Recurrent Episodes of Involuntary Masticatory Spasms Induced by Continuous Infusion of Oxaliplatin

Oxaliplatin-containing regimens are now considered standard therapeutic options for patients with metastatic colorectal cancer (1). Oxaliplatin has a very good safety profile, and the dose-limiting toxicity of oxaliplatin is neurosensory toxicity (2). In approximately 90% of patients, oxaliplatin is associated with acute reversible neurotoxicity that is characterized by the rapid onset of cold-induced distal dysesthesia and/or paresthesia, jaw pain, eye pain, pain in the arm used for drug infusion, ptosis, leg cramps, and visual and vocal changes (3–5). At high cumulative doses of oxaliplatin, persistent and chronic sensory neuropathy can develop, with continuous, non–cold-related paresthesiae, superficial and deep sensory loss, and eventually sensory ataxia and functional impairment (4).

We present six case reports of patients with oxaliplatin-associated neurotoxicity who also had atypical and similar acute neurosensory symptoms characterized by recurrent episodes of involuntary masticatory spasms. All patients with metastatic colorectal carcinoma received the same chemotherapy regimen containing continuous infusion of oxaliplatin (70 mg/m² for 12 hours on days 1 and 8) plus oral capecitabine (2000 mg/m² per day). After each oxaliplatin infusion, all patients reported recurring paroxysmal episodes of painful involuntary masticatory spasms that were characterized by mouth opening or lateral shift of the mandible followed by muscle relaxation failure. These episodes started 6–24 hours after the beginning of each oxaliplatin administration, recurred several times a day, and lasted for 48–72 hours. These spasms were easily provoked by mouth movements, such as eating and talking, and caused difficulties in speech or mastication. They usually lasted only a few seconds and were not induced or exacerbated by cold. No episode was associated with hypocalcemia or hypomagnesemia. After a complete oto-rhino-laryngology examination, oromandibular dystonia and temporomandibular dysfunction were completely excluded in each patient. No patient had a history of limited mouth opening, typical of temporomandibular disorders, or had previous neurologic diseases. One patient had previously received eight cycles of a 2-hour oxaliplatin infusion without reporting an episode of masticatory spasm. The infusion time was reduced to 2 hours in two patients, and no masticatory spasm episode was reported.

The acute neurotoxicity seen with oxaliplatin is related to acute peripheral nerve hyperexcitability (6). Moreover, recent data indicate that oxaliplatin may act on the voltage-gated sodium channel to increase the excitability of sensory neurons (6). For these reasons, we postulate that a possible abnormal and prolonged oxaliplatin-induced hyperexcitability state of trigeminal fibers results in the described paroxysmal episodes of painful involuntary occlusion of the jaw. This hypothesis is supported by the demonstration that the remodeling of voltage-gated sodium channels in the neuronal membrane has been proposed as a mechanism of trigeminal ectopic hyperexcitability that occurs in several types of masticatory spasms (7).

We suggest that prolonged exposure to oxaliplatin induces a prolonged abnormal function of voltage-gated sodium channels in the neuronal membrane of trigeminal nerve. Thus, we believe that the high incidence of the described neurotoxicity in our patients (six of 13 patients treated with continuous infusion of oxaliplatin) is strictly related to the duration of drug infusion.

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