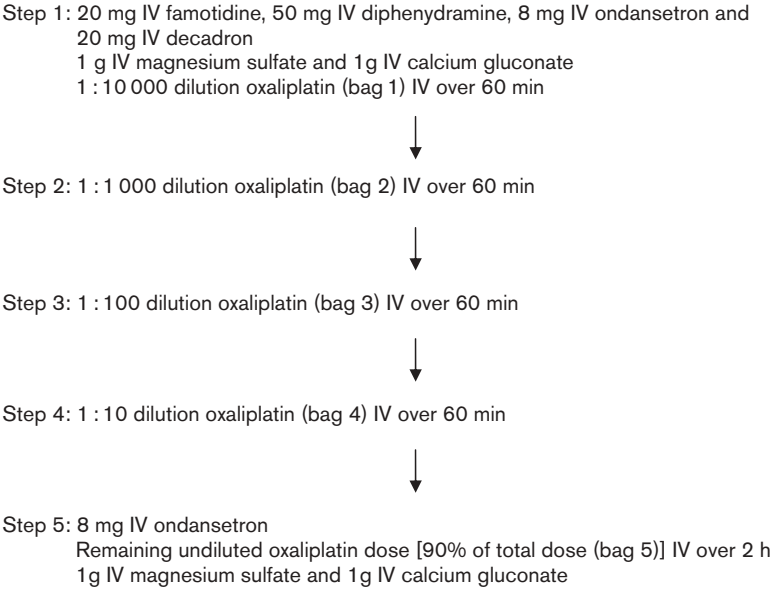
Due to her prior HSR to oxaliplatin, she was referred to our clinic for further evaluation and management options. When the patient came to our clinic 2 weeks following her last dose of chemotherapy, she reported grade I hand–foot syndrome and mucositis since starting the chemotherapy as well as occasional palpatations, intermittent constipation, bloating, abdominal pain, decreased energy level, right arm pain with residual right wrist neuropathic pain and nausea. Her earlier complaints of chest pain, headaches and visual impairment after receiving the oxaliplatin had all resolved within a 48-h time frame.

Initial physical evaluation was notable for an isolated systolic hypertension of 148, scant, healing oral mucosal ulcers, a well-healed, nontender, midline scar, and discoloration and skin peeling of the hands and fingertips bilaterally. The remaining examination including cardiopulmonary and neurologic assessments as well as lymph node survey was unremarkable.

Given the patient's young age, her stage IIIc disease with a poorly differentiated tumor exhibiting lymphovascular invasion and known micrometastatic disease, we favored continuing therapy with oxaliplatin, 5-FU and FA using the mFOLFOX-6 regimen. This regimen consists of oxaliplatin (85 mg/m^2) as a 2-h infusion on day 1, FA (400 mg/m^2) infusion on day 1, 5-FU (400 mg/m^2) bolus followed by a subsequent 46-h continuous infusion of 5-FU dosed at 2400 mg/m^2. As the patient had previously demonstrated severe oxaliplatin hypersensitivity with this drug, she warranted desensitization before further chemotherapy.

Therefore, the patient was admitted to our medical intensive care unit for desensitization to oxaliplatin. Given the patient's previous oxaliplatin neuropathies, we modified a previous desensitization protocol [4] by also administering intravenous calcium gluconate and magnesium sulfate. These salt solutions have decreased oxaliplatin-induced neuropathy in advanced stage colorectal patients receiving oxaliplatin, 5-FU and FA [15]. The patient received four serial dilutions (1 : 10 000, 1 : 1000, 1 : 100 and 1 : 10) of the total oxaliplatin dose prepared in 100 ml of dextrose 5% in water (Fig. 1). Starting at the lowest dose (bag 1), each oxaliplatin dilution was infused over 60 min with careful monitoring of vital signs in the medical intensive care unit. A final infusion bag (bag 5) containing 90% of the total dose in 500 ml of dextrose 5% in water was then infused over 2 h. In addition to intravenous famotidine (20 mg), diphenydramine (50 mg), ondansetron (8 mg) and decadron (20 mg), we also administered 1 g each of intravenous magnesium sulfate and calcium gluconate 30 min before the first dose of oxaliplatin (Fig. 1). The patient also received an additional dose of ondansetron (8 mg) before the final oxaliplatin infusion (bag 5) (Fig. 1). Intravenous calcium gluconate 1 g and magnesium sulfate 1 g were also repeated after the final oxaliplatin infusion. The patient received all of the oxaliplatin without developing any of the side effects manifested during the prior treatments with oxaliplatin. She continued with the remainder of cycle 1 of the mFOLFOX-6 regimen, which was complicated by the development of paroxysmal atrial fibrillation during the 5-FU infusion. The atrial fibrillation resolved following the administration of intravenous fluids and metoprolol which the patient has continued to take for hypertension. Our patient has received a total of nine cycles of FOLFOX-6 at our facility. For the nine cycles after desensitization, we used the same premedications discussed above. In addition, 1 g each of magnesium sulfate and calcium gluconate were given before and after the 4-h administration of oxaliplatin. The patient has not developed the severe reactions that occurred prior to the oxaliplatin desensitization.

