Case Report

Chronic Oxaliplatin-Based Chemotherapy in a Primary Ampullary Adenocarcinoma Patient without Significant Peripheral Neuropathy: Case Report and Literature Review

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Keywords

Oxaliplatin · Ampullary adenocarcinoma · Peripheral neuropathy · FOLFIRINOX · Carbohydrate antigen 19-9

Abstract

Peripheral neuropathy is the most common dose-limiting toxicity associated with oxaliplatin. We report on a 61-year-old female patient with advanced primary ampullary adenocarcinoma who received 35 cycles of FOLFIRINOX (5-fluorouracil, irinotecan, and oxaliplatin) chemotherapy. The patient has tolerated this treatment without developing significant peripheral neuropathy.

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Background

Oxaliplatin is a third-generation platinum agent that has been an integral part of the treatment of colorectal and certain pancreatobiliary malignancies. Oxaliplatin is given in combination with fluoropyrimidines such as 5-fluorouracil or capecitabine in the setting of

colorectal cancer as adjuvant or palliative treatment [1, 2]. Oxaliplatin is widely used in combination with a 5-fluorouracil and irinotecan (FOLFIRINOX) regimen in advanced pancreatic cancer based on results from the ACCORD trial by Conroy et al. [3].

Oxaliplatin is also active in other pancreatobiliary malignancies such as cholangiocarcinomas and periampullary adenocarcinomas when given in combination with either fluoropyrimidines or gemcitabine [4–6].

Oxaliplatin is associated with mild hematological toxicities and gastrointestinal side effects are not uncommon, including nausea, vomiting, diarrhea, and abdominal pain. Drug-induced fever and hypersensitivity have been reported [6]. However, oxaliplatin-related neurotoxicity is by far the most common side effect and dose-limiting toxicity.

Case Presentation

A previously healthy 61-year-old Caucasian female presented with jaundice preceded by vague abdominal pain, anorexia, and weight loss for 3 weeks. Initial CT scans revealed findings highly suggestive of periampullary malignancy with dilated pancreatic and biliary ducts. Biopsy was consistent with primary ampullary adenocarcinoma. Staging revealed pulmonary metastases. Palliative biliary decompression was performed and resulted in significant symptomatic improvement. Baseline carbohydrate antigen 19-9 (CA 19-9) was 835 kU/L (normal <37 U/L); complete blood counts were within normal ranges. The AST level was 286 U/L (normal range 10–40 U/L), ALT 291 U/L (normal range 7–56 U/L), alkaline phosphatase 1,283 U/L (normal range 44–147 U/L), and total bilirubin 347 µmol/L (normal range 3–25 µmol/L). Palliative FOLFIRINOX chemotherapy started, with oxaliplatin dosed at 85 mg/m². The patient had a significant clinical improvement after a few cycles of chemotherapy with a gradual decrease in her bilirubin, liver enzymes, and CA 19-9 level.

Objective response to chemotherapy was noted after 12 cycles with significant shrinkage of the primary lesion and pulmonary metastases. She then took a break from chemotherapy and was monitored with clinical assessments, blood tests, and CT scans that continued to show stable disease for 9 months. Eventually, her cancer progressed and she restarted FOLFIRINOX. She again responded to treatment, confirmed by restaging a CT scan which showed an interval decrease in her primary lesion and metastases, and she subsequently took a second break from treatment.

The patient remained stable for almost 1 year until CT scans revealed disease progression with a significant raise in her CA 19-9. The decision was made to restart FOLFIRINOX treatment. She has now had 12 cycles, has shown further response to treatment supported by CT findings and declining CA 19-9 levels, and is currently on her third break from chemotherapy. The last treatment course was complicated by myelosuppression on a few occasions, causing a delay in treatment of no more than a week. This prompted dose reduction of FOLFIRINOX by 15–20%. Grade 1–2 acute sensory peripheral neuropathy lasting for 2–3 days was the only neurological side effect reported by the patient, with complete resolution prior to each cycle. This patient has had 35 cycles of FOLFIRINOX to date and she is likely to be rechallenged with the same regimen when her disease progresses. Tolerance of this amount of FOLFIRINOX without neuropathy is extremely rare.

Discussion

Oxaliplatin is associated with acute and chronic neurotoxicity. The acute form occurs in more than 85% of patients. Acute neurotoxicity usually develops rapidly within 24–72 h and may include sensory and motor findings like perioral paresthesia, pharyngolaryngeal dysesthesia, cold sensitivity, paresthesia and dysesthesia of the hands and feet, and muscle cramps. Patients may also experience jaw stiffness, dyspnea, dysphagia, and ocular changes [7, 8].

Oxaliplatin-induced acute neurotoxicity is thought to be secondary to chelation of calcium by oxalate (a metabolite of oxaliplatin), with transient activation of disinhibited peripheral nerve voltage-gated calcium-dependent sodium channels leading to hyperexcitability of peripheral nerves [9–13].

Acute changes in axonal excitability are less noticeable with later treatment cycles, probably due to chronic nerve dysfunction and sensory loss, masking acute side effects at a higher cumulative dose.

With chronic neurotoxicity, cumulative sensory neurotoxicity is the dose-limiting toxicity of oxaliplatin. Typical symptoms are dysesthesia and paresthesia of the extremities of gradually prolonged duration, which eventually persist between treatment cycles and increase in intensity with the cumulative dose. This chronic neurotoxicity can severely affect activities of daily living. In an analysis of Alliance N08CB trial patients treated with oxaliplatin, tingling was the most severe symptom, followed by numbness and then pain [8].

The incidence and severity are predominantly related to cumulative dose, although other factors like preexisting diabetes and severity of acute neuropathy may contribute. Patients with more severe acute neurotoxicity during the first cycle of therapy may experience more chronic sensory toxicity [8].

Oxaliplatin-induced neurotoxicity improves after discontinuation of therapy in the majority of cases. However, it may continue to worsen for a few months after treatment is discontinued (coasting phenomenon). Neuropathy is at least partially reversible in approximately 80% of patients; half of these patients report complete resolution within 8 months after treatment discontinuation.

Coasting phenomenon is when symptoms of peripheral sensory neurotoxicity start or worsen after oxaliplatin is discontinued. This phenomenon occurs in approximately 10–15% of patients completing oxaliplatin-based chemotherapy and is not well understood [7].

There are no agents recommended for the prevention of chemotherapy-induced peripheral neuropathy. For the treatment of symptomatic peripheral neuropathy, the best available data support a moderate recommendation for treatment with duloxetine. Other agents under investigation include tricyclic antidepressants (such as nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine [14].

There are reports suggesting increased susceptibility to oxaliplatin-induced peripheral neuropathy with pharmacogenetic variations in genes encoding for drug transporters (ABCC1, ABCG1, and SLC22A2), detoxification enzymes (MPO, GSTA1, GSTM1/3, GSTP1, and GSTT1), DNA repair mechanisms (ERCC2, XPA, XRCC1, and ERCC1) and integrin $\beta 3$ (an integral cell-surface protein known to participate in cell adhesion and in cell surface-mediated signaling) Leu33Pro polymorphism. Available data remain controversial and further research is required.

Conclusion

This case suggests that some patients with platinum-sensitive disease can tolerate prolonged courses of treatment with FOLFIRINOX without significant peripheral neuropathy. It also confirms that FOLFIRINOX is an active, safe, and well-tolerated option for patients with ampullary adenocarcinoma.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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