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LETTER

Oxaliplatin-Induced Hyperexcitability Syndrome in a Patient with Pancreatic Cancer

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Summary

A recent pooled analysis and a meta-analysis suggested a survival benefit of gemcitabine-platinum doublets when compared with single agent gemcitabine in pancreatic cancer. Sensory neurotoxicity is a potentially limiting toxicity associated with oxaliplatin therapy. In this letter, we describe a case of a patient with metastatic pancreatic cancer who developed acquired neuromyotonia while receiving intravenous oxaliplatin as part of her treatment. It is a condition characterized by cramps, muscle twitching, weakness, myotonia and pseudomyotonia (slow muscle relaxation after forceful contraction). Her symptoms were ameliorated after initiation of pregabalin. We postulate that hyperexcitability syndrome associated with administration of oxaliplatin can be treated with pregabalin. Future studies will be needed to confirm this as well as to determine the long-term adverse effects associated with pregabalin.

Introduction

Neurotoxicity is the principal and dose-limiting toxicity of oxaliplatin, with two distinct syndromes. Long-term administration of oxaliplatin produces a sensory neuropathy, with loss of sensation and dysesthesia in the distal extremities. Development of sensory neuropathy is correlated with the cumulative dose of oxaliplatin, which is also true for cisplatin. Oxaliplatin also produces a unique syndrome of acute neurosensory toxicity.

Shortly after infusion of oxaliplatin, patients develop striking paresthesia and dysesthesia of the hands, feet, and perioral region, jaw tightness, and unusual pharyngolaryngo-dysesthesia. The latter is characterized by a loss of sensation of breathing without any objective evidence of respiratory distress but may rarely involve laryngospasm. 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. The differences in symptom onset and clinical spectrum suggest a different mechanism for the acute and chronic forms of oxaliplatin-associated neurotoxicity. 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 by 6 to 8 months. The likelihood of symptomatic improvement on discontinuation of oxaliplatin correlates inversely with cumulative dose [1].

We previously published a case of a 54-year-old female undergoing chemotherapy with gemcitabine and oxaliplatin for stage II-B pancreatic adenocarcinoma demonstrated striking signs of reversible, peripheral-nerve hyperexcitability after administration of oxaliplatin. The clinical features are similar to those seen in neuromyotonia, a disorder associated with abnormal function of voltage-gated potassium channels in peripheral nerves. We now describe a second case of a patient with hyperexcitability syndrome after treatment with oxaliplatin. This report is clinically relevant as platinum remains the agents of choice to be combined with gemcitabine as well as CONKO-003 (Charité Onkologie) study showed survival benefit of folinic acid plus 5-fluorouracil plus oxaliplatin (FOLFOX) in gemcitabine-refractory pancreatic cancer. Other cases of hyperexcitability syndrome in the literature include papers by Saif and Hashmi [2], Lahrmann *et al*. [3], and Forte *et al*. [4].

Case Report

This patient was a 39-year-old female who initially presented with obstructive jaundice. ERCP showed a 2 cm mass in the pancreatic head and a fine needle aspirate of the lesion revealed pathologic findings

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consistent with pancreatic adenocarcinoma. She underwent Whipple's procedure and adjuvant chemoradiation with gemcitabine and capecitabine. However, her CEA levels continued to rise and a PET scan showed increase in intensity and the extent of abnormal FDG activity at the surgical bed suspicious for recurrent disease. CT scan confirmed the suspicion. A new treatment option including gemcitabine, oxaliplatin and panitumumab was offered to the patient. At completion of cycle 2 oxaliplatin infusion, she experienced significant muscle cramping of hands and feet. She was unable to sit still due to discomfort and her hands became rigid. She was given intravenous diphenhydramine, magnesium sulfate and calcium gluconate. After several minutes, the muscle contractions resolved. She had a few recurrences for 2-3 days after, each lasting several minutes. In retrospect, she had vague recall of similar mild sensations after cycle one. In addition, she had recurrence of temporomandibular junction pain with eating. A sharp jaw pain occurred after taking the first few bites of each meal. It then resolved and she was able to continue eating without any pain. It is worth noting that patient did not have any autoimmune disorder nor she was taking any medications that may have predisposed her to acquired neuromyotonia. She was started on pregabalin 50 mg *per os* three times a day and subsequently did not have these symptoms.

