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Case Report

Complete Response to Sorafenib in an HCV/HIV Coinfected Patient with Infiltrative Hepatocellular Carcinoma and Portal Vein Thrombosis

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Abstract

The case presented here is one of the few documented instances in the literature of a complete response to sorafenib in an infiltrative hepatocellular carcinoma (HCC) and the only one in an HCV/HIV coinfected patient. The patient, already affected by chronic HCV-related liver disease and HIV on antiretroviral therapy, was diagnosed with infiltrative HCC with portal vein thrombosis. A treatment regimen with sorafenib was initiated, resulting in a complete response and normalization of the AFP marker. Sorafenib therapy was thus discontinued after more than five years, with no recurrence noted on subsequent follow-up visits.

This case, unique in the literature due to the patient's dual HCV/HIV+ status, highlights that although exceedingly rare, complete responses to sorafenib are possible. Additionally, the scarcity of complete response cases underscores the issue of timing for therapy discontinuation, demonstrating that long-term treatment can be feasible and well-tolerated even in patients with multiple comorbidities.

Keywords: Infiltrative hepatocellular carcinoma; Sorafenib; HIV+/HCV+; portal vein thrombosis; TKI; complete response.

Introduction

Hepatocellular carcinoma (HCC) ranks as the fourth leading cause of cancer-related deaths worldwide and is responsible for 75%-85% of primary liver cancers. The primary risk factors for HCC include viral hepatitis, alcohol-related liver disease, and non-alcoholic fatty liver diseases, with these latter factors being one of the main causes of increased incidence of HCC cases in Western countries [1-3].

Sorafenib, an oral multi-tyrosine kinase inhibitor (TKI) blocking VEGFR, RAF, c-KIT, and PDGFR-β has represented for many years the standard first-line systemic treatment of advanced HCC [4].The European multicenter SHARP trial reported a median overall survival (mOS) of 10.7 months in sorafenib-treated patients compared to 7.9 months in the control group, but with a low objective response rate (2% of partial responses), and no cases of complete response [5]. The treatment scenario of HCC

changed with the results of two recent large randomized phase 3 trials, the IMbrave150 and the HIMALAYA trials, which showed the superiority of immune checkpoint inhibitor (ICI) atezolizumab plus anti angiogenic bevacizumab or ICI combination durvalumab plus tremelimumab over sorafenib [6,7]. Since then, the role of sorafenib is now confined as a subsequent therapy or when the previously mentioned combination therapies are contraindicated.

Infiltrative HCC accounts for approximately 7–20% of all HCC cases and it is characterized by the dissemination of small nodules that can spread throughout the liver parenchyma. It is also linked to a high likelihood of portal vein invasion and thrombosis (68–100%) [8, 9]. The dissemination and vascular invasion characteristic of this HCC subtype make surgical resection and local regional treatments particularly challenging, resulting in a poorer prognosis compared to other subtypes. However, systemic treatments approved for other HCC subtypes remain the standard of care for this variant as well.

In our case report, we describe the case of a clinical and radiological complete response to sorafenib in an HCV/HIV coinfected patient with infiltrative HCC and portal vein thrombosis.

Case Presentation

In July 2005 a 43 years-old Caucasian male patient was diagnosed with active genotype 3a hepatitis C and he was subsequently treated with PEG-IFN and ribavirin, achieving a sustained virologic response. Moreover, a previous occult HBV infection was detected. A few years later, the patients tested positive for HIV infection, and was first treated with abacavir/lamivudine/zidovudine (from 2007 to 2014,) later simplified to abacavir/lamivudine (2015) and then, after an acute myocardial infarction, he was switched to nevirapine-raltegravir therapy from 2015 onward, with good viral and immunological control.

In May 2018 the patient presented at our institution with severe abdominal pain and fever. A contrast-enhanced chest-abdomen computed tomography (CT) scan showed the presence of portal vein thrombosis extending from the confluence of the splenic vein and superior mesenteric artery to the origin of segmental branches, along with cavernous transformation and diffuse heterogeneity of liver parenchyma with several nodular lesions (Figure 1). The first alpha-fetoprotein (AFP) level measured 37619 ng/mL at diagnosis. Based on CT images, AFP levels, and the concomitant chronic liver disease, a diagnosis of diffusive infiltrative HCC with neoplastic portal vein thrombosis was performed [10].

In June 2018 sorafenib therapy was initiated at a reduced dose of 600 mg/day due to suboptimal clinical conditions. During hospitalization, anticoagulant therapy was started, and antiretroviral therapy was changed to emtricitabine/tenofovir disoproxil plus raltegravir. Furthermore, due to severe abdominal pain that limited performance status of the patient (ECOG PS 1), analgesic therapy with opioid was started.

