

Treatment with Brivanib alaninate as a second-line monotherapy after Sorafenib failure in hepatocellular carcinoma

A case report

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Abstract

Rationale: Hepatocellular carcinoma (HCC) is one of the most frequent causes of cancer-related death worldwide. Its poor prognosis is due to the high invasiveness of the disease and limited efficacy of available treatments.

Patient concerns: We reported an HCC patient who developed lung metastases 1 year after HCC resection. Sorafenib was then initiated; however, disease progression was noted 3 months later. Sorafenib therapy was initially maintained due to lack of effective alternatives, but disease progression continued.

Diagnoses: HCC patient with lung metastases, and pulmonary portal, and mediastinal lymph node metastases (stage IVB).

Interventions: Brivanib alaninate was used alone as second-line therapy.

Outcomes: All metastases showed increased size on radiographic imaging approximately 3 months after brivanib alaninate was initiated. However, 2.5 months later, the lung metastases significantly decreased in size or disappeared. The pulmonary portal, and mediastinal lymph node metastases also significantly decreased in size. At 9.5 months after brivanib alaninate initiation, the pulmonary portal, and mediastinal lymph node metastases nearly disappeared, and the lung metastases continued to decrease in size. Alpha fetoprotein (AFP) level showed the same change pattern as the tumor-response observed on radiographic imaging. The total duration of brivanib alaninate treatment was 11 months, which was stopped due to repeated grade 2 thrombocytopenia. The other side effects were tolerable. Fifteen months after initiation of brivanib alaninate, the patient remained in very good condition without evidence of disease progression.

Lessons: Brivanib alaninate alone as second-line therapy showed excellent antitumor efficacy for an HCC patient with numerous lung and lymph node metastases. It may exert its antitumor effects in a delayed-onset fashion. We suggest that patients receive brivanib alaninate for a long duration to fully determine its efficacy.

Abbreviations: AFP = alpha fetoprotein, CT = computed tomography, CTCAE 4.0 = Common Terminology Criteria for Adverse Events 4.0, FGF = fibroblast growth factor, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, mOS = overall survival, mTTP = median time to progression, PD = progression disease, PR = partial response, RECIST 1.1 = Response Evaluation Criteria In Solid Tumors 1.1, SD = stable disease, VEGF = vascular endothelial growth factor.1.

Keywords: brivanib alaninate, excellent effect, HCC, late onset, second-line

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally and the third leading cause of cancer deaths.^[1]

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It accounts for 90% of primary liver cancers, and can be caused by chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol abuse, and other factors.^[2,3] In China, most HCC is caused by HBV infection, which shows poorer prognosis.^[3,4] Sorafenib was the first systemic therapy to be approved by the United States Food and Drug Administration to treat advanced HCC in 2007, and approval in China immediately followed in 2008.^[3] It remains the standard first-line treatment of HCC worldwide.^[5] Regorafenib was the first drug to show survival benefit in HCC patients with disease progression after sorafenib treatment; overall survival of HCC patients was prolonged to 10.6 months compared with 7.8 months for patients treated with placebo.^[6] Cabozantinib and ramucirumab have also shown survival benefit as second-line therapy in HCC patients with disease progression on sorafenib.^[1,2]

Brivanib alaninate is an orally administered alanine prodrug of brivanib, and is the first orally bioavailable selective dual inhibitor of fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) signaling.^[7] It showed promising antitumor effects in preclinical mouse models and in 2 phase II clinical trials of HCC patients.^[7,8] However, the primary endpoint was not reached in phase III clinical trials.^[9,10]

Nonetheless, brivanib alaninate may still have antitumor effects in HCC patients due to its novel antitumor mechanism.^[11] In this study, we report an HCC patient with numerous lung metastases, and pulmonary portal, and mediastinal lymph node metastases that were resistant to sorafenib therapy. He was then treated with brivanib alaninate, which showed very good antitumor effects, although they were delayed in onset. This study was approved by the West China Hospital institutional review board (2017 TRAIL No. 46), and informed written consent was obtained from the patient for publication of this case report and accompanying images.

