Severe disabling sensory-motor polyneuropathy during oxaliplatin-based chemotherapy

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Oxaliplatin-based combination chemotherapy is an option for first-line therapy of metastatic colorectal cancer. It is associated with acute hyperexcitability of motor and sensory nerves, and a cumulative sensory axonal neuropathy. We describe a 56-year-old male with metastatic colorectal cancer treated with oxaliplatin and capecitabine who developed a rapidly ascending motor and sensory neuropathy, which rendered him wheelchair-bound. Heightened clinical suspicion for possible oxaliplatin-induced motor neuropathies may be warranted. *Anti-Cancer Drugs* 15:733–735 © 2004 Lippincott Williams & Wilkins.

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Case report

A 56-year-old male was diagnosed 3 years earlier with stage III colon cancer, but he received no adjuvant therapy after his initial surgery. A local recurrence occurred 1 year after his diagnosis, and was treated with radiation therapy and 5-fluorouracil. Progressive disease was documented about 6 months later and irinotecan was instituted for 10 months until he experienced disease progression in the liver. He was then referred to our clinic to consider further therapy options. His performance status was good (ECOG 0) despite multiple co-morbidities including asthma, hypertension, deep vein thrombosis, osteoarthritis and gout. He had no history of neurological conditions or collagen vascular diseases, had not smoked for over 20 years, used alcohol on a limited basis, and the family history was unremarkable. After giving written, informed consent, he was enrolled in an Institutional Review Board-approved clinical trial involving oxaliplatin 130 mg/m^2 given over 2 h i.v. on day 1 and capecitabine 3150 mg given orally twice daily on days 1–5 and 8–12 out of a 21-day cycle.

His baseline neurologic examination was normal. As per protocol, nerve conduction studies and an electromyogram that were performed prior to initiating therapy were normal. Baseline laboratory tests revealed a normal blood urea nitrogen, creatinine, electrolytes, glucose, liver function tests, white blood cell count, differential and platelets. The hemoglobin and hematocrit were 13.7 g/dl and 41.3%, respectively, with normochromic, normocytic indices. In addition, the serum T4 was 1.07 μg/dl, thyroid stimulating hormone was 1.73 μU/ml and an anti-nuclear antibody (ANA) test was negative. As anticipated, he developed acute neurotoxicity following each of the first three doses of oxaliplatin which consisted of dysesthesias of mild/moderate severity lasting up to 4 days, transient visual disturbance lasting a single day during cycle 2, and grade 1 paresthesias which resolved in 4, 8 and 13 days, respectively. His neurologic examinations, repeated at the start of each 3-week cycle, were unremarkable. Although the patient developed a mild rash involving the trunk and face with each cycle of therapy, he did not develop any signs or symptoms of palmar–plantar erythrodysesthesia, and no dose reductions in either oxaliplatin or capecitabine were required. On the seventh day after his fourth cycle of chemotherapy (cumulative oxaliplatin dose of 520 mg/m^2), he complained of paresthesias in his thighs and buttocks. His symptoms progressed over the following weeks with ascending numbness, paresthesias, dysesthesias and reduced strength in the extremities. He had no respiratory problems, and had complete control of his head and neck muscles. However, the progressive disability resulted in multiple falls, although no fractures were sustained. Neurological exam performed by a consulting neurologist revealed normal cranial nerves, 4/5 and 3/5 muscle strength in the upper and lower extremities, respectively, and reduced pin prick sensation in the lower limbs with altered proprioception and vibration sense, also predominantly in the lower limbs. Deep tendon reflexes were absent; plantar flexion responses were seen bilaterally. Laboratory tests including serum glucose, vitamin B_{12}, folate, methylmalonic acid and a paraneoplastic profile (including Hu, Yo, Ri, CAR LEMS, Ma1 and Ma2) were normal. The cerebrospinal fluid (CSF) was acellular, the glucose was normal, but the protein was elevated to 144 mg/dl. Magnetic resonance imaging (MRI) with gadolinium enhancement of the spine demonstrated cervical spondylosis, but no impingement on the spinal cord; no

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masses were seen within the cord or in the epidural area. Compared to the normal baseline studies, nerve conduction and electromyogram studies revealed approximately 50% reduction in motor nerve amplitudes (with relative sparing of the conduction velocities) and undetectable sensory nerve conduction. These findings were consistent with an axonal sensorimotor polyneuropathy.

While capecitabine may produce paresthesias and dysesthesias in the context of palmar–plantar erythrodysesthesia, the clinical features are distinct from oxaliplatin-associated neurotoxicity in that the symptoms are limited to the palms and soles, and are accompanied by redness, swelling, and potentially blister formation and exfoliation of skin. Although the patient experienced grade 1 skin rash involving the trunk and face, he did not have symptoms of hand/foot syndrome. His blood glucose levels and serum creatinine (obtained on 24 occasions while he was on-study) averaged 116 and 0.7 mg/dl. Therefore, the main differential diagnoses were Guillain–Barre syndrome or oxaliplatin peripheral sensory polyneuropathy. Based on the clinical presentation of predominantly sensory abnormalities temporally associated with oxaliplatin and nerve conduction studies demonstrating an axonopathy, oxaliplatin was suspected as a causal factor. Chemotherapy was discontinued and the patient underwent intensive physiotherapy in a rehabilitation facility for 3 months. Corticosteroids were not used. He regained some ambulatory function, although he still required wheelchair assistance. His sensory symptoms improved slightly, but dysesthesias remained problematic. Six months later he complained of the acute onset of diplopia; brain metastases were confirmed, and he received whole brain radiation and corticosteroid therapy. Twelve months after the initial presentation of his ascending neuropathy, the patient died from disease progression.

