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Case report

Pulmonary toxicity of continuous infusion 5-fluoro-2′-deoxyuridine

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This report describes a patient who developed pulmonary toxicity, manifest by dyspnea on exertion, a low pO_2, a normal FEV_1 and FVC, and a low DLCO while receiving 5-fluoro-2′-deoxyuridine (FUDR) by intermittent continuous i.v. infusion. No other cause of his low DLCO could be identified. The dyspnea on exertion and DLCO improved gradually after the FUDR was discontinued. This case was felt to represent a previously undescribed toxicity of the continuous i.v. infusion of FUDR.

Key words: Chemotherapy, 5-fluoro-2′-deoxyuridine, infusional chemotherapy, pulmonary toxicity, renal cell cancer.

Introduction

Continuous i.v. infusion of 5-fluoro-2′-deoxyuridine (Floxuridine) (FUDR) has been studied widely in patients with metastatic colon cancer[1–3] and renal cell cancer.[4–8] The most common toxicities of FUDR given by continuous i.v. infusions include nausea, stomatitis and diarrhea.[1,6,9,10] This report describes a case of pulmonary toxicity from continuous infusion of FUDR.

Case report

AB is a 77 year old white man who was doing well until October 1990 when he developed gross hematuria. Work-up revealed that he had prostate cancer, with extra-capsular extension and a left renal cell carcinoma. Chest X-ray and computed tomography (CT) scan showed multiple small bilateral pulmonary nodules. His PSA was 59 μg l and a bone scan was normal. He underwent a left nephrectomy and adrenalectomy. A splenectomy was also performed due to a capsular tear sustained during mobilization of the left adrenal gland. Biopsy of one of the pulmonary nodules revealed metastatic renal cell cancer. In October 1990, a Medtronic infusion pump was placed subcutaneously in the upper chest and FUDR (Hoffmann-La Roche, Nutley, NJ) treatment was begun at 0.25 mg/kg/day × 14 by continuous i.v. infusion using a sinusoidal format[6,5,11] every 28 days. He was also started on Luprolide 7.5 mg i.m. every 4 weeks. He was first seen in the Oncology Clinic at the University of Minnesota in January 1993, at which time he was tolerating treatments very well and denied any history of nausea, diarrhea, cough, dyspnea on exertion, weight loss, excess fatigue, fever, chills, sweats or urinary symptoms. His past medical history included an appendectomy in 1941, hernia repair in 1982, gout, degenerative joint disease and hypertension which was treated intermittently for 10 years with Dyazide. He did not smoke or use alcohol. He had been retired for many years and had no known exposure to toxins. His family history was unremarkable. Medications included Dyazide 1 p.o. qd, KCl 20 mEq p.o. qd, allopurinol 200 mg p.o. qd, Luprolide 7.5 mg i.m. q 4 weeks and FUDR 0.25 mg/kg/day continuous i.v. infusion with a sinusoidal pattern for 2 weeks of every 28 days.

The physical examination was unremarkable and revealed a healthy looking elderly man in no acute distress. The blood pressure was 144/80 mm Hg, temperature 37°C, pulse 70 and respirations 14. The lungs were clear to ausculation and cardiac examination revealed a regular rhythm with normal S1 and S2 without murmur. The abdomen was benign without mass or organomegaly. There was no edema or lymphadenopathy. Rectal exam revealed several hard nodules on the prostate. Laboratory tests showed a white blood count of 11.1×10^9 l, hemo-

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globin 12.9 g/dl, platelet count 285 × 10^9/l, bilirubin 0.7 mg/dl, alkaline phosphatase 79 U/l, AST 41 U/l, LDH 768 U/l (NL = 275–645) and PSA 1.1 μg/l. Subsequent LDH values were all normal. A chest CT scan showed no evidence of metastasis. Given the complete response of his metastatic disease and lack of side effects of treatment, the FUDR was continued. In November 1993, after 37 cycles of FUDR infusion, he stated that he had been having gradually worsening dyspnea on exertion for 6 months that had become significant to him in the last 1–2 months. He got short of breath after walking half a block or walking up a flight of stairs, but denied chest pain, orthopnea, palpitations, edema, cough or fever. His physical examination was unchanged and a chest X-ray was normal. An echocardiogram revealed normal left ventricular size and function. A ventilation-perfusion scan showed low probability for pulmonary embolism and a chest CT scan with high resolution cuts did not show any evidence of interstitial lung disease. Pulmonary function testing revealed an FEV_1 of 3.02 l (103% predicted) and an FVC of 4.11 l (109% predicted). The DLCO was 8.08 cm^3/min/mm Hg which was 33% of predicted. An arterial blood gas on room air showed a pH of 7.49, pCO_2 of 32 mm Hg and pO_2 of 58 mm Hg. Oxygen saturation was 93% on room air but fell to 81% with walking. On 2 l of O_2 via nasal cannula his resting O_2 saturation was 99%, but again decreased to 82% with exercise.

