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MINI REVIEW

UGT1A1 polymorphism and hyperbilirubinemia in a patient who received sorafenib

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Abstract
Purpose To report a single case of uridine glucuronosyltransferase 1A1 (UGT1A1) polymorphism and hyperbilirubinemia in a patient who received sorafenib.
Methods A 63-year-old man with cirrhosis was diagnosed with hepatocellular carcinoma. His cirrhosis was categorized as Child-Pugh A, total bilirubin concentration was 24 μmol/L (normal range <20 μmol/L). The patient was enrolled in a phase I trial combination study of cyclophosphamide and doxorubicin combined with sorafenib.
Results After a single infusion of doxorubicin and cyclophosphamide and 7 days of sorafenib, he presented with an elevated bilirubin concentration (48 μmol/L). Unconjugated bilirubin was 38 μmol/L and conjugated was 10 μmol/L. The patient was found to have one mutant allele (*UGT1A1*28*).
Conclusions The isolated increase in serum bilirubin levels in our patient was probably due to sorafenib-induced UGT1A1 inhibition that manifested itself due both to the patient having one *UGT1A1*28* allele and the presence of underlying liver disease. Bilirubin elevations in patients treated with sorafenib could indicate progression or drug toxicity; hence, these possibilities need to be ruled out. We would suggest that when patients develop hyperbilirubinemia while taking sorafenib for any indication, consideration be given to obtaining a fractionation of bilirubin and consideration of UGT1A1 genotyping in order to exclude a Gilbert's syndrome as possible reason for the hyperbilrubinemia. Further studies are warranted to analyze the impact of sorafenib treatment on unconjugated bilirubin blood levels in patients with Gilbert's syndrome.

Keywords Hepatocellular carcinoma · Sorafenib · Hyperbilirubinemia · UGT1A1 polymorphism

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Case report

A 63-year-old Caucasian male with a history of hepatitis C virus infection since 1997 was diagnosed in November 2007 with stage I (T1, N0, M0) hepatocellular carcinoma (HCC). He also had cirrhosis-induced portal hypertension, manifested by esophageal varices, hypertensive gastropathy, and hemorrhoids. The patient was treated with nadolol for portal hypertension, and had no other concomitant medications. He received one session of transarterial chemoembolization, but developed perihepatic lymph node metastases (confirmed by biopsy) in April 2008. The patient was then enrolled in a phase I trial of doxorubicin, cyclophosphamide, and sorafenib. At the time of study enrollment, his cirrhosis was categorized as Child-Pugh class A, total bilirubin concentration was 24 μmol/L (normal value, <20 μmol/L), serum albumin concentration was 37 g/L (normal range, 35–50 g/L), and INR was 1.1 (0.8–1.2). Neither ascites nor encephalopathy was present.

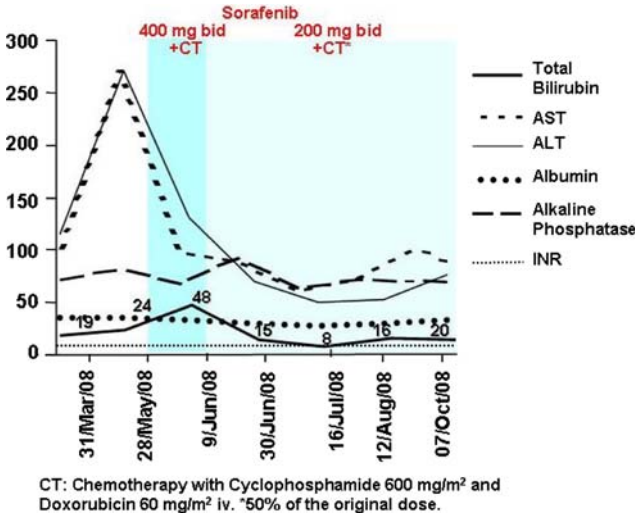

Fig. 1 Behavior of liver function markers

Alanine transaminase (ALT) was 271 U/L (0–50 U/L), aspartate transaminase (AST) was 271 U/L (0–40 U/L), and alkaline phosphatase was normal (82 U/L).

