Fatal hemobilia in advanced hepatocellular carcinoma invading biliary tract after treatment with sorafenib and biliary stenting

Sorafenib, a multikinase inhibitor, is now the standard treatment of advanced hepatocellular carcinoma (HCC) [1, 2]. Several clinical studies assessing sorafenib in advanced HCC have shown that it is generally a well-tolerated drug. The main side-effects are gastrointestinal disorders like diarrhoea and hand–foot syndrome [1–3]. No significant increase of hemorrhagic events was observed in cirrhotic patients with advanced HCC treated with sorafenib, even in patients with Child–Pugh B cirrhosis [4]. However, a recent meta-analysis showed a significant two-times increased risk of bleeding events with sorafenib and sunitinib [5]. Most events were of low grade, but some were reported as fatal, mainly in pulmonary neoplasms. In patients with advanced HCC treated with sorafenib, only one bleeding-related death due to intracranial haemorrhage was reported [3, 5].

We report here for the first time two cases of fatal hemobilia in patients who presented with HCC invading biliary tract and who received sorafenib after optimal endoscopic biliary drainage.

These two patients with cirrhosis of liver were admitted to the hospital for jaundice and the radiological investigations including a magnetic resonance imaging cholangiopancreatography revealed hypervascularised tumour, evocating HCC, with tumoural biliary luminal invasion. Aiming to relieve obstructive jaundice, endoscopic retrograde cholangiopancreatographic examinations were carried out for both patients. For patient 1, three plastic stents were placed into the right and left hepatic ducts, and for the second patient, a metallic stent was placed into the common bile duct. Cytologic analysis from biliary brushing was positive for malignant cells in the two cases.

After stenting, patients recovered well with Eastern Cooperative Oncology Group performance status 0 and Child B – Pugh 7 score due to the persistence of an elevated bilirubin; there were no other abnormalities indicating profound liver function impairment. Sorafenib was started, in both patients/C24 3 weeks after stenting, at the dose of 400 mg twice daily.

After sorafenib therapy, both patients were admitted to the emergency unit with hemorrhagic shock on the 7th and 2nd day, respectively.

In both cases, upper gastrointestinal endoscopy showed fresh blood emerging from the biliary stent and endoscopic retrograde cholangiopancreatography confirmed the hemobilia. Both patients died of hemorrhagic shock, despite supportive care, transfusion of blood products, endoscopic procedures and attempt at angiographic embolisation.

To our knowledge, these are the first reports of fatal uncontrollable hemobilia in patients with advanced HCC treated with a short course of sorafenib.

The peculiarity of these two similar cases was the biliary luminal invasion by the tumour (hilar tumour in case 1 and metastatic lymph nodes in case 2) causing obstructive jaundice and requiring endoscopic biliary stenting.

In these cases, questions should arise concerning the eventual relationship between sorafenib and bleeding occurring from hypervascular tumours invading the biliary tract. Indeed, the cause and as well as the timing of the observed events clearly indicate a close relationship between sorafenib administration and subsequent hemobilia, despite a short course of treatment. One may also question the additional role of stenting procedures to account for the bleeding episodes.

In summary, these two cases raise the question of potential contraindication of sorafenib in advanced HCC with direct involvement of the biliary ducts requiring endoscopic stenting. The safety and dosage of sorafenib in this particular subgroup of advanced HCC patients must be evaluated more widely.

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disclosure

None of the authors declare conflicts of interest.

references


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