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5-Fluorouracil-induced Hyperammonemic Encephalopathy-A Case Report and Literature Review

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Hyperammonemic encephalopathy is a rare side effect of 5-fluorouracil (5-FU). We present a 58-year-old male with adenocarcinoma of ascending colon who was treated with salvage chemotherapy that consisted of infused 5-FU (2400 mg/m^2) for 46 hours, irinotecan (180 mg/m^2) for 90 minutes and bevacizumab (5 mg/kg) for 90 minutes every two weeks. Sudden onset of conscious disturbance developed after completion of the fourth cycle of chemotherapy. He presented to our emergency room with hyperammonemic encephalopathy and acute kidney injury. After fluid resuscitation and administration of lactulose for 3 days, he recovered well and his renal function became normal. We reduced the dose of 5-FU (1200 mg/m^2) in the fifth cycle of chemotherapy. He completed the fifth cycle of chemotherapy well without development of hyperammonemia. When patients undergoing chemotherapy comprising 5-FU present with conscious disturbance, hyperammonemia should be considered and acute kidney injury should be prevented.

Key words: 5-fluorouracil, hyperammonemic encephalopathy

INTRODUCTION

5-FU is a common anti-cancer agent for treating a broad range of solid tumors, including head and neck, and gastrointestinal cancer. The common side effects of 5-FU include nausea, vomiting, diarrhea or bone marrow suppression with low-grade toxicity but are well tolerated. Neurotoxicity, such as hyperammonemic encephalopathy, is a rare side effect of 5-FU.[1] Dehydration and infection had been reported to be predisposing factors of hyperammonemic encephalopathy of 5-FU.[2] Here, we present a 58-year-old patient with adenocarcinoma of ascending colon who developed hyperammonemic encephalopathy and acute kidney injury after salvage chemotherapy consisting of 5-FU. He recovered well after fluid resuscitation and administration of lactulose. Hyperammonemia was successfully prevented by reducing the dose of 5-FU in the subsequent courses of treatment.

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CASE REPORT

A 58-year-old man was diagnosed as having adenocarcinoma of ascending colon with liver metastasis. He underwent salvage chemotherapy that consisted of infused 5-FU (2400 mg/m^2) for 46 hours, irinotecan (180 mg/m^2) for 90 minutes and bevacizumab (5 mg/kg) for 90 minutes every two weeks. Severe nausea and vomiting developed 2 days after completion of the fourth cycle of chemotherapy. Thereafter, he presented to our emergency room with conscious disturbance. Physical examination findings were as follows: body temperature of 36.2°C, pulse rate of 98 beats/min, respiratory rate of 19 breaths/min, and blood pressure of 96/50 mmHg. Neurological examination revealed a Glasgow Coma Scale score of 11, confused mental status, reversible somnolence, lethargy and dysarthria. Laboratory findings were as follows: white blood cell count of $9.95\times10^3/\mu$L, hemoglobin of 13.3 g/dL, platelets of $385\times10^3/\mu$L, blood urea nitrogen of 43 mg/dL (normal range: 6-20 mg/dL), creatinine of 2.9 mg/dL (normal range: 0.7-1.2 mg/dL), potassium of 5.7 mmol/L (normal range: 3.5-5.1 mmol/L), and am-

monia of 1020 μg/dL (normal range: 27-102 μg/dL). Computed tomography (CT) of brain showed neither metastatic lesions nor hemorrhage. He was referred to our department under diagnosis of hyperammonemic encephalopathy and acute kidney injury.

On admission, he was treated with fluid resuscitation and administration of lactulose. Three days later, he recovered well without neurological sequelae. Follow-up laboratory findings were as follows: blood urea nitrogen of 24 mg/dL, creatinine of 1.3 mg/dL, potassium of 3.9 mmol/L, and ammonia of 31 ug/dL.

