Sorafenib Therapy for Hepatocellular Carcinoma in an HIV–HCV Coinfected Patient: A Case Report

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ABSTRACT

Background/Aims. HIV and hepatitis C virus (HCV) share common modes of transmission, resulting in about 33% incidence of coinfection among people infected with HIV. The survival benefit from highly effective antiretroviral therapy (HAART) for HIV infection is resulting in an increased incidence of hepatocellular carcinoma (HCC) in this population. There are no reports to date regarding the coadministration of HAART and sorafenib for hepatocellular carcinoma.

Methods. We report the case of a 42-year-old male patient coinfecting with HIV and HCV who developed advanced HCC not amenable to curative therapy. The patient was treated with sorafenib, an oral multikinase inhibitor shown to lead to a longer median survival time and time to progression in patients with advanced HCC.

Antiretroviral therapy was continued during sorafenib therapy.

Results. The patient achieved a partial tumor response after 3 months and continued to respond at subsequent assessments. His serum α -fetoprotein normalized from 2,172 IU/ml to 2 IU/ml. He had durable stable disease after 23 months of therapy. Antiretroviral therapy was efficacious (CD4⁺ lymphocyte count, 377/ μ l; HIV viremia, <50 copies/ml). The simultaneous administration of these therapies was well tolerated. No grade 3 or 4 toxicities were observed. Exacerbation of pre-existing hypertension, grade 2 diarrhea, and grade 1 skin reaction were observed.

Conclusions. This is the first report in which sorafenib has been successfully used to treat HCC in a patient with HIV–HCV coinfection. *The Oncologist* 2010;15:142–145

BACKGROUND

The association between chronic hepatitis C virus (HCV) infection and a higher risk for developing hepatocellular carcinoma (HCC) is well established, and the increased

prevalence of HCV infections in the U.S. and Europe has resulted in a higher incidence of HCC [1]. Coinfection with HIV results in greater replication [2] and accelerates the clinical course of HCV [3, 4].

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Meanwhile, the availability of safe, highly active antiretroviral therapy (HAART) has profoundly changed the natural history of HIV infection, transforming it into a chronic disease with a much reduced impact on life expectancy [5]. The reduction in AIDS-defining malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphomas has been accompanied by an increase in non-AIDS-defining malignancies [6], and HCC secondary to viral hepatitis has emerged as a major source of morbidity and mortality in HIV-infected people [7–11]. The prevalence of chronic HCV in HIV-infected patients is about 33%, but this varies geographically and, because of the shared mode of transmission, is much higher in certain populations, such as injection drug users and hemophiliacs.

The incidence of HCC is reported to be five times higher in HIV–HCV coinfecting people than in those with HCV alone [12] and eight times higher than in the U.S. general population [13]. Moreover, the risk for HCC in HIV–HCV coinfecting patients is unlikely to be modified by the use of HAART; therefore, treatment of HCV infection in HIV-infected patients at risk for cirrhosis is strongly recommended [14]. In addition, routine screening of persons with HCV-related cirrhosis by serial liver imaging and serum α -fetoprotein measurement is recommended [15]. Routine screening facilitates earlier diagnosis, thereby allowing more effective application of curative medical and surgical interventions, such as resection or ablation. Even liver transplant, once thought unfeasible as a result of possible consequences of immune suppression therapy on HIV, can be an option for HIV patients who meet requirements for listing [16], although HCV reinfection remains an unresolved issue [17]. The clinical picture is complicated by concerns over hepatotoxicity and potential drug interactions associated with HAART [18].

Until recently, the therapeutic options for patients with HCC not amenable to resection or transplant were limited to best supportive care; however, the era of targeted therapy has brought better options for such patients. Therapies targeting angiogenesis have shown promise in this highly vascularized tumor. Proof of concept has been provided by sorafenib (Nexavar®; Bayer Schering Pharma AG, Berlin, Germany), the first molecularly targeted therapy to gain approval in advanced HCC, which is now the standard of care for advanced disease. Other targeted therapies in clinical development include sunitinib (Sutent®; Pfizer Limited, Sandwich, UK) and the combination of bevacizumab (Avastin®; Roche Registration Limited, Welwyn Garden City, UK) plus erlotinib (Tarceva®; Roche Registration Limited, Welwyn Garden City, UK).

