Cancer Chemother Pharmacol (1986) 17: 292–293

Cancer Chemotherapy and Pharmacology

Neurologic toxicity associated with hepatic artery infusion HAI of FUdR*

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Summary. A 66-year-old man with hepatic metastases from gastric adenocarcinoma was treated on two occasions with 5-fluoro-2-deoxyuridine (FUdR) via hepatic artery infusion (HAI). The patient developed neurologic signs and symptoms including disorientation, oculomotor defects, ataxia and multifocal myoclonus during both attempts at HAI. Systemic drug toxicity is unusual when FUdR is given via HAI, and neurologic toxicity has not previously been reported. We postulate individual hypersensitivity to FUdR or selective concentration of FUdR in brainstem structures to explain the toxicity in this case.

Introduction

Neurologic toxicity associated with IV 5-fluorouracil (5FU) or 5-fluoro-2-deoxyuridine (FUdR) may occur in patients treated with loading doses or high weekly/monthly doses of drug. The characteristic sign of fluoropyrimidine toxicity is an acute cerebellar syndrome, and disturbances of ocular motility occur infrequently [7]. Systemic FUdR levels in patients treated with hepatic artery infusion (HAI) are 25% of FUdR levels in patients treated with peripheral venous infusion [3]. The high hepatic extraction for FUdR administered via HAI and implanted systems may account for the absence of significant systemic drug toxicity in most cases [5]. We report a patient in whom acute encephalopathy and associated clinical and radiographic signs of brainstem dysfunction began abruptly during hepatic artery infusion of FUdR.

Case report

A 66-year-old man complained of anorexia, weight loss and intermittent right upper quadrant discomfort 8 months after a total gastrectomy for gastric adenocarcinoma. Examination revealed a seemingly chronically ill individual. The liver was enlarged to 16 cm in the midclavicular line. A liver-spleen scan was abnormal and liver biopsy demonstrated metastatic adenocarcinoma. A metastatic work-up, including chest ray, computed tomographic scan of abdomen, and barium studies of upper and lower intestines, revealed only hepatic metastases. Laboratory data included hemoglobin 13.7 g, hematocrit 41.5%, serum glutamic oxalacetic transaminase (SGOT) 23 units/l (normal 0–41 units/l), serum glutamic pyruvic transaminase (SGPT) 78 units/l (normal 0–45 units/l), alkaline phosphatase 457 units/l (normal 30–115 units/l), total bilirubin 0.5 mg%, serum albumin 3.1 g/dl (normal 3.0–5.5 g/dl), and prothrombin time (PT) 11.4 s. Hepatic artery infusion with FUdR was begun at a dose of 35 mg per 24 h.

The following day the patient noted a decrease in abdominal pain. One day later he appeared lethargic and poorly responsive to verbal commands. Abdominal examination demonstrated a liver span of 13 cm. There was no abdominal tenderness and no asterixis. Neurologic examination demonstrated severe, bilateral ptosis; both pupils were miotic (1–2 mm) but reacted to light. There was limitation of elevation, depression, and adduction of the left eye, and a suggestion of incomplete abduction of the right eye. Motor examination showed marked dysmetria of the right upper extremity. FUdR was discontinued. Laboratory data included serum sodium 135 mEq/l (normal 136–145 mEq/l), serum calcium 8.2 mg/dl (normal 8.5–10.5 mg/dl), SGOT 142 units/l, SGPT 40 units/l, alkaline phosphatase 518 units/l, serum albumin 2.5 g/dl, and PT 14.2 s. An abdominal X-ray revealed the HAI catheter properly positioned. A CT brain scan showed only severe, generalized cortical atrophy. Over 4 days the patient's mental status improved. He became alert, had a good appetite, and was oriented as to person, place, and time. However, oculomotor defects persisted. Abdominal pain and right upper quadrant tenderness recurred. FUdR infusion was reinstituted. After 48 h he became disoriented and agitated, with slurred speech. Examination showed that third nerve dysfunction persisted. New findings included ataxia of all limbs and prominent myoclonus. The infusion was discontinued. An EEG showed generalized slow wave activity consistent with a diffuse encephalopathy. CT brain scans now revealed an area of decreased attenuation in the region of the left rostral midbrain. Lumbar puncture demonstrated normal opening pressure. The spinal fluid was acellular with protein 23 mg% and glucose 67 mg% (serum glucose 114 mg%). Bacteriologic and fungal cultures showed no growth. Complete blood counts, arterial blood gases, blood urea nitrogen, and serum creatinine were all within normal limits. Additional laboratory

