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-sigmoid resection had disease progression and the patient underwent palliative chemotherapy to treat patients with disseminated colorectal carcinoma (1).

Venous treatment with irinotecan was initiated 1 hour after the initiation of the irinotecan infusion; in other cases, 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 nonhuman primates. 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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