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CASE REPORT

Thalidomide induces complete remission of advanced hepatocellular carcinoma

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Summary Hepatocellular carcinoma (HCC) is one of the most prevalent human cancers in the world, but its prognosis is extremely poor. HCC is considered a hypervascular tumor. Thalidomide, which has been known to inhibit growth factor-induced neovascularization, is a convenient alternative to target therapy such as sorafenib. We report a 65-year-old male patient with alcoholic liver cirrhosis that was diagnosed having multiple HCCs during surveillance. The patient was assessed as inoperable and unsuited for transhepatic arterial chemoembolization or systemic chemotherapy. After discussing the therapeutic alternatives, he decided to receive low-dose thalidomide (100 mg daily) therapy. Fortunately, follow-up liver biochemical tests, serum α-fetoprotein level, and dynamic computed tomography showed complete remission of the HCCs 4.5 months after thalidomide treatment and this was documented for more than 22 months without evidence of tumor recurrence.

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent human cancers in the world, especially in Asia and Africa, but its prognosis is extremely poor. Surgical resection and local radiofrequency ablation therapy are curative in only a minority of patients and systemic chemotherapy is difficult for HCC patients to tolerate because liver function reserve is often impaired due to underlying cirrhosis, which is accompanied by hypersplenism and peripheral cytopenia. HCC is a relatively chemoresistant tumor and is highly refractory to cytotoxic chemotherapy. Transhepatic arterial chemoembolization (TACE) is the most widely used locoregional treatment for patients with intermediate stage HCC, but it is contraindicated in patients with main portal vein thrombosis or poor liver function reserve. Sorafenib, an oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis, is the standard of care for patients with advanced stage disease. However, sorafenib for advanced HCC is still not easy for Asian physicians to prescribe due to high cost. Therefore, advanced and unresectable HCC remains incurable, with a median

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survival of <6 months. Generally, HCC is considered a hypervascular tumor. Increased levels of vascular endothelial growth factor and high microvessel density have been found in HCC. Therefore, inhibition of angiogenesis represents a potential therapeutic target. Thalidomide, which has been known to inhibit growth factor-induced neovascularization, is a convenient alternative to treatment with cytotoxic agents. We report a male patient with alcoholic liver cirrhosis and advanced HCC after thalidomide treatment that achieved complete HCC remission.

Case report

A 65-year-old man was a victim of alcoholic liver cirrhosis (Child—Pugh class B) with ascites under diuretics (oral furosemide 80 mg and spironolactone 200 mg daily) control and received periodic HCC surveillance every 4 months for 14 years. Unfortunately, his α-fetoprotein (AFP) level was highly elevated and abdominal ultrasonography detected multiple liver tumors in November 2005. Physical examination revealed jaundice, mild hepatomegaly with a span of 13 cm on the right middle clavicle line and an irregular margin with a hard consistency that measured 2 cm below the right costal margin. The spleen was impalpable. No fever, skin rash, ascites, spider angioma, or palmar erythema was noted. Laboratory studies disclosed the following results: hemoglobin, 13.5 g/dL; leukocytes, 5.2×10^9/L; platelets, 110×10^9/L; albumin, 3.6 g/dL, globulin, 3.1 g/dL; total bilirubin, 4.2 mg/dL (normal, <1.3 mg/dL); serum aspartate aminotransferase (AST), 222 U/L (normal, <34 U/L); serum alanine aminotransferase (ALT), 51 U/L (normal, <36 U/L); alkaline phosphatase, 210 IU/L (normal, <94 IU/L); prothrombin time, 12.4 seconds (control, 10.0 seconds); international normalized ratio, 1.12; and AFP 4935 ng/mL (normal < 3 ng/mL). Hepatitis B surface antigen and antibody to hepatitis C virus were both negative. Abdominal ultrasonography showed multiple hyperechoic and mixed echoic tumors in cirrhotic parenchyma, the largest being 5.9 cm in diameter, without the presence of ascites. Dynamic computed tomography (CT) showed multiple arterially enhanced tumors, mainly in the right lobe having a portal- and delayed-phase washed-out appearance. The invasion of tumors into the main portal trunk and its proximal branches with suspicion of biliary tree compression are shown in Fig. 1A. The tumors were considered HCCs because of the presence of the characterized arterial vascularization and rising AFP levels. This patient appeared to be asymptomatic and was staged as Barcelona Clinic Liver Cancer (BCLC) stage C.