In the following months there was a progressive improvement in the patient's clinical condition, in particular a significant pain relief with complete cessation of pain medication, weight gain, and resumption of work activities. The first CT scan after the start of therapy, performed on September 2018, showed disease stability, while AFP levels started a rapid and progressive decline and its complete normalization by March 2020, 19 months after starting treatment.

Since July 2019, due to the onset of grade 1 hand-foot syndrome (HFS), the dose of sorafenib was further reduced to 400 mg/day. In September 2020, due to grade 2 HFS recurrence, a personalized dosing schedule was implemented: 200 mg for 21 days, followed by a break of 7 days. This regimen was maintained with good tolerance until treatment discontinuation. Notably, during treatment with sorafenib, the patient continued the antiretroviral therapy, maintaining adequate viral control and leading a fully normal life. The antiretroviral therapy was modified in December 2022, in favour of dolutegravir plus lamivudine.

Subsequent CT scans showed progressive reduction in the thrombosis and in the parenchymal infiltration (Figure 2). In February 2024a 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) scan showed no focal tracer hyper-fixation points, and in April 2024, a hepatospecific contrast-enhanced MRI revealed significant improvement in the thrombosis, with loss of the previously noted neoplastic thrombus and absence of parenchymal lesions (Figure 3).

Given the complete response observed at radiological scans and the normalization of the biomarker AFP, the decision was made to discontinue treatment and keep the patient under close clinical and radiological surveillance. Subsequent contrast-enhanced abdominal CT scans, performed every three months, and monitoring of AFP levels, showed no disease recurrence. At the time of the publication of this article, the patient is still alive, leading a normal life, and continuing his follow-up program.

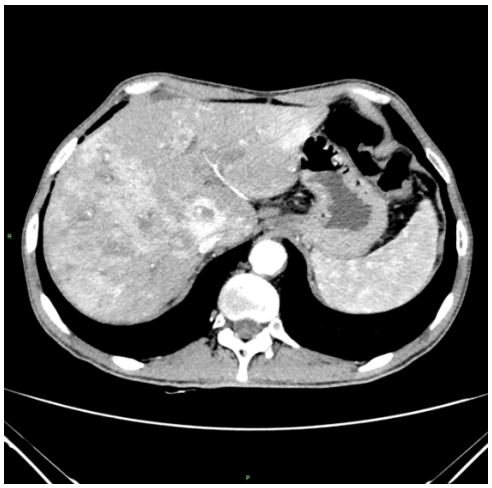

Figure 1: May 2018: Axial CT image in the late arterial phase shows enhancing nodules and neoplastic thrombosis, consistent with infiltrative HCC.

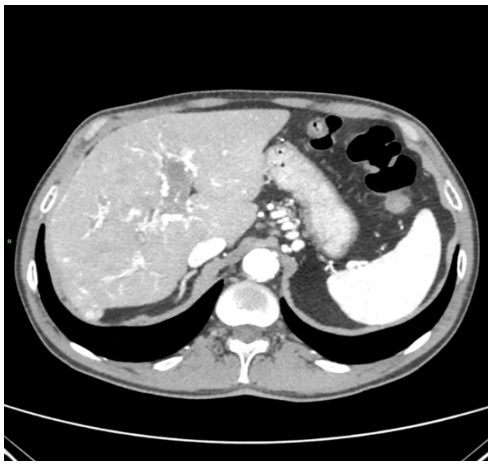

Figure 2: March 2021: Axial CT image in the late arterial phase shows complete resolution of the nodular areas, with persistent but non-vascularized thrombosis.

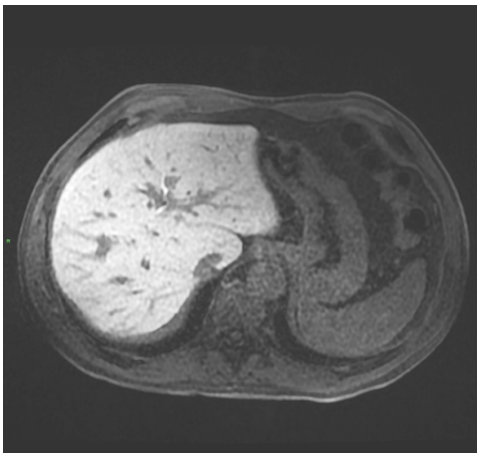

Figure 3: April 2024 MRI hepatobiliary phase image with hepato-specific agent showing complete response on liver parenchyma.