Discussion

Single agent gemcitabine has been the main stay of treatment approved for advanced pancreatic cancer. Many clinical trials have compared the efficacy of combination therapies to gemcitabine in the last decade. Recently, a survival benefit was demonstrated for gemcitabine-platinum combination therapy compared to single agent gemcitabine.

Oxaliplatin, a platinum derivative, causes two types of neuropathy mainly acute and chronic. Acute neuropathy can begin during the infusion, within minutes to hours, or within 1-2 days of administration. This type of neuropathy is usually self-limited, often resolving within days. Signs and symptoms associated include paresthesia, hypoesthesia, and dysesthesia, which usually begin in the feet or hands. The neuropathy can also be associated with shortness of breath or difficulty swallowing, but without laryngospasm or bronchospasm. Patients have also experienced an unusual sensation in the tongue, jaw spasms, eye pain, and muscle spasms or cramps, which are sometimes described as stiffness in the hands or feet or the inability to release the grip. A feeling of pressure in the chest has also been reported. Acute neuropathy may be triggered by exposure to cold temperatures and often returns on retreatment [5, 6]. This acute neuropathy causes a variety of distressing, but transient, symptoms due to peripheral sensory and motor nerve hyperexcitability [7]. This nerve hyperexcitability can manifest as a distinct syndrome that clinically exhibits as neuromyotonia known as hyperexcitability syndrome. It is perhaps a rare but also the most important neurological syndrome that warrants immediate dose reduction or drug withdrawal in clinical practice.

Neuromyotonia is a rare condition characterized by muscle stiffness, slowed muscle relaxation, and increased sweating, and less commonly paresthesia [8]. It has several causes. It may be autoimmune mediated or associated with neuropathy [9], or a rare side effect of drugs, radiotherapy, or toxins [10, 11, 12]. The exact mechanism of neuromyotonia in humans is largely unknown; however, it is postulated that either persistent sodium channel activity or decreased potassium conductance can be a mechanism for producing axonal hyperexcitability and repetitive discharges in human nerve cells. Non-inactivating sodium channels in sensory axons are thought to produce the repetitive discharges that underlie paresthesia [13]. Direct autoimmune blockade of voltage-gated potassium channels [14, 15] and exposure of sodium channels in paranodal regions [13] has also been implicated. Pregabalin, like gabapentin, is an amino acid derivative of gamma-amino butyric acid, it is pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid, and has a similar pharmacological profile to gabapentin [16, 17]. Pregabalin has been shown in studies to provide equivalent efficacy to gabapentin, however, at much lower doses [18]. Because lower dosages can be used to treat neuropathic pain, it is likely that pregabalin will be associated with fewer dose-related adverse events. Part of the reason why pregabalin requires a lower dosage is that it has a much higher bioavailability (90 *vs*. 33-66%) and a rapid absorption (peak 1 h). Also, plasma concentrations increase linearly with increasing dose [19]. This is not true with gabapentin. Gabapentin is slowly absorbed (peak 3-4 h post-dose) and more importantly, plasma concentrations have been found to have a non-linear relationship to increasing doses. Since pregabalin has been found to have distinct pharmacokinetic advantages over gabapentin, and the efficacy of treating the neuropathic symptoms with gabapentin has not been completely successful [20], we opted to treat our patients with pregabalin for hyperexcitability secondary to oxaliplatin that was being administered to her for the treatment of her pancreatic cancer.

Conflict of interest The authors have no potential conflicts of interest

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