Discussion

Oxaliplatin is a platinum-based cytotoxic agent that exerts is cytotoxic effects through the formation of DNA adducts that interfere with DNA replication and transcription. The distinctive 1,2-diaminocyclohexane carrier ligand of oxaliplatin results in bulkier DNA adducts compared to those seen with cisplatin or carboplatin and likely contributes to the differences in efficacy and toxicity seen with these agents. Oxaliplatin was first approved in Europe for metastatic colorectal cancer based on evidence of an improvement in progression-free survival in combination with 5-fluorouracil compared to 5-fluorouracil alone [1]. Recent trials have suggested that it may be the optimal regimen for first-line treatment of metastatic colorectal cancer and could soon become the standard of care for adjuvant therapy [2,3].

With the increasing use of oxaliplatin combination chemotherapy in the community, an increased understanding of the associated toxicities is vital. The dose-limiting toxicity of oxaliplatin is chronic sensory neurotoxicity; unlike cisplatin, other side-effects such as nephrotoxicity, ototoxicity and alopecia are rarely seen. The chronic neurotoxicity manifests as a cumulative sensory neuropathy causing patients to complain of paresthesia and dysesthesias; these symptoms tend to increase in intensity and duration as the cumulative dose of oxaliplatin increases. The sensory neuropathy is usually predictable, and can respond to dose reductions and occasionally symptom control medications. After discontinuation of oxaliplatin, approximately 75% of patients will have partial or complete recovery [1,4]. Patients receiving oxaliplatin also experience an acute neuropathy that is unique to oxaliplatin [5]. This neuropathy can include a multitude of sensory and motor dysfunctions including diplopia, jaw stiffness, pharyngolaryngeal dysesthesia, cold-induced paresthesia, neuromyotonia and other signs of peripheral nerve hyperexcitability. Serial electromyograms and nerve conduction studies done prior to and within 24–48 h after oxaliplatin therapy have shown repetitive compound muscle action potentials following an electrical stimulus or voluntary contraction, and neuromyotonic discharges, which resolved prior to the next dose of oxaliplatin (3 weeks later) [5]. In contrast, follow-up studies in six patients after 8–9 cycles of therapy showed a significant decrease in the sensory nerve action potential of the median, ulnar, radial and sural nerves, without a change in conduction velocity, pointing to the loss of sensory fibers or sensory neurons [6]. No changes were seen in either the amplitude or velocity of motor nerves in these same patients [6].

Chemotherapy-induced peripheral neuropathies are usually sensory due to axonal damage, and motor abnormalities are rare [7]. The occurrence of mixed sensory and motor polyneuropathy could not be explained by epidural spinal cord compression or intramedullary spinal cord metastasis (based on the negative contrast MRI of the spine), and laboratory tests did not support a contribution from metabolic causes or a paraneoplastic syndrome. The patient did not have a history or symptoms of collagen vascular disease, and a pre-treatment ANA test was negative. The only laboratory abnormality found was an elevated CSF protein without pleocytosis. This can be found with Guillain–Barre syndrome, which is a term applied to at least five distinct maladies that are characterized by acute inflammatory demyelinating polyradiculoneuropathies that have a rapid onset over a few days, attributed to immunologic factors [8]. Weakness predominates in three main Guillain–Barre subtypes and in two of these, sensory loss also occurs, but does not predominate. Despite the acute presentation and evidence of some motor weakness, the most likely diagnosis was felt to be oxaliplatin-related toxicity. There

is no published information concerning CSF findings in patients who develop oxaliplatin-related neuropathy. Electrophysiologic studies in our patient demonstrated a diffuse sensorimotor axonopathy. In light of the known neurotoxic effects of oxaliplatin, the increasing duration of paresthesias over the first 3 cycles of therapy experienced by our patient, and the constellation of symptoms, signs and objective findings, oxaliplatin-related toxicity is probable. Even though the patient developed symptomatic brain metastasis leading to diplopia 6 months later, the bilateral nature of his symptoms, and the gradual, although incomplete, improvement in the paresthesias and muscle weakness in the absence of anti-cancer or corticosteroid therapy make it unlikely that small, intracerebral metastases caused his ascending neuropathy.

Oxaliplatin chemotherapy is now an essential drug used in the treatment of colorectal cancer. Its use in other cancers is expanding. Acute neurotoxicity, characterized by transient symptoms (lasting seconds, minutes or a few hours) reflecting peripheral sensory and motor nerve hyperexcitability, occurs frequently. The cumulative neuropathy is predominantly sensory. Our case demonstrates the potential for oxaliplatin administration to be associated with a catastrophic disabling neuropathy that may also have a motor component. Further studies are required to accurately determine the effect of oxaliplatin on motor nerves not only with the acute neuropathy, but also to determine if delayed or cumulative motor abnormalities can occur.

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