Discussion

For many years sorafenib has represented the standard first-line treatment for HCC, before the approval of atezolizumab/bevacizumab and durvalumab/tremelimumab combinations. The disease control rate achieved with sorafenib is typically due to disease stability. The rate of partial response to sorafenib is notably lower compared to the other possible treatments (11% in IMbrave150, 5% in Himalaya and 2% in SHARP trial) [5-7]. Usually, complete responses are a sporadic event in patients with HCC, occurring in 1% of patients in the IMbrave study and 0% in Himalaya trial and the SHARP study, with only few cases documented in the literature [11-14]. Our patient, who received diagnosis of infiltrative HCC with clinical and laboratory features of aggressive disease like elevated AFP and severe abdominal pain, experienced a sustained complete response with associated prolonged significant clinical benefit.

A possible reason for the remarkable effects of sorafenib observed in this case is the concomitant HIV therapy. In fact, another paper reported the case of a complete response in a patient with HBV/HIV infection showing regression under HAART therapy, suggesting a potential synergistic effect of HAART, and particularly of HIV protease inhibitors with sorafenib [15].

However, our case is particularly unique due to the presence of HIV-HCV coinfection, as there are no other documented cases of complete response to sorafenib in infiltrative HCC in such patients. HIV positivity in HCC patients warrants further investigation; in developed countries, it is estimated that approximately 25% of HIV patients are HCV positive, while 6-14% are HBV positive [16]. With the advent of HAART, the survival of HIV+ patients has improved, increasing the prevalence of HBV or HCV related-hepatitis among these patients, and HCC has thus emerged as a common non-AIDS defining cancer [17].

The uniqueness of this case is also supported by a French study, which compared two cohorts of HIV+/HCV+ versus HIV-/HCV+HCC patients, finding a significantly higher incidence of infiltrative HCC in the HIV+/HCV+ cohort, generally with a poorer prognosis in this subgroup [18]. However, data on the efficacy of available therapies in HIV+ patients remain limited, as HIV infection is an exclusion criterion in most studies, so the available data comes primarily from clinical practice, with its inherent limitations.

Another noteworthy aspect of this case is the extended treatment duration, approximately 5 years and 8 months, which sparks the question of when to stop oncological treatments in cases of complete response. A Korean case series reported that between 523 patients with advanced HCC, seven achieved complete response with sorafenib therapy. Of those 7 cases, 5 patients underwent continuous treatment with sorafenib, of which only one experienced a recurrence, on the other hand 2 patients stopped treatment and both experienced a recurrence [13]. In a Spanish case series of 1119 patients, 12 showed a complete response; of these, 5 patients did not stop sorafenib and had no recurrence, while 7 patients interrupted the therapy, with 5 of them experiencing a disease recurrence [14].

The HFS was reported as one of the most frequent G3 adverse effect of the SHARP trial [5]; similarly, it was the only significant adverse effect observed in our patient. Furthermore, dermatological toxicity in general appears to be associated with improved survival and it is almost always present in patients who have achieved response to the treatment [14,19]. Other potential side effects associated with prolonged exposure to sorafenib and other tyrosine kinase inhibitors are cardiovascular and nephrological toxicities [20]. In the case of our patient, due to the lack of conclusive data on recurrence rates following complete response and considering the patient's treatment tolerance, a customized schedule was devised (200 mg for 21 days, followed by a break of 7 days), allowing prolonged treatment duration while allowing the patients to maintain a good quality of life during treatment.

A limitation of our study is the lack of a biopsy, which, although not mandatory for an HCC diagnosis, would have been useful in assessing molecular patterns that might predict response to sorafenib, especially given the exceptional response achieved.

Conclusion

We report a rare case of an HCV/HIV coinfected patient with infiltrative HCC and portal vein thrombosis which demonstrated a complete and sustained response to sorafenib. Additionally, this case shows the feasibility and, arguably, the necessity of personalizing treatment during prolonged therapies to maximize patient tolerance. The timing of treatment discontinuation in patients with complete response is still unclear, given the lack of robust data. Further studies that aim to investigate the mechanism and predictive factors of complete response to TKIs including the potential concomitant role of viral aetiology are needed.

Declarations

Contributors: All authors contributed to planning, literature review and conduct of the review article. All authors have reviewed and agreed on the final manuscript.

Competing Interests: BG received a research grant from INCYTE and IPSEN and he is a member of the advisory board for INCYTE, LILLY and TAIHO. The others authors declare no competing interests.

Patient Consent for Publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Ethics Approval and Consent to Participate: the patient was treated according to the ethical guidelines of the 1975 Declaration of Helsinki. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Availability of Data and Materials: Not applicable

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