Regional lipiodolized chemotherapy for cholangiocarcinoma associated with oral contraceptives

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Summary: We describe a case of cholangiocarcinoma in a young woman, who presented with cholestatic jaundice following oral contraceptive ingestion. Following diagnostic laparotomy she received intra-arterial 'lipiodolized' chemotherapy. Intravenous mitozantrone was given for 2 years and she is asymptomatic, with computed tomographic evidence of tumour response, 27 months after diagnosis. We suggest that this form of treatment is of value for cholangiocarcinoma.

Introduction

Whilst there have been frequent reports of hepatocellular carcinoma in users of oral contraceptives, cholangiocarcinoma is rare. We describe such a case, which responded to 'T'-tube drainage and chemotherapy by intra-arterial and intravenous routes.

Case report

A 29 year old receptionist presented in August 1984 following two 5-day episodes of cholestatic jaundice in two months associated with pruritus and 12 kilogram weight loss. She had taken 'Ovranette' (levonorgestrel 250 µg and ethinyloestradiol 30 µg, Wyeth Laboratories), for one year (1977–1978) and 'Microgynon 30' (levonorgestrel 250 µg and ethinyl-oestradiol 30 µg, Schering Pharmaceuticals), for the 4 years before presentation, but had no previous illness.

Physical examination was unremarkable. Bilirubin was 32 µmol/l, aspartate aminotransferase (AST) 86 U/l (normal 10–40), alanine aminotransferase (ALT) 228 U/l (10–45), alkaline phosphatase (ALP) 813 U/l (35–120), gamma glutamyl transferase (GGT) 389 U/l (7–46), albumin 43 g/l (30–45); erythrocyte sedimentation rate (ESR) 45 mm in first hour; full blood count and prothrombin time were normal. Percutaneous cholangiogram and abdominal computed tomographic (CT) scan showed mass lesions involving the porta hepatis and laparotomy was performed. Multiple tumour masses were found in

both lobes of liver and the common bile duct. Biopsies were taken and a 'T'-tube inserted. All biopsies showed cholangiocarcinoma.

Post-operatively she had selective hepatic arteriography and intra-arterial chemotherapy infused, comprising doxorubicin 26 mg (0.5 mg/kg) in 1.25 ml of 'Urografin 290' (meglumine diatrizoate 52.1%, w/v, and sodium diatrizoate 7.9%, w/v, Schering Pharmaceuticals), and 5.0 ml of 'Lipiodol Ultra Fluid' (iodized oil fluid injection BP, May & Baker).

There were no complications following the procedure and she was discharged 5 days later with the 'T'-tube still in place but spigotted.

Subsequently she received mitozantrone 12 mg/m² 3-weekly for 2 years. Serial abdominal CT scans at 3, 6, 12, 18 and 24 months have revealed progressive reduction, of more than 50%, in the size of the original intrahepatic abnormalities and low attenuation of the tumour mass consistent with complete necrosis. She remains asymptomatic 27 months after laparotomy with her 'T'-tube *in situ* and has enjoyed a normal lifestyle since commencing chemotherapy. In March 1986 bilirubin was 8 µmol/l, AST 30 U/l, ALT 25 U/l, ALP 134 U/l and GGT 66 U/l.

Since she is at present asymptomatic, with satisfactory CT scan appearances, an observation policy is being pursued and no further surgery or chemotherapy is planned.

Discussion

Baum *et al.*¹ first reported the association of benign hepatic tumours and ingestion of oral contraceptives and many more cases have been reported. There have been numerous reports of hepatocellular carcinoma in

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oral contraceptive users.^{2, 3, 4} Ten cases of cholangiocarcinoma have been reported,^{2, 4, 5} and six cases of mixed cholangiocarcinoma and hepatocellular carcinoma.^{2, 3} However, the incidence of cholangiocarcinoma is low in women of reproductive years and a causal relationship with oral contraceptive use is difficult to demonstrate.

Following palliative 'T'-tube drainage our patient had a single dose of intra-arterial doxorubicin administered in lipiodol and urografin. This method ('lipiodolized' chemotherapy) has resulted in high tissue levels of doxorubicin in hepatoma with much lower levels in liver parenchyma after 16 days, giving an equivalent effect to that of prolonged intra-arterial infusion, without its risks. Lipiodol may also cause embolization of tumour as necrosis followed its use in hepatomas and 'lipiodolized' treatment was effective in producing tumour shrinkage before surgery in 10 of 13 hepatomas.⁶

The 27-month asymptomatic survival of this patient who had an unresectable tumour exceeds the median survival of under one year reported for similar patients who had palliative bypass for drainage⁷ and indeed compares favourably with results reported following radical resection.⁸ This is unlikely to be due to

withdrawal of hormone support from a hormone dependent tumour since other cases in the literature have not regressed following oral contraceptive withdrawal. The relative contributions of the initial intra-arterial therapy and the later prolonged intravenous chemotherapy to tumour regression are difficult to elucidate. Response of cholangiocarcinoma to any therapy would be expected to be slow in view of the known slow cell turnover in these tumours and the delayed regression over two years could be attributed to either or both modalities of treatment.

We emphasize the significance of oral contraceptive ingestion in young women who present with cholestasis and the importance of full investigations of such patients. In this case 'lipiodolized' intra-arterial chemotherapy appears to have been efficacious and we suggest that its value in the treatment of cholangiocarcinoma is worthy of further study.

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