2. Case presentation

A 51-year-old man presented to the outpatient department of West China Hospital about 1 year ago. Two years prior, he was discovered to have a liver mass on physical examination. In addition, he was diagnosed with HBV infection and liver cirrhosis. Entecavir treatment was initiated from July 2015, and he underwent a right hemihepatectomy with repair of the vena cava and portal vein, and cholecystectomy on July 15, 2015. Postoperative pathologic examination showed poorly differentiated hepatocellular carcinoma (grade 3). The hepatic capsule was invaded, and the surgical margin was tumor-free. The Ishak score was 4. The tumor stage was stage I. Postoperative alpha fetoprotein (AFP) level was 11.46 ng/mL. He then underwent regular follow-up. Thirteen months after surgery, he was found to have multiple lung metastases (stage IVB disease). The AFP level was 102.70 ng/mL. Sorafenib 400 mg twice daily was

initiated, but progressive disease (PD) as defined by the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1)^[12] was observed 3 months later. Sorafenib treatment was continued due to the lack of effective alternatives. Follow-up computed tomography (CT) examination 10 months later showed further disease progression; although the liver was tumor-free (Fig. 1A), numerous lung metastases, and pulmonary portal, and mediastinal lymph node metastases were observed (Fig. 2A, Fig. 3A, Fig. 4A, Fig. 5A, Fig. 6A). The tumor stage remained IVB. The AFP level was 3723.00 ng/mL. At this point, sorafenib was stopped and brivanib alaninate 800 mg daily was initiated. Approximately 3 months later, CT examination showed that the lung and lymph nodes metastases had increased in size; there were no new metastases (Fig. 2B, Fig. 3B, Fig. 4B, Fig. 5B, Fig. 6B), and the liver remained tumor-free (Fig. 1B). The AFP level increased to 10149.00 ng/mL. The tumor response was evaluated as stable disease (SD), and the patient continued treatment with brivanib alaninate. Two and a half months later, CT examination showed that the lung metastases had all decreased in size, with some disappearing entirely. The pulmonary portal, and mediastinal lymph node metastases also decreased in size remarkably (Fig. 2C Fig. 3C, Fig. 4C, Fig. 5C, Fig. 6C). The liver still remained free of any tumor (Fig. 1C). The AFP level decreased to 170.74 ng/mL. The result of treatment was evaluated as partial response (PR). Nine and a half months after brivanib alaninate was initiated, CT examination showed that the lung metastases continued to decrease in size; the pulmonary portal, and mediastinal lymph node metastases nearly disappeared (Fig. 2D, Fig. 3D, Fig. 4D, Fig. 5D, Fig. 6D). The AFP level decreased to 24.94 ng/mL. The