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data included serum calcium 9.1 mg/dl, SGOT 161 units/l, SGPT 71 units/l, alkaline phosphatase 617 units/l, serum albumin 3.2 g/dl, and PT 10.9 s. A radionuclide hepatic arteriogram demonstrated inhomogeneous distribution of tracer to both lobes of the liver without simultaneous activity in the lungs. The hepatic catheter was removed. The patient's clinical condition deterioriated over 3 weeks and he expired. Postmortem examination performed elsewhere showed a recent pulmonary embolus and widespread metastases to lungs, spleen, and bone marrow; but no evidence of invasion of brain parenchyma. The cavernous sinuses were free of tumor, and there was no sign of carcinomatous metastasis to the meninges. Serial brain sections revealed no focal lesions; however, detailed thin sectioning of the brain stem was not available for review.

Discussion

The temporal relationship between the onset of neurologic symptoms and signs and drug administration on two occasions suggests that HAI of FUdR resulted in neurologic toxicity in our patient. Mental status changes, generalized ataxia, and multifocal myoclonus indicated diffuse brain dysfunction. No metabolic imbalance or infectious agent was present to account for the clinical findings. Although much of the liver was replaced with tumor there was no rapid deterioration in liver function or evidence of asterixis to suggest hepatic encephalopathy as a cause of the patient's rapid change in mental status on two separate occasions. Additionally, histopathologic examination revealed no sign of central nervous involvement with tumor and no evidence of intracranial vascular occlusive disease. The findings of a partial third nerve palsy with associated contralateral ptosis and preserved pupillary function suggest involvement of the oculomotor nuclear complex located in the rostral midbrain [6]. CT scans revealed a low-density lesion in that region. Disturbance of ocular motility is a rare manifestation of 5FU neurotoxicity. Bixenman et al. postulated selective toxicity on brainstem regions governing ocular vergence mechanisms in two patients with complaints of diplopia and findings of cerebellar dysfunction while receiving IV 5FU [5]. Detailed neuropathologic examination demonstrated no structural brainstem changes in one case; oculomotor findings were reversed with discontinuation of the drug in the second case.

We considered the possibility that the neurologic signs were due to a remote effect of carcinoma. Paraneoplastic cerebellar degeneration is occasionally associated with cranial nerve palsies, and at times the onset of symptoms can be abrupt [2]. As a rule, however, symptoms and signs develop over weeks to months and delirium is uncommon. Moreover, postmortem examination did not demonstrate the pathologic changes typically found in that condition.

Koenig and Patel have postulated that fluorocitrate, a catabolite of 5FU, may exert a direct toxic effect on cerebellar neurons, thru inhibition of the Krebs cycle [4]. They were able to demonstrate elevated brain tissue citrate levels in cats with fluorouracil neurotoxicity. Further, they demonstrated elevated citrate levels in whole blood in two patients treated with 5FU infusion. With a high hepatic extraction ratio, systemic toxicity during HAI of FUdR is unlikely in most cases. We were unable to demonstrate significant intrahepatic shunting in our patient. Individual hypersensitivity to FUdR or perhaps selective concentration of FUdR in brainstem structures might explain the clinical findings in this case.

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Received October 18, 1985/Accepted January 9, 1986