Two large, phase III trials demonstrated that the orally active multikinase inhibitor sorafenib is effective in leading

to a longer median overall survival time and time to progression in patients with advanced HCC [19, 20]. Sorafenib blocks tumor cell proliferation by targeting cellular signaling at the level of Raf-1 and B-Raf serine-threonine kinases, and exerts an antiangiogenic effect by targeting vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 and platelet-derived growth factor receptor tyrosine kinases [21].

Despite the clinical relevance of HCC in HIV–HCV coinfection, no data have been published to date regarding the use of sorafenib for HCC in HIV–HCV coinfecting patients.

CASE REPORT

A 42-year-old male coinfecting with HIV and HCV was diagnosed in September of 2007 with multifocal HCC not amenable to curative therapy. His HCV infection (genotype 3a) was discovered in 1995, but he refused antiviral therapy. A liver biopsy was not performed at that time for the same reason. There were no clinical or laboratory signs of cirrhosis but his aspartate aminotransferase and alanine aminotransferase levels were consistently two- to fivefold greater than the upper limits of normal. His HBV-DNA and hepatitis B surface antigen were negative.

His HIV infection was also diagnosed in 1995, but it was untreated until 2000 when HAART was prescribed and continued until 2005. HAART was started again in August 2007, as a result of viremia (190,000 copies/ml) and a reduction in CD4⁺ lymphocytes (156/ μ l). This new therapy consisted of the combination of emtricitabine (Emtriva®; Gilead Sciences International Limited, Cambridge, UK), 200 mg once daily plus tenofovir disoproxil (Viread®; Gilead Sciences International Limited, Cambridge, UK), 245 mg once daily, plus atazanavir sulfate (Reyataz®; Bristol-Myers Squibb Pharma EEIG, Uxbridge, UK), 200 mg twice daily (bid). In February 2008, persistently high viremia (70,000 copies/ml) prompted the substitution of atazanavir with darunavir (Prezista®; Janssen-Cilag International NV, Beerse, Belgium), 600 mg, plus ritonavir (Norvir®; Abbott Laboratories Limited, Maidenhead, UK), 100 mg bid. His HIV infection was characterized as stage B3 and the patient was asymptomatic. The only concomitant disease was hypertension, which had been treated with irbesartan/hydrochlorothiazide (Winthrop Pharmaceuticals, Guildford, UK) combination therapy since 2004.

The patient had undergone routine liver cancer screening with serial liver imaging and serum α -fetoprotein levels that were unremarkable until July 2007 when liver ultrasonography revealed multiple suspected nodules. In September 2007 a computed tomography (CT) scan of the chest and of upper and lower abdomen confirmed multiple solid

Figure 1. Sequence of images of contrast-enhanced abdominal CT scan, late phase. (A): Abdominal CT scan at the time of diagnosis of HCC (September 1, 2007). (B): Abdominal CT scan after 3 months on sorafenib (February 26, 2009). (C): Abdominal CT scan after 17 months on sorafenib (April 7, 2009).

Abbreviations: CT, computed tomography; HCC, hepatocellular carcinoma.

nodules in the right lobe of the liver with diameters of 10–25 mm. In addition, thrombosis of the portal vein was detected. A chest scan was negative. Biopsy by ultrasound-guided fine-needle aspiration revealed moderately differentiated HCC. At diagnosis, his $CD4^+$ lymphocyte count was $156/\mu\text{l}$ and his HIV viremia was 223,000 copies/ml.

In November 2007, the patient started therapy with sorafenib (400 mg bid). A baseline disease assessment in October 2007 had shown significant progression of the HCC nodules since the previous examination, the largest lesion measuring 7 cm in longest diameter (Fig. 1A), whereas the portal vein thrombosis was unchanged. His serum α -fetoprotein was 2,172 IU/ml and his Karnofsky performance status score was 60.

