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The role of sorafenib in downsizing hepatocellular carcinoma prior to liver transplantation and in treating tumor recurrence

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Abstract

Sorafenib is shown to improve survival in patients with advanced hepatocellular carcinoma (HCC). However, it has as yet not been tested in the liver transplantation (LT) setting. We report a 55-year-old man with multifocal HCC (stage B) related to hepatitis B virus cirrhosis (Child-Pugh B), initially treated with transarterial chemoembolization. After five months, sorafenib was added due to lack of response. This enhanced the downsizing of the tumor and eventually led to a surgically successful LT after 4 months of combined treatment. Sorafenib was re-initiated 15 months post-transplant due to skeletal tumor recurrence and led to patient's clinical improvement. The patient remains in good clinical condition 3 years after LT. Sorafenib was well tolerated throughout the entire period of administration with no serious or unexpected adverse events. We conclude that sorafenib can be safely used as a bridge to LT and in transplanted patients in case of HCC recurrence.

Keywords Sorafenib, hepatocellular carcinoma, liver transplantation, transarterial chemoembolization, tumor recurrence

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Introduction

The diagnosis of hepatocellular carcinoma (HCC) is often made at a stage exceeding published criteria for liver transplantation (LT). In addition, the risk of HCC recurrence remains significant (around 10%) even when these criteria are strictly applied [1].

Sorafenib, a multi-kinase inhibitor with antiproliferative and antiangiogenetic properties, is shown to improve survival in patients with advanced HCC [2]. Preliminary results in similar populations have recently demonstrated that the combination of sorafenib with transarterial chemoembolization (TACE) is safe and may result in better overall outcomes [3-5]. However, the safety and efficacy of this regimen as a bridge for LT or the use of sorafenib in case of HCC recurrence have not as yet been investigated.

We report the case of a 55-year-old man with HCC, who was treated with TACE and sorafenib followed by LT with post-transplant sorafenib re-administration.

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Case report

The patient was evaluated in the outpatient clinic for prolonged anorexia and significant weight loss (8 kg during the previous 3 months). His medical history was significant for untreated chronic hepatitis B virus (HBV) infection [antiHBe (+)] and peptic ulcer disease. His family history included HBV infection of his mother and siblings, complicated by HCC in his youngest brother.

On physical examination, abnormal findings included ascites, splenomegaly and skin stigmata of liver cirrhosis. His laboratory examinations were: AST= 50 IU/L, ALT= 46 IU/L, platelets= 110,000 /mm^3, albumin= 3.4 mg/dL, bilirubin= 1.8 mg/dL, INR= 1.8, alpha-fetoprotein (aFP)= 71 ng/mL, HBsAg (+), HBV-DNA= 2.1x10^5 IU/L. A multiphase computed tomography scan (CT) revealed moderate amount of ascitic fluid and three liver lesions, sized 2, 3 and 4 cm, respectively,

with radiologic features compatible with HCC. No evidence of portal vein thrombosis was present. His tumor was classified as stage B according to the Barcelona Clinic Liver Cancer (BCLC) staging system.

The patient was started on antiviral treatment with lamivudine (100 mg/day) plus adefovir (10 mg/day) and diuretics. He subsequently underwent a total of 5 TACE sessions using cisplatin, mitomycin, lipiodol and microspheres (Embospheres 300-500 μ, Biosphere Medical®) with 4 to 6 weeks' intervals. After the fifth session radiologic evaluation using published criteria for response showed a 1 cm decrease in each initial lesion [6]; nevertheless, four small (about 1 cm) new lesions that could represent HCC nodules were also detected. TACE induced only temporary minor adverse events. The patient remained in good clinical condition (Child-Pugh class B) without any other complications or evidence of extrahepatic disease as documented by imaging studies. In light of these findings, sorafenib was added to the patient's treatment at a dose of 400 mg b.i.d.. Sorafenib was initially well tolerated. However, the dose was decreased to 200 mg b.i.d. due to diarrhea one month later. The patient was subsequently treated with 2 more TACE sessions without sorafenib discontinuation, with no additional side effects.