Three weeks later, he received the fifth cycle of chemotherapy with the same chemotherapy agents as the fourth cycle of chemotherapy, but with a reduced dosage of 5-FU (1200 mg/m^2). Two days after completion of the fifth cycle of chemotherapy, his ammonia level was 35 ug/dL. He completed the fifth cycle of chemotherapy smoothly without developing hyperammonemia.

DISCUSSION

The common side effects of 5-FU in clinical settings are gastrointestinal toxicity and bone marrow suppression.[1] The manifestations of gastrointestinal toxicity include nausea, vomiting and diarrhea which are characterized by epithelial damage. Bone marrow suppression often occurs when administering 5-FU as a bolus. Other side effects of 5-FU include ocular toxicity and dermatologic toxicity, such as alopecia and pigmentation of fingernails. Neurotoxicity, such as hyperammonemic encephalopathy, is a rare side effect of 5-FU.[2-3]

Yeh and Cheng had reported that the incidence of 5-FU-induced hyperammonemic encephalopathy in patients undergoing chemotherapy with high-dose 5-FU infusion was 5.7%. The onset of 5-FU-induced hyperammonemic encephalopathy after receiving infusional 5-FU can range from 0.5 to 5 days.[4] Dehydration, renal failure and infection were reported to be the predisposing factors of 5-FU-induced hyperammonemic encephalopathy.[2] The diagnostic criteria of 5-FU-induced hyperammonemic encephalopathy include: (1) onset of encephalopathy during or shortly after 5-FU infusion, (2) exclusion of other problems that can affect patients' consciousness, such as electrolyte imbalance, sepsis, stroke and hypoglycemia, and (3) exclusion of other medications that induced encephalopathy.[2,5-6] Our patient presented with severe nausea and vomiting one day prior to this admission. Severe nausea and vomiting can cause dehydration and acute kidney injury which aggravated the risks of 5-FU-induced encephalopathy. Patients who received chemotherapy of 5-FU infusion should be educated to prevent dehydration. When vomiting and diarrhea occur, adequate fluid supplement should be considered.

The definite treatment and antidote for 5-FU-induced hyperammonemic encephalopathy remain unclear. The sequelae of neurotoxicity induced by 5-FU have significant correlation with the duration of hyperammonemic encephalopathy.[7] Immediate discontinuation of 5-FU infusion is important in initial treatment of 5-FU-induced hyperammonemic encephalopathy. Lactulose and neomycin may be employed to reduce gastrointestinal sources of ammonium.[8-9] Tissue hypoperfusion caused by dehydration may increase protein catabolism, nitrogen formation and the concentration of ammonium. Fluid supplement and antiemetics should be administered to prevent dehydration. However, intensive monitoring of patients' vital status is the most important management of hyperammonemic encephalopathy.[10]

The mechanisms of 5-FU-induced hyperammonemic encephalopathy remain unknown. Some theories indicate that fluoroacetate and accumulated ammonia play major roles. Fluoroacetate, which is the end-product of 5-FU catabolism, inhibits the urea cycle and leads to reduced catabolism of ammonia. Ammonia is also a product of 5-FU that may accumulate after the administration of high-dose 5-FU. The production of ammonia depends on the dose of 5-FU infusion.[11-13] Our patient developed hyperammonemic encephalopathy after salvage chemotherapy with high-dose 5-FU (2400 mg/m^2); However, he completed the next course of chemotherapy with half-dose 5-FU (1200 mg/m^2). Hyperammonemic encephalopathy was successfully prevented. When patients present with 5-FU-induced hyperammonemic encephalopathy, reducing the dose of 5-FU in the subsequent chemotherapy may be considered.

In conclusion, if patients develop conscious disturbance during or after high-dose 5-FU infusion, hyperammonemic encephalopathy should be considered. Dehydration should be prevented by educating patients about adequate fluid supplement and administering antiemetics. If 5-FU remains the major chemotherapeutic drug, reducing its dose may be a good option to prevent hyperammonemic encephalopathy.

DISCLOSURE

All authors declare no competing financial interests.

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