Long-term response of hepatocellular carcinoma to sorafenib in a patient with HFE-haemochromatosis

ABSTRACT
In the literature there has been only one case report of cirrhotic patient with hepatocellular carcinoma (HCC) and with a history of hereditary haemochromatosis treated with sorafenib for six months. Herein, we describe a case of a primary non-cirrhotic patient who was incidentally diagnosed with haemochromatosis during prolonged therapy with sorafenib due to HCC. A 53-year-old primary non-cirrhotic man with advanced HCC was treated with sorafenib at 400 mg twice daily since October 2010 following percutaneous ablation treatment of the largest nodule. He was seronegative for hepatitis B and C virus. After two years of kinase inhibitor therapy, the liver changes with cirrhotic features suggesting hemochromatosis were discovered on repeated imaging. The diagnosis of associated iron-overload disease was confirmed by genotypic expression — he was homozygous for the HFE gene C282Y mutation. Maintaining cancer stabilisation by continuing sorafenib therapy at the fixed standard dose for six years, he has undergone thirty-five phlebotomies until now.

Key words: hepatocellular carcinoma, hemochromatosis, sorafenib

Introduction
Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with increasing incidence, and is the third most frequent cause of cancer-related death worldwide. Most HCC patients present with advanced and multifocal disease at the time of diagnosis and are of poor prognosis. Cirrhosis, which is present in approximately 80–90% of HCC patients, is the most important risk factor for this malignancy regardless of aetiology and may be caused by chronic viral hepatitis, alcoholic liver disease, autoimmune disease, exposure to hepatotoxins, and metabolic disease including haemochromatosis, alpha-1 antitrypsin deficiency, as well as non-alcoholic fatty liver disease associated with obesity, insulin resistance, and type 2 diabetes [1]. Several environmental factors and molecular abnormalities are additional risk factors for this malignancy [1–3]. Co-existence of multiple causes of liver injury increases the risk of HCC development.

Altered iron homeostasis is one of the processes leading, via chronic liver damage, to HCC development [1, 2]. Significant iron deposition, in the absence of hemochromatosis, in cirrhotic livers of various cases of cirrhosis was documented [4]. Hereditary hemochromatosis is an autosomal recessive disorder that leads to progressive iron accumulation, with nonspecific symptoms such as cirrhosis, diabetes mellitus, cardiomyopathy, and endocrinopathy, which typically begin in adulthood. This disease is not uncommon in the Caucasian population. It is associated with an increased risk of HCC, which occurs predominantly in patients with cirrhosis at the time of diagnosis. The genetics of hemochromatosis are complex with strong environmental disease modifiers [5]. Most cases have been linked to mutations in genes
associated with iron homeostasis. There have been three major variants in the high Fe (HFE) gene associated with the disease: C282Y, H63D, and S65C. The clinical penetrance of these mutations is highly variable. The homozygosity for the C282Y polymorphism in the HFE gene accounts for > 80% of haemochromatosis iron phenotypes in Caucasians, and occurs in 0.3–0.6% of persons of European descent [5]. The clinical penetrance of iron overload in many C282Y homozygotes is mild [6]. The HFE 282Tyr mutation almost completely prevents the formation of a complex between the mutant HFE protein and the transferrin (TF) receptor (TFR), allowing high-affinity TF binding to the TFR. This binding results in an increased cellular uptake of iron [7]. A second missense mutation in the HFE gene, H63D, is found in about 4% of patients with hereditary haemochromatosis, but its role in iron overload is still debated [7]. Rare, non-HFE-related hereditary iron overload includes defects of genes TFR2, which codes for the second TFR, and HAMP and HJV, which code for hepcidin and haemojuvelin, respectively, which are responsible for juvenile haemochromatosis. Moreover, ferropor- tin disease (a special dominantly inherited clinical form of iron overload due to JK mutations of the SLC40A1 gene) and inherited mutations in the ceru- loplasmin gene (acueruloplasminaemia), which lead to the impairment of iron release from cells [8, 9]. As well as acquired or environmental, other genetic fac- tors may influence iron absorption or iron stores. For instance, GNPAT D519C was reported recently as a factor strongly associated with markedly increased iron stores in C282Y homozygotes [6].

