Diffuse advanced hepatocellular carcinoma after HCV eradication in an HIV-infected patient: A unique complete response to sorafenib

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Dear Editor,

Hepatocellular carcinoma (HCC) represents 90% of all primary liver tumors and is the sixth most common cancer worldwide. Liver cirrhosis is the main risk factor for HCC, and HCC is the leading cause of death in chronic liver disease (CLD) patients (1). According to current guidelines, HCC should be staged and managed following the Barcelona Liver Clinic Staging System (BCLC) (1). Advanced HCC is defined by vascular invasion, extrahepatic dissemination, or mildly compromised performance status and has a mean survival of 6 months (1). Sorafenib, a tyrosine-kinase inhibitor with antiangiogenic and antiproliferative activity, is recommended for advanced HCC treatment. [2] Randomized controlled trials (RCTs) only showed a modest impact in delaying disease progression, prolonging survival by just 3 months (1).

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causative agents of liver disease. Coinfection with human immunodeficiency virus (HIV) worsens the course of viral hepatitis, causing rapid progression of fibrosis (2). The introduction of highly active antiretroviral therapy (HAART) increased longevity in HIV-infected patients, and consequently, the manifestations of end-stage liver disease in these patients became even more common (2). Although HCC prognosis is worse for HIV patients, guidelines recommend using the same HCC treatment as for HIV-negative patients (2). Nevertheless, a few interesting anecdotal cases of sorafenib therapy in this population have been reported (2-4).

A 69-year-old man infected with HIV for 15 years was referred to our gastroenterology outpatient clinic because of suspected HCC in a surveillance ultrasound. The patient was under HAART with abacavir/lamivudine and dolutegravir. His medical history included liver cirrhosis associated with genotype 1a HCV infection that had achieved sustained virologic response (SVR) after completing treatment with sofosbuvir/ledipasvir 3 months earlier. The patient was asymptomatic, had good performance and nutritional status, and presented without portosystemic encephalopathy, jaundice, or ascites. His CD4 cell count was 520 cells/nL and liver tests were normal. CLD scores included Child–Turcotte–Pugh class A and MELD-Na of 7 points; nevertheless, there was a major elevation of serum alpha-fetoprotein (3378 ng/mL). Magnetic resonance imaging (MRI) showed an heterogeneous area involving the left hepatic lobe with diffusion restriction, washout in the venous phase, and an associated left-branch portal vein thrombosis (Figure 1). The definitive diagnosis of diffuse advanced HCC (stage C of BCLC) was made and daily 800 mg sorafenib was started. After 3 months of therapy, serum alpha-fetoprotein was normalized (1.9 ng/mL) and repeat MRI showed significant improvement with presence of only 5 nodules with few millimeters without contrast uptake. Additionally, marked reduction in portal vein thrombosis was observed with complete loss of arterial enhancement (Figure 2). Criteria for complete tumor response were achieved. After 2 years of follow-up, the patient is undergoing treatment with only mild diarrhea controlled with loperamide. Repeat MRI displayed the same residual nodules associated with cavernous transformation of the left portal branch.

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Good performance and immunological status was preserved.

HIV and HCV share common transmission routes resulting in approximately 33% incidence of coinfection (3). Current antiviral therapies are highly effective to achieve SVR in HCV-infected patients, improving fibrosis and decreasing admissions because of CLD decompensation (1). Recent studies indicate that eradication of HCV significantly reduces HCC incidence (1). However, the risk of liver cancer post-HCV SVR persists over time in patients with advanced fibrosis; higher age; and other cofactors such as obesity, diabetes, and alcohol consumption. In addition, the increase in life expectancy associated with HAART contributes for HCC development in HIV patients even after removing other risk factors (2). Furthermore, the HIV-induced immunosuppression, the cytopathic effect on liver parenchyma which contributes to increase inflammation and fibrosis, and the hepatotoxicity of some HAART drugs may also predispose patients to HCC (2).

HCC treatment response is determined using the modified Response Criteria in Solid Tumours (mRECIST).

