Abstract. Neurological complications of both fluorouracil (5-FU) and its oral prodrug, capecitabine, have been described in the literature. This study reported the case of a 70-year-old female with metastatic adenocarcinoid of the rectum who developed hyperammonemic encephalopathy, following infusional 5-FU therapy, manifesting itself as intractable nausea, vomiting, confusion and disorientation. Interestingly, when the patient was rechallenged with the fluoropyrimidine analog, capecitabine, neither hyperammonemia nor symptom recurrence was observed. 5-FU is an integral component of effective anti-neoplastic treatment for metastatic colorectal cancer, but is often discontinued when neurotoxicity develops. This case highlighted the use of capecitabine as an alternative for patients who have demonstrated evidence of 5-FU-induced hyperammonemic encephalopathy. Re-challenging the patient with capecitabine, at a low daily dose intensity, accounted for the overall tolerability of the treatment, as demonstrated by normal ammonia levels and the lack of neurological symptoms.

Fluorouracil (5-FU), a pyrimidine antimetabolite, has been widely used in the chemotherapy of neoplasms involving the gastrointestinal tract, breast and ovary, since its introduction in 1957 (1, 2). Common adverse effects of 5-FU therapy include bone marrow suppression, manifesting itself as anemia, thrombocytopenia/neutropenia, nausea, vomiting, diarrhea, mucositis and hand-foot syndrome. Neurological side-effects with 5-FU were initially described by Moertal et al. and by Reihl and Brown in 1964 who reported eighteen and four patients, respectively, with cerebellar ataxia associated with 5-FU therapy (reviewed in Ref. 3). 5-FU-induced hyperammonemic neurotoxicity is uncommon with the currently used infusional dose (2400 mg/m² over 46 h every two weeks) but has been reported in up to 5.7% of patients receiving high-dose infusional therapy, i.e. 24-h infusion of 2600 mg/m²/week (4). The time interval between the initiation of chemotherapy and the onset of hyperammonemic encephalopathy is variable and has been reported as ranging from 0.5 to 5 days in a study by Liaw et al. (5).

Capecitabine, an orally administered prodrug of 5-FU, is currently licensed for the treatment of colorectal and breast cancer. The ease of oral administration and its reduced systemic toxicity due to its selective activation in tumor tissue makes capecitabine an appealing chemotherapeutic agent. In addition to its antineoplastic action, the reported adverse effects of capecitabine also appear to be related to its conversion to 5-FU. The frequency of capecitabine-induced neurotoxicity has been reported as ranging from 0.1 to 0.5% in the package insert information. This study reports the case of a patient who showed evidence of hyperammonemic encephalopathy related to 5-FU without recurrence of symptoms on administration of its prodrug, capecitabine.

Case Report

A 70-year-old Caucasian female with a history of localized adenocarcinoid of the rectum, initially treated by a transanal excision of her tumor, presented seven years later with biopsy-proven metastatic disease to the liver and left ovary. She was treated primarily with sandostatin, with a lack of response, but subsequently achieved good disease control with repeated liver chemoembolization over a one-year period. However, she eventually developed progressive disease with the appearance of numerous lung lesions and a new malignant left pleural effusion, along with the enlargement of hepatic metastases. She was subsequently started on a combination chemotherapy regimen of folinic acid, 5-FU and oxaliplatin (FOLFOX) and bevacizumab, administered every two weeks. Folinic acid was dosed at 400 mg/m², 5-FU at 2.4 g/m² as a 46 h continuous
infusion, oxaliplatin at 85 mg/m² and bevacizumab was given at 5 mg/kg. Oxaliplatin was discontinued after eight cycles (four months) due to the development of grade 3 neuropathy and the patient was maintained on 5-FU, folinic acid and bevacizumab. Given her symptoms of worsening 5-FU-induced nausea and vomiting, a chemotherapy break was instituted. A repeat computed tomography (CT) scan four months after the chemotherapy break showed progressive disease and she was rechallenged with 5-FU, folinic acid and bevacizumab.

Two days following the completion of her second cycle of 5-FU infusion, she was admitted with a one-day history of intractable nausea and vomiting associated with extreme weakness, mild diarrhea and confusion, rapidly progressing to lethargy and disorientation. Her Glasgow Coma Scale score on presentation was 11. At the time of admission, the patient was taking the following medications at home: atenolol, hydrochlorothiazide, omeprazole, warfarin, multivitamins, aprepitant and dexamethasone with chemotherapy. None of these medications had been recently instituted. Her complete blood count and electrolytes were within normal limits. A CT scan of the head did not reveal any intracranial pathology such as bleed, metastasis or stroke. Blood and urine cultures were negative for infection. Liver function tests were as follows: aspartate aminotransferase 53 IU/l (normal range: 15-46 IU/l), alanine aminotransferase 50 IU/l (normal range: 11-66 IU/l), alkaline phosphatase 79 IU/l (normal range: 38-126 IU/l), total bilirubin 0.6 mg/dl (normal range: 0.2-1.3 mg/dl). The only significant laboratory finding was an elevated ammonia level of 203 μmol/l (normal range: 11.0-51.0 μmol/l).