After a single infusion of cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2) and treatment with sorafenib 400 mg twice daily for 7 days, he was found to have a twofold increase in bilirubin concentration to 48 µmol/L. Interestingly, albumin and alkaline phosphatase levels remained stable, whereas AST and ALT concentrations did subside (Fig. 1). Given that isolated increases in serum bilirubin levels are not a common adverse event in patients treated with sorafenib, particularly in patients with Child-Pugh A cirrhosis [1–3], and because the patient's mild bilirubin elevation prior to treatment was discordant with the minimal involvement of his liver, we proceeded to fractionate his bilirubin and genotype him for uridine diphosphate glucuronosyltransferase (UGT) 1A1. His hyperbilirubinemia was predominately unconjugated; unconjugated bilirubin was 38 µmol/L; conjugated fraction was 10 µmol/L. In terms of UGT1A1 genotype, the patient was found to have one mutant allele (*UGT1A1*28*); approximately 40 ng of the patient DNA was subjected to amplification by polymerase chain reaction (PCR); the amplification primers used have been previously described [4]. Control DNAs from individuals known to have a 6/6, 6/7 and 7/7 genotype were included in the genotype analysis. A 98 and 100 bp fragment pattern was obtained for the patient indicative of a 6/7 genotype. After 4 months of sorafenib treatment, serum bilirubin concentration had normalized to 21 µmol/L but was 100% unconjugated. Currently, he is continuing to receive sorafenib at a reduced dose due to hand–foot skin reaction (HFSR), as well as the same regimen of cytotoxic chemotherapy at 50% of the original dose, with better tolerance and achievement of stable disease.

Discussion

At present, around 20 different UGTs have been identified in humans and rats, classified into two families—UGT1 and UGT2—according to their sequence homology. Many of them exhibit tissue specific patterns of expression; factors that determine these patterns have not yet been clarified [5]. UGT1A1 is the most abundant UGT1 isoform expressed in liver; and is involved in bilirubin glucuronidation. More than 100 genetic variants of this isoform have been described. Homozygosity for *UGT1A1*28* is associated with Gilbert's syndrome, a mild unconjugated nonhemolytic hyperbilirubinemia, which does not lead to hepatitis or chronic liver disease, and usually remains undiagnosed. Approximately 40% of Caucasians have at least one *UGT1A1*28* allele, and the incidence of Gilbert's syndrome in this population is approximately 5–10% [6, 7]. The clinical phenotype may not be apparent as frequently as the determined genotype, due to environmental factors such as alcohol-induced hepatic bilirubin glucuronidation, reducing serum bilirubin levels and causing a latent condition; drugs, smoking, age and gender might affect the measured phenotype; indicating that the UGT1A1*28 genotype has an incomplete penetrance [8–10]. UGT1A1 plays an important role in metabolizing chemotherapeutic agents, including the well-characterized example of irinotecan [11]. UGT1A1 may also have a role in etoposide metabolism [12].

Sorafenib is a novel, multi-targeted anticancer agent that prevents tumor growth by inhibiting tumor-cell proliferation (via the Raf/MEK/ERK signaling pathway), and tumor angiogenesis (by targeting the receptor tyrosine kinases of vascular endothelial growth factor 2 and 3, and platelet-derived growth factor). After its oral administration, 19% of the dose is excreted in urine, almost exclusively as glucuronide conjugates of parent drug or metabolites, and 77% of the dose is excreted in feces (50% as unchanged drug) [3, 13, 14]. Sorafenib is subjected to two biotransformation pathways in humans: cytochrome P450 3A4 (CYP3A4)–mediated oxidation and UGT1A9–mediated glucuronidation. Due to the contribution of these two biotransformation pathways, sorafenib is considered less susceptible than other agents to drug–drug interactions with CYP3A4 inhibitors. Sorafenib in vitro is a moderate-to-strong inhibitor of CYP2B6 and CYP2C8, and a strong inhibitor of UGT1A1 and 1A9. Therefore, it may increase exposure of drugs that are metabolized by these pathways [15]. Theoretically, sorafenib could cause elevations of bilirubin due to UGT1A1 inhibition in susceptible individuals with low UGT1A1 levels, such as patients with Gilbert's syndrome. In these individuals, the hyperbilirubinemia would be expected to be predominately unconjugated.