A 19-fold increased risk of HCC among C282Y homozygotes with cirrhosis due to chronic viral hepatitis and alcoholic liver disease was demonstrated [10]. In this study the other HFE allele constellations (C282Y/H63D compound heterozygotes, H63D homozygotes) were not associated with the increased risk of HCC.

Sorafenib, an oral multikinase inhibitor with activity against Raf-1, B-Raf, VEGFR-2, PDGFR, and c-Kit receptors, has a potent antiangiogenic and proapoptotic activity and, therefore, presents a marked antitumoral effect, including HCC. Sorafenib has become a standard therapy in advanced HCC on the basis of the results reported by two randomised, placebo-controlled trials: the SHARP (Sorafenib HCC Assessment Randomised Protocol) and the Asia-Pacific trial [11, 12]. In these tri- als, the median time to progression and overall survival were 5.5 months and 2.8 months, and 10.7 months and 6.5 months, respectively.

Here we present a case of a primary non-cirrhotic patient incidentally diagnosed with hereditary haemochromatosis during prolonged therapy with sorafenib due to advanced HCC.

**Case report**

A 53-year-old, non-cirrhotic man (Child-Pugh class A) with HCC started sorafenib treatment at 400 mg, orally, twice daily in October 2010. Previously, between July and September 2010, he underwent three percu- taneous ethanol injections (PEIs) of the largest liver nodule. HCC was revealed incidentally in February 2010 based on ultrasound and computed tomography (CT) during a diagnostic process of alopecia and fatigue (Fig. 1A), and was confirmed by a liver biopsy (Figure 2A and B). At that time, no cirrhosis was found. The patient denied alcohol abuse and hepatitis infection. He had well-controlled hypertension. His father died due to gastric cancer, and his twin was diagnosed with colon cancer. His Eastern Cooperative Oncology Group (ECOG) performance status was 1. Physical examination revealed hepatomegaly and mild skin hyperpigmentation. The liver function parameters were mildly elevated (transaminases ALT and AST, CTC grade 1), alpha-fetoprotein (AFP) level was normal.

![Figure 1. CT liver scans.](image-url)
In November 2014 the patient was successfully treated due to a heart attack with balloon angioplasty on second obtuse marginal (OM 2) branch and drug-eluting stent implantation (DES) on the left anterior descending artery. He is being administered acetylsalicylic acid, clopidogrel, lercanidipine hydrochloride, carvedilol, nebivolol, and indapamide.

Hand-foot skin reaction (HFSR) (grade 2, resolved to grade 1) was the only adverse event he experienced during sorafenib therapy. He remains in good condition, and his ECOG performance status is 1. The liver function parameters continue to be mildly elevated (transaminases ALT and AST; CTC grade 1), and glucose and AFP levels are within the normal range.

**Discussion**

The case reported here presents HCC developed in the absence of cirrhosis, an event generally infrequent, also in haemochromatosis individuals. A meta-analysis that included nine studies (1102 HCC cases and 3766 controls), mainly from European populations, provides evidence that the \( HFE \) C282Y polymorphism confers increased genetic susceptibility to HCC but not to liver cirrhosis [7]. This analysis did not find an association of H63D mutation with HCC. The role of \( HFE \) C282Y as well as compound heterozygosity for C282Y/H63D in an increased HCC risk, but not liver cirrhosis, was confirmed recently in an updated systematic review and meta-analysis of 5758 cases and 14,741 controls [13]. Additionally, H63D polymorphism in developing non-cirrhotic HCC in the African population.

The relationship between iron and HCC is complex [14]. Iron can act as a modulating co-factor in a range of chronic liver diseases and can accelerate the development of liver injury, fibrosis, cirrhosis, and ultimately HCC. Pollicino et al. [15] reported a case of a 43-year-old man with HFE-haemochromatosis, seronegative for hepatitis B and C infections, who developed HCC in the absence of severe liver damage. An occult HBV infection was found based on the molecular analyses, performed on both tumoural and non-tumoural liver tissue specimens taken at the time of orthotopic liver transplantation due to HCC recurrence. The authors suggested that the combination of haemochromatosis and occult HBV infection might have led to a sequence of cellular events that determined the development of HCC even in the absence of cirrhosis.

