Central Nervous System Toxicity Induced by Irinotecan

Irinotecan is a semisynthetic derivative of camptothecin that requires bioactivation to form the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). The antitumor activity SN-38 is mediated through its inhibition of topoisomerase I. Irinotecan is used mainly to treat patients with disseminated colorectal carcinoma (1).

A 46-year-old man who was diagnosed with a sigmoid carcinoma and liver metastasis and underwent palliative sigmoid resection had disease progression while receiving capecitabine. Intra-venous treatment with irinotecan was initiated: 550 mg (350 mg/m² every 3 weeks) given continuously over 90 minutes. Atropine, dexamethasone, and granisetron were administered as pre-medications. The patient sporadically used ibuprofen and paracetamol before and during treatment, and his serum bilirubin level was normal.

The patient developed acute dysarthria at the end of the first infusion of irinotecan. An immediate neurologic examination revealed mild ataxia of the left arm and leg. A computed tomography scan of the brain revealed no abnormalities. These symptoms and signs slowly waned and finally disappeared 8 hours after discontinuation of the irinotecan infusion. With the patient’s consent, irinotecan treatment was repeated according to schedule. A total of nine cycles of irinotecan treatment were administered; during each treatment cycle, the patient had the same symptoms but the intensity and duration of the symptoms decreased with each infusion. Otherwise, the treatment was well tolerated by this patient.

Common toxic effects associated with irinotecan are nausea, vomiting, diarrhea, cholinergic-like syndrome, bone marrow suppression, and stomatitis (1). Our case is the fourth reported case of central nervous system (CNS) toxicity (2–4). In one case (4), dysarthria developed 1 hour after the initiation of the irinotecan infusion; in other cases (2,3), symptoms developed even sooner. In one case (3), dysarthria progressed to nonfluent aphasia. Imaging studies were normal in all cases (2–4). Neurologic symptoms completely subsided within hours in two cases (2,3) or, in one case (4), during the irinotecan infusion. In all three cases (2–4), the symptoms repeated at each cycle of irinotecan infusion. To our knowledge, ours is the first report of tachyphylaxis of toxicity involving irinotecan, in which the central nervous system toxicity associated with this medication waned even though the same dose was given.

The mechanism by which CNS toxicity occurs after irinotecan infusion is unclear. SN-38 is detected in plasma very soon after the start of irinotecan infusion. Plasma concentrations of irinotecan and SN-38 peak by the end of irinotecan infusion (5). The plasma concentration can be described by a triphasic model, in which the terminal phase half-lives of irinotecan and SN-38 are 14.2 hours and 13.8 hours, respectively (6). There are no data on the pharmacokinetics of irinotecan or SN-38 in cerebrospinal fluid (CSF) in humans. However, one study in irinotecan-infused nonhuman primates found that the level of irinotecan in the CSF was 14% of the plasma level; no SN-38 could be detected intrathecally (7). Clearance of irinotecan is unaltered during repeated infusion cycles (5,6), making it unlikely to be the cause of the tachyphylaxis of toxicity.

In conclusion, irinotecan may cause reversible central nervous system toxicity, which will reoccur after repetitive irinotecan infusions. Tachyphylaxis seen in our patient is unexplained, as is the pathogenesis of the toxicity.

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REFERENCES


NOTES

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