

Severe Generalized Weakness, Paralysis, and Aphasia following Administration of Irinotecan and Oxaliplatin during FOLFIRINOX Chemotherapy

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Key Words

Irinotecan · Oxaliplatin · FOLFIRINOX · Paralysis · Aphasia · Weakness · Dysarthria · Neurologic side effects

Abstract

Background: Irinotecan is commonly used in combination with oxaliplatin as a component of FOLFIRINOX chemotherapy for several gastrointestinal malignancies. The purpose of this case report is to describe a patient who developed acute paralysis and aphasia while receiving her initial infusion of irinotecan. **Case Report:** A 67-year-old woman with newly diagnosed metastatic pancreatic adenocarcinoma presented for her first cycle of FOLFIRINOX chemotherapy. During her infusion of irinotecan, she developed acute onset of generalized weakness, paralysis of all extremities, and nonfluent aphasia with complete inability to communicate. This episode was self-limited and resolved within 2 h. Prior to subsequent infusions she received intravenous repletion of potassium and had no recurrence of symptoms. **Discussion:** In selected cases, coadministration of irinotecan and oxaliplatin may result in severe generalized weakness and aphasia, which may be triggered by underlying electrolyte disturbances. Careful monitoring and correction of potassium may help prevent this reaction.

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Introduction

Irinotecan is a topoisomerase I inhibitor derived from camptothecin, an alkaloid compound extracted from deciduous trees indigenous to Eastern Asia. Its antineoplastic activity is mediated by its inhibition of double-stranded DNA replication through stabilizing the cleavage complexes of topoisomerase I. Its most common use is in the treatment of colorectal cancer. However, since 2010, it has been combined with 5-fluorouracil, leucovorin, and oxaliplatin in the regimen known as FOLFIRINOX, which has been utilized as an effective therapy in patients with metastatic pancreatic cancer as well as other cancers.

The most commonly cited adverse effects of irinotecan include late-onset diarrhea and bone marrow suppression, with clinically significant neutropenia and thrombocytopenia. A less frequent, acute cholinergic syndrome with resultant symptoms of diaphoresis, hypotension, anxiety, and abdominal cramping with diarrhea may result in severe discomfort and dehydration that can be life-threatening. Atropine is commonly administered with the chemotherapy infusion both for the prevention and treatment of this syndrome.

Oxaliplatin is a third-generation platinum derivative that has shown to be an effective therapy in several malignancies, most commonly gastrointestinal cancers. Side effects of oxaliplatin include a dose-limiting severe peripheral sensory neuropathy that is chronic in onset. Less commonly, acute sensory disturbances that may be modulated by cold temperatures may occur. These effects are thought to be mediated by an interaction with voltage-gated sodium channels in peripheral nerves.

Here we report the case of a patient with a rare complication of combination therapy with irinotecan and oxaliplatin, i.e. severe generalized weakness, paralysis, and aphasia, and provide a synopsis of the current literature as well as a proposed therapeutic approach.

Case Report

A 67-year old Asian woman with a history of poorly controlled diabetes presented with newly diagnosed metastatic pancreatic adenocarcinoma. In November 2013, she received her first cycle of palliative chemotherapy using FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m² IV, and 5-FU 2,400 mg/m² IV by continuous infusion over 48 h without a bolus, with dexamethasone 10 mg and ondansetron 12 mg IV as premedication). Prior to beginning therapy with FOLFIRINOX, her electrolyte levels were checked, which revealed mild hypokalemia (3.5 mEq/l, normal values 3.5–5.0) with normal serum sodium and calcium (Na 137 mmol/l, Ca 8.7 mg/dl). She completed the oxaliplatin infusion over 2 h without adverse reaction. Following this, she was given 1 mg atropine IVP prior to infusion of irinotecan and leucovorin. Halfway through the irinotecan infusion, she developed acute onset of generalized weakness, paralysis of all extremities, and nonfluent aphasia with complete inability to communicate. Throughout this, she was awake, alert, and aware of her surroundings, with stable vital signs. At this time, the infusion was stopped and she was given a second dose of atropine 1 mg as well as an IV bolus of 1 l normal saline. She was monitored carefully and observed to return close to her baseline status within 1–2 h. Neither the infusion of irinotecan nor the 5-FU infusion was restarted, and she was discharged to her home with appropriate follow-up.