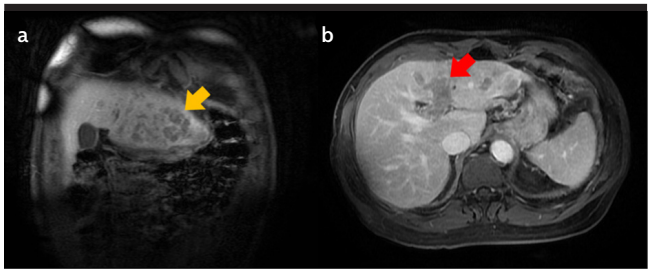

Figure 1. a, b. Abdominal MRI at HCC diagnosis. a) Nodular and heterogeneous area involving the left liver lobe with diffusion restriction and washout in the venous phase (yellow arrow). b) Left-branch portal vein thrombosis (red arrow).

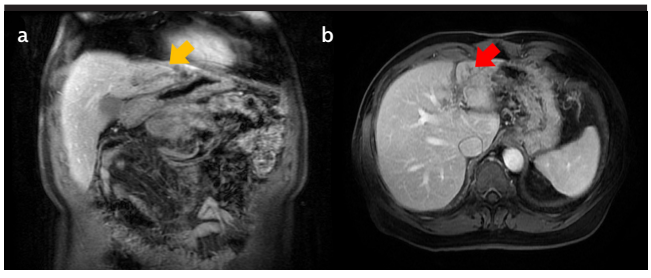

Figure 2. a, b. Abdominal MRI at 3 months of sorafenib therapy. a) Significant improvement in the multinodular expression, being confined to residual millimetric nodules without contrast uptake (yellow arrow). b) Marked reduction in portal vein thrombosis without arterial enhancement (red arrow).

Complete response is defined through disappearance of any intratumoral arterial enhancement in all target lesions as occurred in this patient (1). Sorafenib has proved to increase mean survival in patients with advanced HCC from 7.9 months to 10.7 months and to prolong the mean time for radiologic progression from 2.8 months to 5.5 months (1). Complete tumor response is rare, although it has been previously reported (2, 3). Unfortunately, clinical or molecular biomarkers to predict response are not available. Several mechanisms are involved in the acquired resistance to sorafenib and consequently loss of drug response. These mechanisms include inhibition of PI3K/Akt and JAK-STAT pathways, activation of hypoxia-inducible factors, and epithelial-mesenchymal transition (1, 5).

Most sorafenib RCTs excluded HIV-infected patients and few data regarding its use in this population is available (1). Chelis et al. (3) achieved complete tumor response in a patient with advanced HCC and HIV–HBV coinfection. De Nardo et al. (2) reported 2 cases of partial tumor response in HIV-HCV coinfected patients. A case series was published by Berretta M and his collaborators in 2013, where 27 consecutive HIV-HCC patients were treated with sorafenib and concomitant HAART, 3 patients achieved partial response, 12 remained stable, and 12 showed progression (4). The mean survival was 12.8 months, which was higher than that reported in RCTs for HIV-negative patients (4).

Because complete responses to sorafenib in immunocompetent HCC patients are very rare, its occurrence in immunocompromised HIV-infected patient in this case raises the possibility of a synergistic effect of sorafenib with HAART. Indirect evidence supports this hypothesis (2). First, some drugs used in HAART such as ritonavir have demonstrated that they inhibit PI3/AKT/mTOR pathway where sorafenib also acts. Second, the need of sorafenib dose reduction was described in HIV patients under HAART to avoid toxicity without compromising therapeutic response. Third, sorafenib is metabolized in the liver through CYP3A4, and concomitant use of inducers or inhibitors of this cytochrome in HAART may modify drug concentration and improve its action. Finally, good immune-virological response to HAART was maintained throughout sorafenib therapy (2).

To the best of our knowledge, this is a unique case that displays a complete tumor response to sorafenib in a HIV-infected patient with liver cirrhosis after SVR for HCV. We propose its use on a case-by-case basis in HIV

patients with advanced HCC who are not candidates for other therapies. RCTs are required to confirm safety and drug effectiveness in combination with HAART.

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