Fig. 1



Summary of Oxaliplatin Desensitization Protocol Using Calcium and Magnesium Salts.

Discussion

The addition of oxaliplatin to 5-FU and FA improves the adjuvant treatment of colon cancer by increasing the rate of disease-free survival in patients at 3 years to 78% compared with that of 72% in patients treated with 5-FU and FA alone [1,2]. Additionally, there was a statistically significant decrease in cancer-related events in the group treated with oxaliplatin, 5-FU and FA (21.1 versus 26.1%) [1,2]. Our patient was relatively young with a poorly differentiated stage IIIc colon cancer exhibiting lymphovascular invasion. Merkel *et al.* [16] demonstrated that the 5-year survival of patients with stage III colon cancer varies from 30 to 80% based on the three separate subdivisions: stage IIIa, stage IIIb and stage IIIc. Our patient had stage IIIc disease and, among stage III colon cancer patients, carried the worst prognosis with a predicted 5-year survival of 30% without additional chemotherapy [16]. Therefore, we chose to offer additional adjuvant oxaliplatin-containing chemotherapy with mFOLFOX-6.

As the patient's prior treatment was hampered by severe HSRs to oxaliplatin, she warranted an oxaliplatin desensitization before proceeding with further therapy. HSR to oxaliplatin occurs in up to 16% of patients receiving this drug with less than 1% of patients experiencing a severe HSR [4–12]. Rarely, patients develop anaphylactic reactions or severe reactions such as those exhibited by our patient. Management of the mild reactions to oxaliplatin includes the administration of steroids and antihistamines before subsequent cycles [7–12].

Oxaliplatin also causes an acute transient neurotoxicity in nearly all patients during or shortly after receiving this organoplatin [3]. The acute neurotoxicity symptoms are peculiar in that they are often induced or aggravated by exposure to cold, and can manifest as distal sensory and motor toxicity [3]. This acute transient toxicity may be prevented by the infusion of divalent ions such as magnesium and calcium [15]. In addition, the administration of these salts has been shown to significantly decrease grade III distal paresthesias and enable patients to recover from neuropathy after oxaliplatin treatment [15].

It is unclear to what extent the calcium and magnesium salts contributed to the success of the oxaliplatin desensitization, as our protocol also incorporated increasing the oxaliplatin infusion time and used famotidine, diphenydramine, ondansetron, and decadron premedications (Fig. 1). Although the prior neuropathy may have been a localized reaction to oxaliplatin which resolved on its own, evidence in the literature suggests that administering calcium and magnesium salts before oxaliplatin infusions can prevent paresthesias [15]. Therefore, these salt solutions may have a role in preventing oxaliplatin-induced neuropathy, however, their contributions to successful oxaliplatin desensitizations remain unknown.

Our case report is the first one describing the incorporation of calcium and magnesium salt solutions in an oxaliplatin-desensitization protocol. The evidence for the effects of these salts in preventing acute neurotoxicities of oxaliplatin is based on retrospective data and we are

reporting one patient who received this desensitization protocol. Therefore, prospective studies are warranted to confirm the specific contributions of calcium gluconate and magnesium sulfate in preventing acute neurotoxicities of oxaliplatin, and to determine if these salts improve oxaliplatin desensitizations in colorectal cancer patients requiring this organoplatin for adjuvant therapy.

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