She returned 2 weeks later for cycle 2 of her FOLFIRINOX therapy and felt completely well. Prior to initiating the infusion, her electrolyte levels were checked, which showed a low-normal potassium level of 3.7 mEq/l with otherwise normal electrolytes. She received 20 mEq IV KCl supplementation leading to an improvement in the potassium level to 4.4

mEq/l immediately preceding the infusion. She was then given her second cycle of FOLFIRI-NOX with identical doses of the drugs as in the first cycle and was able to complete all of the therapy without recurrence of the symptoms previously experienced at her initial infusion. She was able to continue on therapy without event for a total of 3 cycles before she transferred her care to an institution closer to her home and was lost to follow-up.

Discussion

To date, there have been 9 reported cases of significant central nervous system toxicity during or following the administration of irinotecan, both with and without concurrent oxaliplatin administration. All of these cases involved the development of dysarthria, with 2 of them leading to a complete motor aphasia and 1 case with associated ataxia [1–5]. In each case, these symptoms developed with the initial infusion of irinotecan and completely resolved with time. The duration of symptoms ranged from as little as 15 min to as long as 8 h. The duration of symptoms appeared to be related to the dose of irinotecan, with doses <200 mg/m² having a quicker return to baseline (15–45 min) in comparison to larger doses of >200 mg/m² (2–8 h). The pathophysiology of these adverse reactions remains poorly understood.

Irinotecan and its primary active metabolite, SN-38, bind strongly to plasma proteins and tissues resulting in high plasma distribution. In animal models, irinotecan and its metabolites have been found to cross the blood-brain barrier into the central nervous system [6]. In 2 patients in whom neurologic symptoms developed during irinotecan administration, Hamberg et al. [4] examined the pharmacokinetics of irinotecan and SN-38 and found both of these values to be within the normal range. The acute onset of symptoms shortly after beginning irinotecan infusion also suggests that the manifestation of these symptoms is not dose or duration dependent. Therefore, it is unlikely that altered systemic clearance of irinotecan mediates the presence or absence of neurologic symptoms in these patients.

The degree of severe generalized weakness seen in our patient following administration of irinotecan has not previously been reported in the literature. Though no imaging of the brain was performed in our patient, CT and MRI performed in prior similar cases have failed to show any evidence of stroke or other acute CNS abnormalities to explain the clinical presentation. Our patient was found to have mild hypokalemia (3.5 mEq/l) prior to chemotherapy (which may have been even lower following hydration and drug administration), which may have contributed to her profound weakness and inability to move and speak while maintaining a normal sensorium. One case of acquired Fanconi syndrome (characterized by proximal tubular dysfunction resulting in electrolyte wasting of potassium, calcium, phosphate, and uric acid) has been reported following combination therapy with capecitabine, irinotecan, and bevacizumab, but a single offending agent was not identified [7]. Correcting our patient's electrolytes prior to the subsequent infusions and ensuring continued stability of these values throughout the infusion was the only change in the treatment plan and resulted in no recurrence of symptoms. We postulate that close monitoring and repletion of potassium was the factor that prevented further neurologic symptoms.

As irinotecan alone has not previously been implicated in electrolyte-based neurologic complications, we also consider that the findings in our patient were not caused by irinotecan alone, but rather by combination therapy with oxaliplatin as administered in FOLFIRI-NOX. Two prior case reports have noted the acute onset of severe neurologic deficits (including generalized weakness, limb weakness, dysarthria, ophthalmoparesis, and coma) during and shortly after the administration of oxaliplatin, which our patient received prior to initia-

tion of irinotecan [8, 9]. In both reported cases, the patients were found to have hypokalemia and hypomagnesemia. These electrolyte derangements were mild in the case reported by Krexner et al. [9] (K 3.1 mEq/l, Mg 0.37 mmol/l) and much more severe in the case reported by Basso et al. [8] (K 1.7 mEq/l), which appears to correlate with the severity of symptoms. In these cases, symptoms developed during the oxaliplatin infusion or within 15 min of completion. Our patient tolerated her oxaliplatin therapy without complications during the infusion, but it is possible that the coadministration of oxaliplatin and irinotecan may have increased the risk of developing these reversible neurologic effects. If this is the case, those patients receiving combination FOLFIRINOX therapy may be at significantly higher risk of developing neurologic side effects than those receiving FOLFOX therapy alone.

From our experience in this patient, and from our review of the literature, we conclude that in selected cases, the coadministration of irinotecan and oxaliplatin (as is used in FOLFIRINOX) may result in severe generalized weakness and aphasia. It appears that this may be triggered by underlying and unsuspected electrolyte disturbances. We believe that a careful correction of these abnormalities into the upper ranges of normal as needed, both prior to beginning and during the infusion of oxaliplatin/irinotecan, may prevent this reaction. While the symptoms may be transient and self-limited, they may equally be severe. Without knowledge of their etiology and the appropriate therapy, patients may be denied further treatment or may be reexposed to a serious adverse reaction.

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