The patient was assessed as inoperable and unsuited for TACE or systemic chemotherapy. Attending a clinical trial with target therapy was suggested initially, but the patient refused. He agreed to receive thalidomide (50 mg capsule; TTY Biopharm, Taipei, Taiwan) 50 mg twice daily after obtaining written informed consent and followed at an outpatient clinic. Three weeks after thalidomide therapy, he occasionally complained of skin eruptions with itching. There was no fever, nausea, constipation, vomiting, fatigue, or somnolence. Laboratory studies disclosed the following: AST, 436 U/L; ALT, 94 U/L; total bilirubin, 5.2 mg/dL; and serum AFP, 7350 ng/mL. He continued to take thalidomide 100 mg daily without specific complaint. Follow-up liver biochemical tests after 3 months of thalidomide therapy showed the following: AST, 44 IU/L; ALT, 29 IU/L; total bilirubin, 1.8 mg/dL; and serum AFP, 13 ng/mL. The clinical course is shown in Fig. 2. Dynamic CT showed significant regression of the portal vein thrombi and complete remission of tumors 4.5 months after initial diagnosis (Fig. 1B). Thalidomide dose was reduced to 50 mg daily after 9 months treatment because of serum AFP and ultrasonography showing no evidence of HCC recurrence. Abdominal CT or ultrasonography at 20 months after thalidomide therapy showed complete tumor regression (Fig. 1C). The AST, ALT, and AFP levels remained within normal limits. Unfortunately, he succumbed to a perforated duodenal ulcer with multiple organ failure 22 months after initial diagnosis.

Discussion

The clinical, laboratory, and image modalities on presentation and the subsequent clinical course of this particular patient indicated that he was a patient with HCC who showed complete response to oral thalidomide therapy.

HCC is a highly prevalent disease in many Asian countries, accounting for 80% of victims worldwide. This patient

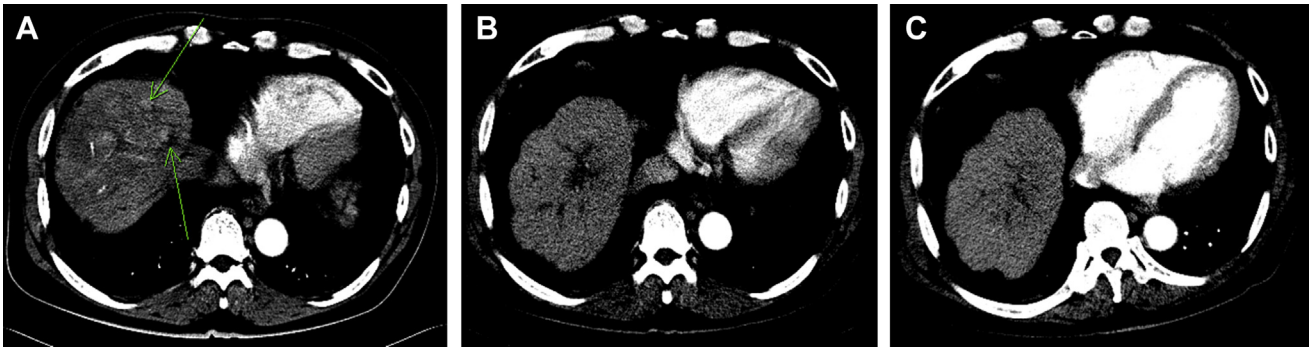

Figure 1 (A) Prior to thalidomide therapy, multiple arterially enhanced tumors were located in the right lobe (arrow), and multiple infiltrating tumors were located in the central portion of the liver with portal vein thrombi. (B) Follow-up examination after 4.5 months of thalidomide therapy showed complete remission of liver tumors and significant regression of portal vein thrombi. (C) Follow-up examination after 20 months of thalidomide therapy showed complete remission of liver tumors and portal vein thrombi.