HCC arising in non-cirrhotic liver in genetic haemochromatosis has already been a subject of case reports [2, 16]. Co-existence of HCC and haemochromatosis in a patient receiving sorafenib is a rare real-life condition,
with scarce clinical data. So et al. [17] reported a patient with a 25-year history of hereditary haemochromatosis, with cirrhosis and unresectable metastatic HCC, who had a rapid and clinical response during six months of sorafenib therapy, and this effect was maintained for six months after therapy discontinuation. His serum AFP level was found to be 13.599 ng/mL. This patient tolerated the therapy well, except for the onset of grade 1 diarrhoea, which was well controlled without dose reduction. Our patient is the second reported case treated with sorafenib due to HCC coexisting with haemochromatosis.

The question arises whether a test for haemochromatosis should be incorporated into the initial work-up in our patients. Universal screening for haemochromatosis is not recommended [18]. On the other hand, the majority of patients with haemochromatosis, without timely appropriate treatment, develop hepatic fibrosis and cirrhosis due to hepatic iron accumulation. Thus, in the case of haemochromatosis it is recommended that ultrasound surveillance are conducted at intervals of 3–6 months [19–21]. In this case, advanced serum ferritin level assessment and prior diagnosis of haemochromatosis would provide earlier introduction of treatment, and consequently might reduce the risk of damage of the liver and other organs. Serum ferritin measurement, as was used in our patient, is the most useful parameter in the diagnosis and monitoring of iron loading disease. There are, however, several clinical conditions that are associated with high ferritin, including inflammation, cell necrosis, neoplasms, and alcohol consumption [5]. Among other serum iron parameters, namely low (or normal) total iron-binding capacity (TIBC) or as an alternative to TIBC unsaturated iron binding capacity (UTIBC) and high serum iron, elevated transferrin saturation index (TSI) along with hyperferritinaemia are the principal biochemical findings in haemochromatosis [5]. Of note, in this patient the serum AFP level continues to be within normal range.

Hepatic resection, liver transplantation, and ablative therapies, including open and percutaneous radiofrequency (RFA) and PEI, are, according to the guidelines, the first-line treatment options for HCC [19, 22]. Ablation methods are recommended in cases of unresectable early HCC. The preferred method of local treatment in this group of patients is RFA or, less popular in clinical practice, PEI, which was used in our advanced HCC case. Patients with intermediate and advanced HCC undergo different TACE (transarterial chemoembolisation) modalities, such as selective TACE or drug-eluting beads (DB-TACE), or systemic therapy. Recently, transarterial radioembolisation (TARE) using microspheres of Yttrium-90 is being introduced. Moreover, recent approaches combine TACE with RFA or TACE with sorafenib [19, 23]. The role of radiotherapy in HCC needs further evaluation [24].

Disease stabilisation, as achieved in our patient, is typical with sorafenib therapy for HCC. Except for the above case of the patient described by So et al., the phenomenon of complete response of HCC following sorafenib therapy has been reported by others [25]. Further advances in the identification of biomarkers predicting prognosis of HCC and response to sorafenib or other treatments for this condition may facilitate more personalised treatment in such oncological patients [26, 27].

The toxicity profile of sorafenib therapy is generally mild and manageable. The most common adverse effects of sorafenib are diarrhoea, fatigue, weight loss, and HFSR or palmar-planar erythrodysesthesia syndrome. However, serious toxicities, mostly diarrhoea and HFSR, led to discontinuation of sorafenib treatment in 11% of patients entered into randomised trials [11, 12]. In the presented case of HCC associated with haemochromatosis with evidence of active liver disease, no worsening of liver function was observed, and a full standard dose of sorafenib could be maintained for six years of the therapy.

In conclusion, HCC coexisting with haemochromatosis in a patient without cirrhosis is rare. Sorafenib is an effective and well-tolerated long-term therapy in HCC patients with associated haemochromatosis. This iron-overload disease should be kept in mind in patients who develop HCC.

References


