Two cases of severe liver injury possibly related to 5-Fluorouracil and calcium folinate

5-Fluorouracil (5-FU) is used to treat a variety of tumours, often in combination with calcium folinate. The activity of 5-FU is associated with the inhibition of thymidylate synthase (TS), with calcium folinate prolonging the inhibition of thymidylate synthase.[1] 5-FU and calcium folinate have been shown to increase significantly 1-year survival in advanced colorectal cancer in a meta-analysis.[2] Whereas 5-FU causes multisystem toxicity, severe drug-induced liver injury does not appear to have been described except after hepatic arterial infusion.[3] In relation to combination therapy, a syndrome of ascites, hyperbilirubinaemia and hypoalbuminaemia, has been reported following 5-FU and *N*-phosphonacetyl-L-aspartate for the treatment of hepatic metastases.[4] There appear to be no reports of severe liver injury following 5-FU and calcium folinate. We describe two cases of severe drug-induced liver injury in association with bolus i.v. 5-FU and calcium folinate.

The first patient was a 66-year-old man who presented with jaundice 6 weeks after completing a 30-week course of once-weekly bolus i.v. 5-FU (750 mg) and calcium folinate (35 mg), for treatment of Duke's C colonic carcinoma. The patient had liver function tests (LFT) within normal limits before commencing chemotherapy, when he was not receiving any medication. At presentation, LFT showed a hepatocellular picture, with increased alanine aminotransferase (ALT) 866 U/L, aspartate aminotransferase (AST) 644 U/L, bilirubin 525 μmol/L, alkaline phosphatase (ALP) 170 U/L and γ-glutamyltransferase (GGT) 114 U/L. The International Consensus Criteria classifies

drug-induced liver injury using the *R* ratio, the ratio of serum activity of ALT to that of ALP, expressed as multiples above the upper limit of the normal range.[5] A ratio of >5 indicates hepatocellular damage, 2–5 illustrates a mixed picture and a ratio of <2 shows cholestasis. This patient's hepatocellular presentation ($R = 15$) rapidly evolved to a mixed picture ($R = 2$ to 4), which normalized 4 months after presentation. An abdominal ultrasound scan showed that the common bile duct was of normal calibre and there was no evidence of intrahepatic biliary duct dilatation. A liver biopsy showed typical features of intrahepatic cholestasis, which was reported to be consistent with a drug reaction. Causality was assessed using the Naranjo algorithm[6] and Roussel Uclaf causality assessment method (RUCAM),[5] the latter specifically designed for assessment of drug-induced liver injury. Both indicated that it was 'probable' that the liver injury was due to 5-FU and calcium folinate (scores of 6 and 7, respectively).

The second patient was a 62-year-old man who presented with jaundice and dark urine 2 weeks after receiving one cycle (daily for 5 days) of bolus i.v. 5-FU (750 mg) and calcium folinate (36 mg), following resection of a Duke's C carcinoma of the rectum. LFT at presentation showed increased ALT (433 U/L), AST (187 U/L), bilirubin (63 μmol/L), ALP (425 U/L) and GGT (487 U/L), suggestive of a mixed picture ($R = 3$). LFT before this presentation were within normal limits and an abdominal ultrasound scan at this time did not show any abnormalities. No further chemotherapy was given because of the temporal relation to 5-FU and calcium folinate. Within 2 weeks the transaminases had returned to normal, leaving a cholestatic pattern ($R < 1$). The ALP, bilirubin and albumin normalized within 4 months leaving a persistently increased GGT (3–4 times normal). The Naranjo[6] and RUCAM[5] algorithms both indicated 'probable' causality (scores of 6 and 8, respectively).

Response to 5-FU is thought to correlate inversely with thymidylate synthase concentrations and expression,[1] with calcium folinate prolonging the inhibition of thymidylate synthase. The expression of thymidylate synthase appears to be determined by the *TYMS* gene promoter, which is polymorphic, and has been shown to be a predictive factor of a wide range of 5-FU toxicities (defined as World Health Organization grades 3 and 4 toxicity).[7] In addition, dihydropyrimidine dehydrogenase, the enzyme responsible for the initial rate limited catabolism of 5-FU, has variable expression and is predictive of 5-FU-associated toxicity (myelosuppression and gastrointestinal toxicity). It is possible that our patients had a genetic predisposition to enhanced 5-FU effect, but this was not investigated. Regardless of this it is important to be aware of the possibility of severe liver toxicity with the i.v. combination of 5-FU and calcium folinate.

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