A Patient with Advanced Hepatocellular Carcinoma Treated with Sorafenib Tosylate Showed Massive Tumor Lysis with Avoidance of Tumor Lysis syndrome

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Abstract

A 33-year-old man presented with pain and palsy of the leg in 2008 for treatment of hepatocellular carcinoma with huge distant metastases. The patient’s tumors had slowly enlarged despite several treatments. Oral administration of sorafenib at 800 mg/day with careful observation was commenced in 2009. Laboratory investigations on day 7 showed massive tumor lysis. An abdominal CT showed multiple low density areas and tumor markers decreased, indicating extended tumor necrosis. In conclusion, clinicians should bear in mind not only the published adverse effects, but also massive tumor lysis, when treating patients with large tumor burden by sorafenib.

Key words: hepatocellular carcinoma, sorafenib, tumor lysis, tumor lysis syndrome

(DOI: 10.2169/internalmedicine.49.3153)

Introduction

Sorafenib tosylate was approved by the Food and Drug Administration (FDA) in 2007 to treat hepatocellular carcinoma (HCC) and could be prescribed in Japan from 2009 to treat unresectable HCC. It is an oral multitargeted kinase inhibitor that inhibits tumor cell proliferation and angiogenesis (1, 2). Sorafenib is believed to mark the beginning of a new era in advanced HCC therapy since it is the first approved molecular targeted agent for HCC and can be prescribed in outpatient clinics. However, the most frequently reported adverse events of sorafenib have been observed in 80% of patients (1). We report a case of HCC who avoided tumor lysis syndrome (TLS) following massive tumor lysis from treatment with sorafenib.

Case Report

A 33-year-old man presented with pain and palsy of the left leg at our hospital in 2008 for further examination and treatment of huge masses in the pelvic cavity (70 mm in diameter) and liver (110 mm in diameter) that had been earlier detected with ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). A specimen taken from a direct tumor biopsy from the sacral bone histologically showed well-differentiated hepatocellular carcinoma (HCC) with monotonous tumor cell proliferation (Fig. 1a) and immunohistologically stained for hepatocyte paraffin 1 (Fig. 1b). Laboratory tests were normal except for levels of serum HCC tumor makers, such as alpha-fetoprotein (AFP) at 2,580 ng/ml, AFP like the Lens culinaris agglutinin-reactive fraction (AFP-L3) at less than 0.5% of total AFP, and prothrombin induced by vitamin K absence or antago-

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Received for publication November 15, 2009; Accepted for publication February 3, 2010
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Figure 1. a) Microscopic examination revealed that the tumor was a well-differentiated hepatocellular carcinoma with monotonous tumor cell proliferation. Hematoxylin and Eosin staining ×100. b) Cells were immunohistologically positive to antibodies against hepatocyte paraffin 1 (Hep Par 1) ×100.

Figure 2. a) Contrast-enhanced computed tomography (CT) right before treatment with sorafenib depicted a maximum 78×63 mm-wide tumor on the right robe in the liver with several small intrahepatic metastases. b) It also showed a maximum 102×110 mm-wide tumor in the pelvic cavity directly infiltrating out of the sacral bone. c) Contrast-enhanced CT on day 14 depicted multiple low density areas in the liver (black arrowheads). d) It also showed multiple low density areas in the pelvic cavity (black arrowheads), indicating extended tumor necrosis by sorafenib.

Proliferating cell nuclear antigen II (PIVKA II) at 781 mAU/mL. The patient’s tumors had slowly become enlarged over 14 months despite several treatments with transarterial chemoembolization and transarterial infusion chemotherapy for both hepatic and pelvic masses. He also suffered from complications of severe cancer pain that were managed by local radiation therapies and several analgesic agents, including morphine.

Oral administration of sorafenib at 800 mg/day with careful observation was commenced in 2009 at an outpatient clinic visit after sorafenib became approved for unresectable HCC in Japan. An abdominal CT right before treatment showed a maximum 78×63 mm-wide tumor (Fig. 2a) with several small intrahepatic metastases and a huge maximum 102×110 mm-wide tumor directly infiltrating out of the sacral bone (Fig. 2b). Pretreatment laboratory tests were as follows: aspartate aminotransferase (AST), 102 IU/L; alanine aminotransferase (ALT), 28 IU/L; lactate dehydrogenase (LDH), 377 IU/L; uric acid (UA), 5.8 mg/dL; phosphorus (P), 3.9 mg/dL; creatinine (Cre), 0.39 mg/dL; potassium (K), 4.3 mmol/L; calcium (Ca), 10.0 mg/dL; AFP, 91,260.
Sorafenib increases the rate of tumor apoptosis by inhibition of the serine-threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs)-1 (flt-1), -2 (KDR/flk-1), and -3 (flt-4) and platelet-derived growth factor receptor (PDGFR)-β (2). Cellular signaling mediated by Raf-1 and vascular endothelial growth factors (VEGFs) has been implicated in the molecular pathogenesis of HCC (5). One isoform of VEGF, VEGF-A, was reported to be expressed and related to angiogenesis along with VEGFR-1 and -2 in relatively well-differentiated HCC (6). Another VEGF isoform, VEGF-C, was found to be related to HCC disease progression together with VEGFR-2 and -3 (7). Clinically, the multicenter European randomized SHARP trial demonstrated a statistically significant survival benefit and disease-control rate according to the Response Evaluation Criteria in Solid Tumors (RECIST) for sorafenib in patients with advanced HCC in 2008 (1). In the present case of histologically well-differentiated HCC with distant metastases, the antitumor effect of sorafenib was clearly observed and resulted in massive tumor lysis.

The most frequently reported adverse events of sorafenib observed in 80% of patients include dermatologic events, such as hand-foot skin reactions, constitutional symptoms, such as weight loss, and gastrointestinal events like diarrhea (1). The present case showed none of these side effects although he only received sorafenib treatment for 7 days. TLS is an oncologic emergency that is caused by the release of intracellular tumor components due to massive tumor lysis, especially in cases that show a large tumor burden, a high proliferative tumor rate, or high sensitivity to cytotoxic therapy. However, with the advent of multi-targeted kinase inhibitors that show effectiveness against solid tumors, an increasing number of reports on TLS in these cases are surfacing (9-11). Recently, a 55-year-old man with HCC who had shown a good initial response to sorafenib later experienced TLS and died after 30 days of continuous treatment (12). Careful observation, especially in the initial period after sorafenib commencement, and earlier discontinuation of the drug may have prevented TLS development. Administration with sorafenib was halted at 7 days in the present case but it still yielded positive results without the onset TLS, indicating that further studies are required to determine the optimal dosage and treatment course with sorafenib in unresectable HCC patients such as the current case.

In conclusion, clinicians should bear in mind not only the published major adverse effects (1), but also the possibility of TLS brought on by massive tumor lysis, when starting treatment of advanced HCC patients with large tumor bur-
den using oral administration of sorafenib.

Acknowledgement
We thank Trevor Ralph for his English editorial assistance.

References