Given the absence of other causes of the low DLCO, coupled with previous reports of myocardial toxicity of 5-fluorouracil (5-FU)[12] and sclerosing cholangitis from intrahepatic arterial FUDR,[9,13] pulmonary toxicity secondary to FUDR was entertained and the FUDR was stopped in November 1993. All other medications were continued unchanged. The pump remained operational and delivered heparinized water (1000 U/ml) at the idential rate as during FUDR treatment. In March 1994 he was feeling better with less dyspnea on exertion and was using O_2 less frequently. The DLCO had increased to 46% of that predicted.

A course of prednisone to be tapered over 18 days was recommended but he declined. In April 1994, the DLCO remained at 44% of predicted. At this time, the patient opted to try a 2 week course of prednisone (40 mg p.o. qd × 4, 30 mg qd × 4, 20 mg qd × 4, followed by 10 mg qd × 2). Two weeks after completing the course of prednisone, he noted gradual improvement in his dyspnea on exertion and his DLCO had risen to 51% of that predicted. One month later the DLCO remained at 51% of that predicted. In December 1994 (13 months after stopping the FUDR) the DLCO was 61% of that predicted.

Discussion

Continuous infusion chemotherapy is gaining increasing interest for the treatment of tumors with low growth fractions, since it increases the chance of active drug being present during the sensitive period of tumor cell metabolism. The toxicities of chemotherapy agents may be quite different when a drug is administered by continuous infusion as compared with intermittent bolus administration.[10,14–19] In addition, a circadian dependence of drug toxicity has been observed for several chemotherapy agents.[5,11,20]

FUDR and 5-FU are commonly adminstered by continuous infusion. The major toxicities of continuous i.v. infusion of FUDR are stomatitis, nausea, mucositis of the intestinal tract and diarrhea.[6,9,10] Other reported toxicities include dermatitis and tear duct stenosis.[2,9,10] The related drug, 5-FU, has similar toxicities as FUDR when given by continuous i.v. infusion, including stomatitis, mucositis and diarrhea.[10,12] Recent studies have confirmed that continuous i.v. infusion of 5-FU can also result in cardiac toxicity; although the mechanism of this toxicity is unclear, vasospasm, autoimmune phenomena and alterations of the coagulation system have been suggested.[12]

FUDR is also commonly administered by continuous infusion into the hepatic artery. The major toxicity of hepatic intra-arterial infusion of FUDR is biliary toxicity, first manifest by a rise in alkaline phosphatase and AST or ALT, progressing to sclerosing cholangitis or acalculous cholecystitis.[9,13,21] Pathologic examinations in these cases have documented bile duct fibrosis in humans and dogs.[9,13,22] The onset of biliary toxicity of hepatic arterial FUDR infusions seems to be delayed by decreasing the initial dose[9,13] and by interrupting the infusion every 2 weeks for 14 days.[13,22] While the etiology of this toxicity is unclear, direct toxicity or its metabolites is assumed to play an important role.[10,13,22,23]

The two major fates of FUDR are activation to 5 - fluro - 2′ - deoxyuridine - 5′ - monophosphate (FdUMP), an active metabolite that inhibits thymidylate synthase[10,24] and metabolism by dihydropyrimidine dehydrogenase (DPD) to α-fluro-β-alanine, an inactive metabolite.[10,24,25] The activities of DPD and other enzymes may be variable in the population,[10,25] and may contribute to the propensity of an indiviaul to develop toxicity from these drugs.

Studies in rats have found that perfused rat lungs extract FUDR at a low rate and metabolize it to 5-FU.[26] In contrast, lung slices were found to have a high capacity to metabolize FUDR to 5-FU.[26] Essentially no enzymatic activity for catabolism of 5-FU was detected in rat lung tissue.[26]

The case described here strongly suggests that the administration of FUDR by continuous infusion can result in pulmonary toxicity manifest by dyspnea on exertion and a fall in DLCO, even though the chest CT scan with high resolution cuts showed no evidence of parenchymal lung disease. No other known causes of a low DLCO could be identified in this patient. The DLCO gradually improved after discontinuation of FUDR, despite the continuation of all other medications, including a continuous infusion of heparin at the same rate as during FUDR administration. The short course of prednisone may have been of some benefit, but a striking improvement was not observed. It is possible that a better response to corticosteroid therapy might have been observed had such treatment been initiated sooner, or if higher doses were used for a longer period of time. We have recently been made aware of two other cases of pulmonary toxicity of FUDR (G Bjarnason and W Hrushesky, personal communication). Whether this toxicity is dependent on the FUDR dose or length of time of administration is unknown, but studies of sclerosing cholangitis secondary to intrahepatic arterial infusion of FUDR[9,13,21–23] would suggest that such associations would be likely. It is also possible that future studies may observe this same toxicity from continuous infusion of 5-FU.

Finally, it is noteworthy that this patient had an excellent response to chemotherapy, being in complete remission 4 years and 4 months after the diagnosis of meatastatic renal cell cancer. Perhaps this toxicity will only be seen with prolonged FUDR treatment.

Conclusion

The administration of FUDR by continuous infusion can result in pulmonary toxicity manifest by dyspnea on exertion and a fall in DLCO. This toxicity appears to be reversible with the discontinuation of FUDR. The role of corticosteroids in the management of this toxicity is unclear.

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