The first disease assessment in February 2008, after 3 months of therapy, showed a partial response. A CT scan of the HCC nodules revealed that the largest lesion had regressed from 7 cm to 4.5 cm (Fig. 1B). His serum α -fetoprotein was 2 IU/ml. The second assessment at 8 months confirmed the partial response with a further reduction in the largest nodule to 3.8 cm, and his serum α -fetoprotein level was within the normal range. Results of the CT scan after 17 months of therapy revealed reduction of nodule to 3 cm (Fig. 1C). CT scan at the most recent tumor assessment after 23 months of therapy showed persistence of residual parenchymal hypodensity in the site of HCC, without contrast enhancement, with the portal thrombosis unchanged. His serum α -fetoprotein was below the upper limit of normal. At that time, the patient's $CD4^+$ lymphocyte count was $377/\mu\text{l}$ and his HIV viremia was <50 copies/ml. Moreover, his Karnofsky performance status score had improved to 90.

The combination of HAART and sorafenib therapy was well tolerated. No clinically significant hematological or hepatic toxicity was observed and there were no grade 3–4 toxicities. The most severe side effect was grade 2 diarrhea, which was managed by interruption of sorafenib treatment until recovery to grade 1 level, following the guidelines for

toxicity management. HAART was not interrupted. This strategy resulted in <10 days off therapy. The patient experienced grade 2 hypertension that was managed by adjustment of antihypertensive therapy. Grade 1 skin reaction was also reported.

DISCUSSION

In recent years, sorafenib has substantially changed the treatment and natural course of advanced unresectable HCC, offering a therapeutic opportunity to patients for whom no effective treatment was available. Despite the emerging role of HCC as a major cause of morbidity and mortality in HIV-infected patients and the approval of sorafenib therapy for advanced HCC, no data have been published regarding the use of sorafenib for HCC in HIV–HCV coinfecting patients. Our experience from this case, though limited by its anecdotal nature, is the first report on the use of sorafenib in this setting. Notably, therapy with sorafenib produced a partial tumor response and normalization of serum α -fetoprotein that remained stable for >23 months. These results are unexpectedly superior to those observed in two major phase III clinical trials, in which the median time to radiological progression was in the range of 2.8–5.5 months and the objective response rates were $<3\%$ [19, 20]. Similarly, in those trials, the median overall survival time was 6.5–10.7 months.

At the same time, HAART for HIV infection was efficacious in reducing virus replication and maintaining adequate levels of $CD4^+$ lymphocytes. Toxicity was mild and in line with that reported in phase III clinical trials with sorafenib. Exacerbation of pre-existing hypertension is a side effect observed with VEGFR blockade by a number of agents [22], whereas diarrhea and skin reactions are among the most common side effects seen with sorafenib [23]. Based on the information currently available, administration of sorafenib in combination with the specific HAART used in this case (the reverse transcriptase inhibitors emtricitabine and tenofovir disoproxil, the protease inhibitors

atazanavir or darunavir/ritonavir) is not expected to cause increased toxicity [24]. A drug interaction is predicted between ritonavir, which induces the phase I detoxifying enzyme cytochrome P450 (CYP)3A2, and sorafenib, a substrate of this enzyme. In vivo studies with a strong CYP3A2 inducer showed a moderate (37%) reduction in sorafenib levels [25]; however, a lack of efficacy was not observed in this case. Recently, emerging data regarding potential complications from combining HAART with classical antineoplastic agents [26] or with targeted therapies [24] have been reviewed, providing a basis for treatment decisions in this complicated scenario.

In conclusion, the introduction of HAART for HIV infection is expected to make end-stage liver disease, and particularly HCC, an issue of great importance in the clinical management of HIV–HCV coinfecting patients. Based on our experience, the concomitant administration of sor-

afenib and HAART appears to be an effective and well-tolerated therapy for HCC in HIV–HCV coinfecting patients, and this observation strongly warrants the design of ad hoc controlled clinical trials for a prospective validation of this approach.

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AUTHOR CONTRIBUTIONS

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