After 3 months of sorafenib treatment the patient was referred for LT evaluation. At time of evaluation for transplant, dynamic triple-phase CT scan of the liver showed foci of lipiodol entrapment but no new lesions with arterial enhancement and/or washout. CT of the chest was negative for metastatic disease. The patient was rapidly decompensating at this time with a biological calculated Mayo End-stage Liver Disease (MELD) score of 25 on the day of listing and 35 on the day of transplant. A successful liver transplant was performed, using a cadaveric graft 10 months after initial diagnosis and 4 months after sorafenib initiation. Pathology of the explanted graft revealed a multifocal, moderately differentiated HCC with the largest nodule measuring 2.5 cm, 0/2 lymph nodes positive for tumor and no vascular invasion, but suggestion of microscopic lymphatic invasion.

The post-transplant course was largely uneventful. However, the patient's aFP started to increase and one year after transplant was already above 1000 ng/mL. Multiple imaging studies were done in the first year post-transplant without evidence of recurrent disease. However, 15 months post-transplant a bone scan was positive in multiple skeletal locations and by 18 months post-transplant the patient had developed a right humeral lesion with pathologic fracture. In view of these findings, sorafenib was re-initiated at a dose of 400 mg b.i.d.. In addition, his immunosuppressive regimen was modified to include everolimus. Treatment was well tolerated. The humerus metastatic bone lesion was treated with radiofrequency ablation (RFA); this resulted in a dramatic decrease in aFP levels (2,000 from a peak of 15,000 ng/mL). The patient continued his regimen without serious adverse events. Currently, 36 months post-transplant, the patient is in stable clinical condition, on ongoing therapy for metastatic recurrent HCC.

Discussion

Adequate experimental evidence provides rationale for the use of combination treatment regimens, including sorafenib, in HCC patients. Angiogenic factors are shown to be overexpressed in the hypoxic area between the necrotic central area induced by TACE and the viable margin neoplastic tissue, implying a possible role for concomitant antiangiogenic treatment [7]. Combination of RFA with sorafenib has showed improved efficacy in a renal cell carcinoma animal model by decreasing the microvessel density and the tumor blood flow and increasing the size of the RFA-induced coagulation zone [8]. Moreover, TACE plus antiangiogenic compound combination therapy was tested in rats with HCCs and showed improved survival rates, as well [9].

Despite the undoubted experimental and limited clinical evidence for enhanced efficacy, the skepticism for combining TACE with an antiangiogenic agent like sorafenib is still in effect, mainly due to presumed increased incidence of adverse events. Sorafenib use is associated with adverse events like diarrhea, weight loss and hand-foot skin reactions.

In our case, the combined use of TACE and sorafenib was generally well tolerated and did not lead to any serious adverse events, except for diarrhea of moderate severity. Of note, sorafenib was discontinued one month before transplantation due to severe liver decompensation, and did not result in significant surgical complications. It was reinitiated in the early post-transplant period due to tumor recurrence, again without remarkable side effects. Although our patient in retrospect exceeded criteria for transplantation at the time of listing, his pretransplant CT scan of the abdomen did not show any active HCC lesion; it was only the pathology report that revealed multifocal HCC with foci of non-necrotic tumor. Therefore, he experienced early tumor recurrence and had a very short tumor-free interval, although he is still alive with good quality of life after multimodal post-transplant treatment including sorafenib. The use of sorafenib in the post-transplant setting is interesting and warrants further evaluation. The rationale of its combination with everolimus is supported by preliminary reports [10].

Overall, this case supports the safety of the combined use of TACE plus sorafenib in patients with HCC awaiting LT. In addition, it shows that sorafenib can be also safely used in the post-transplant setting in case of tumor recurrence. Nevertheless, randomized trials have to verify the safety of such regimens and determine their efficacy before they can be recommended for widespread application.

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