Patients receiving sorafenib generally have a low incidence of significant hematologic side effects. Patients may

experience hypertension, which is manageable, and transient skin-related symptoms manifested either as HFSR or as rash. Fatigue and diarrhea are also common, but generally of low-to-moderate grade. These toxicities commonly resolve once sorafenib is discontinued or after dose adjustment. In a phase II trial, elevated bilirubin levels occurred in 18% of 98 patients with HCC and Child-Pugh A liver disease, and in 40% of 38 with HCC and Child-Pugh B liver disease; notably, elevation of bilirubin was not associated with worsening of other liver enzymes [16]. Elevated bilirubin levels in patients with advanced renal cell carcinoma (RCC) treated with sorafenib have not been reported in phase II or III trials [17, 18]. However, hepatic side effects, including AST and ALT elevations, were present in patients enrolled in a phase II trial performed in patients with metastatic RCC (all grades, 29%; grade 3, 5%; grade 4, 0%) [18]. Furthermore, an increase in bilirubin has not been described as common adverse event of either nadolol given for prophylaxis against esophageal varices in patients with cirrhosis [19] or the AC regimen (doxorubicin and cyclophosphamide). AC chemotherapy is mainly used for breast cancer patients, as neoadjuvant, adjuvant or palliative intent; hyperbilirubinemia and or hepatotoxicity are not common side effects; in fact, several randomized trials have not reported this finding when doxorubicin and cyclophosphamide are administered at standard doses 60 and 600 mg/m^2, respectively, or higher doses [20–24].

It is interesting to note that the frequency of bilirubin elevations closely approximates the allele frequency of *UGT1A1*28*. We speculate that in our patient, UGT1A1 inhibition by sorafenib led to his hyperbilirubinemia. Adding further credence to this possibility was the observation that initially, the bilirubinemia was predominately unconjugated, but after 4 months of sorafenib treatment serum bilirubin concentration had normalized to 21 μmol/L but was 100% unconjugated. The patient's UGT1A1 levels were likely lower than normal for several reasons, including the fact that he carried one *UGT1A1*28* allele, the presence of hepatitis C infection, and the presence of cirrhosis.

We hypothesize that carriers of *UGT1A1*28* with underlying cirrhosis can have significant inhibition of UGT1A1 by sorafenib. With almost 40% of Caucasians having this genotype and an incidence for bilirubinemia in non-HCC patients of less than 5%, routine genotyping for UGT1A1 in all patients is not justified. Should the bilirubin increase during the first cycle of sorafenib treatment, a bilirubin fractionation should be performed to determine if the bilirubin is predominately unconjugated. If the unconjugated bilirubin is not approximately 80% or greater of the total bilirubin the patient may be experiencing hepatotoxicity or disease progression.

Conclusion

The isolated increase of serum bilirubin levels in our patient was probably due to sorafenib-induced UGT1A1 inhibition that manifested itself due both to the patient having one *UGT1A1*28* allele and the presence of underlying liver disease. Bilirubin elevations in patients treated with sorafenib could indicate progression or drug toxicity; hence, these possibilities need to be ruled out. We would suggest that when patients develop hyperbilirubinemia while taking sorafenib for any indication, consideration be given to obtaining a fractionation of bilirubin because UGT1A1 inhibition may be a benign cause of hyperbilirubinemia in patients treated with sorafenib; it may be prudent while awaiting results of bilirubin fractionation to hold sorafenib as this will take less than 24 h in most institutions. If the bilirubin is not predominately unconjugated, other causes such as disease progression causing biliary obstruction are needed to be considered. In the case of our patient, he continued treatment with sorafenib without ill effects and experienced stabilization of his HCC. Further studies are warranted to analyze the impact of sorafenib on increases of unconjugated bilirubin and the association with Gilbert's syndrome.

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