The patient was treated conservatively with lactulose and adequate hydration with close monitoring of her mental status. Subsequently, her ammonia levels began to decrease with a dramatic improvement in her condition. Two days after admission, her ammonia level was 20.6 μmol/l. The patient was alert and oriented to time, place and person and was discharged. The patient presented to the clinic one week later for follow-up. She did not report any other episodes of confusion and her ammonia levels were within the normal range.

As her recent symptoms of intractable nausea, vomiting, confusion and disorientation were attributed to 5-FU-induced hyperammonemia, a decision was made to discontinue her two-day infusion of 5-FU permanently and substitute it with capecitabine. Capecitabine was dosed at 1500 mg/dose twice a day for 14 days every 3 weeks. Bevacizumab was administered at a dose of 7.5 mg/kg on the first day of capecitabine. This regimen was well-tolerated without any significant elevation in ammonia levels or central nervous system-related toxicity (Figure 1). Follow-up CT scans revealed overall stable disease according to the response evaluation criteria in solid tumors (RECIST).

**Discussion**

Encephalopathy from hyperammonemia is an infrequent complication of chemotherapy, and is potentially fatal. It has been reported in patients who have received high-dose cytoreductive therapy for hematologic malignancies (6-8) or following bone-marrow transplantation (12, 13) and also in the treatment of solid organ malignancies with agents such as 5-FU (9-11). Various manifestations of 5-FU-induced encephalopathy have been reported such as confusion, ataxia, dysmetria, nystagmus, focal weakness, generalized seizures and, rarely, coma and death. Yeh and Cheng reported severe manifestations of hyperammonemic encephalopathy in 13/16 of patients and, in two patients, these symptoms were combined with seizures (4). Two main patterns of encephalopathy are recognized (14). The acute form is associated with hyperammonemia and is usually reversible with conservative management. The delayed form is associated with an inflammatory leukoencephalopathy and has been reported in patients receiving 5-FU in combination with levamisole (15-18). Magnetic resonance imaging scans in these cases have demonstrated multifocal enhancing white-matter lesions, while radiological examinations appear usually normal in the acute form.

The following clinical criteria for 5-FU-related encephalopathy have been described by Yeh and Cheng: (i) development of encephalopathy during or shortly after completion of 5-FU administration; (ii) exclusion of other metabolic factors that may affect consciousness and mental functioning such as hypoglycemia, organ failure, electrolyte imbalance, sepsis and central nervous system involvement by cancer; and (iii) exclusion of any adverse effect by concomitant medications (4). Hyperammonemia, lactic acidosis, hyperammonemia-induced hypocapnia and mild to moderate elevation of liver transaminases have been reported in most patients who received 5-FU and developed encephalopathy (14). Brain imaging may be unremarkable but may help to exclude alternate diagnoses such as metastasis or stroke (19). Electroencephalography may reveal diffuse slow waves or theta waves, suggestive of but not specific for metabolic encephalopathy (4).

The exact etiology of 5-FU-induced hyperammonemic encephalopathy has not been clearly elucidated. Koenig and Patel postulated that following high-dose administration of 5-FU, fluorocitrate, the intermediate product of 5-FU metabolism, inhibits the Krebs tricarboxylic acid cycle which in turn causes impairment of the adenosine triphosphatase-dependent urea cycle, resulting in hyperammonemia (2). The osmotic effect of accumulated intracellular glutamine, which is the primary metabolic product of the ammonia metabolism in the brain, has been implicated in the pathophysiology of raised intracranial pressure and cerebral edema, demonstrated in many cases of hyperammonemic encephalopathy (2, 19). The administration
of 5-FU alone is not considered to be a risk factor for the development of hyperammonemia. The potential aggravating factors that have been described in the literature include azotemia, infection, dehydration and chronic constipation. Hypovolemia leads to increased reabsorption of urea from the renal tubules. Infection may lead to increased tissue catabolism and can cause dehydration with or without prerenal azotemia. Chronic constipation may lead to increased ammonia production in the colon through the action of bacterial urease and aminooxidase (5, 20).

Both continuous infusion and bolus 5-FU administration have been implicated in cases of hyperammonemic encephalopathy (4, 5, 22). Lower doses of infusional 5-FU (1000 mg/m² continuous infusion for five days every four weeks) have also been reported to cause this complication (21).

In conclusion, the patient in this case report satisfied the clinical criteria for 5-FU-related encephalopathy. Neither symptom recurrence nor hyperammonemia occurred following the administration of the fluoropyrimidine produg of 5-FU, namely capecitabine. This is the first case of 5-FU-induced encephalopathy that was successfully rechallenged with capecitabine. It was postulated that the patient developed progressive liver dysfunction due to repeated liver-directed chemoembolization followed by oxaliplatin-based therapy. This eventually led to the predisposition to 5-FU-induced encephalopathy. The patient’s subsequent tolerance to capecitabine without the development of hyperammonemia and resultant encephalopathy may be related to the protracted low daily dose intensity of this 5-FU produg. 5-FU forms the backbone of frontline combination treatment of metastatic colorectal cancer. While neurotoxicity is a rare side-effect of 5-FU, its occurrence may be worrisome and preclude further administration of this vital drug. The presented case suggests that capecitabine may still be a viable option for the treatment of colorectal cancer as an alternative to 5-FU in patients who have evidence of 5-FU-induced hyperammonemic encephalopathy.

References


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