Irinotecan-Induced Central Nervous System Toxicty: a Case Report

The semisynthetic derivative of camptothecin, irinotecan (CPT-11), has been used extensively as second-line chemotherapy for metastatic colorectal carcinoma resistant to 5-fluorouracil (5-FU) and has also been studied in other tumor types (1–3). The toxic effects of irinotecan mainly consist of neutropenia, diarrhea, and cholinergic-like syndrome. Other toxic effects include alopecia, nausea and vomiting, anemia, asthenia, thrombocytopenia, stomatitis, and abdominal pain. Occasional elevation of hepatic transaminase levels and skin toxicity have been observed. Rare pulmonary toxicity and mild hand–foot syndrome have been described (4). Although pharmacokinetic data on camptothecin analogues suggest that these compounds can penetrate the central nervous system (CNS) quite readily, only one case of neurologic toxicity has been described (5). This case also consisted of peripheral sensory neuropathy and not of CNS toxicity.

Here we describe the first case, to our knowledge, of CNS toxicity in a patient treated with irinotecan.

A 49-year-old woman with stage IV (American Joint Committee on Cancer, 1993) colorectal carcinoma with liver and lymph node metastases had disease progression despite treatment with 5-FU and folinic acid. She was started on irinotecan at 350 mg/m² infused intravenously over a 1-hour period with granisetron premedication (3 mg, intravenously infused). The patient was subjected to three cycles of this treatment, which was interrupted (after receiving the third cycle) because of disease progression. Shortly after starting the infusion, in all three cycles, she developed dysarthria, a speech disorder resulting from damage to the CNS; this disorder lasted for about 2 hours and then disappeared completely. The patient was given no medication. No other neurologic symptoms were observed, and a neurologic physical examination gave otherwise normal results. A magnetic resonance scan of the brain gave normal results. The treatment was otherwise well tolerated with no vomiting, diaphoresis, diarrhea, or neutropenic fever. The patient’s disease progressed, and she was treated with oxaliplatin (85 mg/m² infused over 2 hours by intravenous infusion on day 1), isovorin (100 mg/m² over 2 hours intravenously infused on days 1 and 2), followed by 5-FU (400 mg/m² bolus and 600 mg/m² intravenous infusion on days 1 and 2 every 2 weeks), and granisetron (3 mg, intravenously) premedication; the patient experienced no dysarthria. During treatment with irinotecan, oxaliplatin, and granisetron, the patient also received orally prednisolone (20 mg in the morning and 10 mg at night), diclofenac (50 mg every 8 hours), metamizole (575 mg occasionally), and famotidin (40 mg every 24 hours) as well as tramadol (100 mg occasionally) given intramuscularly. We do not know if any of these medications interfered with the metabolism of irinotecan. After stopping irinotecan, the patient continued treatment with these medications and experienced no dysarthria. Nine months after developing this toxic effect, the patient was alive and did not experience any further neurologic symptoms.

While Blaney et al. (5) described peripheral sensory neuropathy in one patient after treatment with irinotecan, to our knowledge, this case is the first one of CNS toxicity associated with irinotecan. This toxicity could be related directly to irinotecan, which has a peak plasma concentration immediately after the infusion is completed, or to its metabolite SN-38, which has a peak plasma concentration 30–90 minutes after completion of the infusion (1). This type of toxicity due to irinotecan does not seem to be cumulative, is reversible (at least in our patient), and does not seem to limit dosing or timing of treatment.

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REFERENCES

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