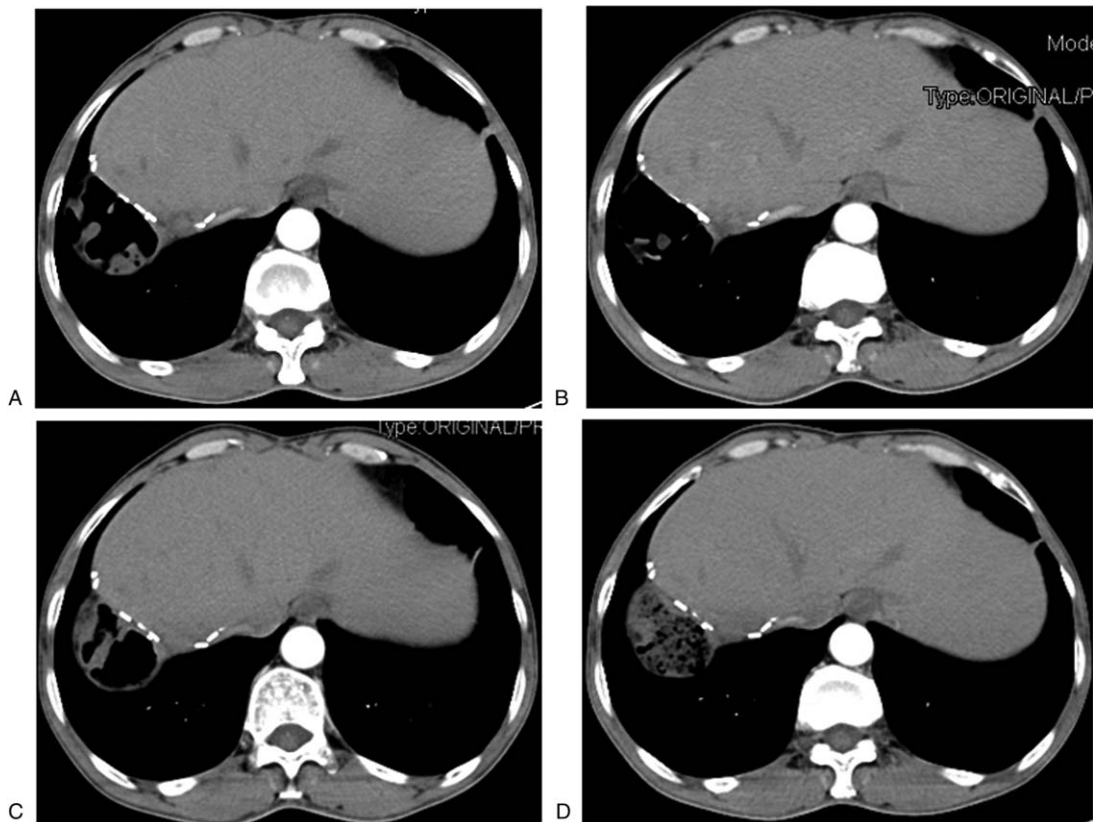


Figure 1. A, The liver before Brivanib alaninate treatment (October 18, 2017). B, The liver about 3 months after Brivanib alaninate treatment (January 18, 2018). C, The liver 5.5 months after Brivanib alaninate treatment (April 12, 2018). D, The liver about 9.5 months after Brivanib alaninate treatment (August 16, 2018).

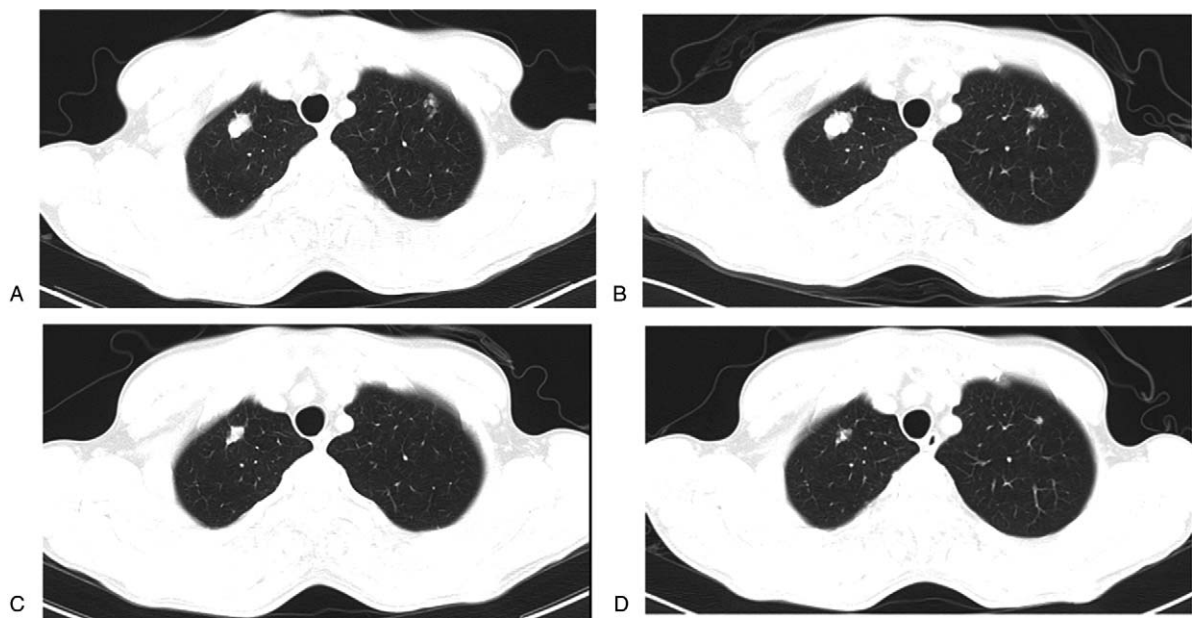


Figure 2. A, The lung metastases before Brivanib alaninate treatment (October 18, 2017). B, The lung metastases about 3 months after Brivanib alaninate treatment (January 18, 2018). C, The lung metastases 5.5 months after Brivanib alaninate treatment (April 12, 2018). D, The lung metastases about 9.5 months after Brivanib alaninate treatment (August 16, 2018).

liver was still tumor-free (Fig. 1D). The total duration of brivanib alaninate treatment was 11 months, which was stopped due to repeated grade 2 thrombocytopenia as defined by the Common Terminology Criteria for Adverse Events 4.0 (CTCAE 4.0)^[13]. Other adverse effects were grade 1 fatigue, grade 2 leukocytopenia, and grade 2 neutropenia. At last follow-up, 15 months after initiating brivanib alaninate, the patient remained in very good condition without evidence of disease progression.

3. Discussion

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths globally.^[11] Over 700,000 new cases are diagnosed each year worldwide, with large geographic variation in both risk factors and incidence.^[2] More than half occur in China, which has the highest incidence in the world (34.4 and 12.2 per 100,000 for males and females, respectively).^[13] The primary etiology of

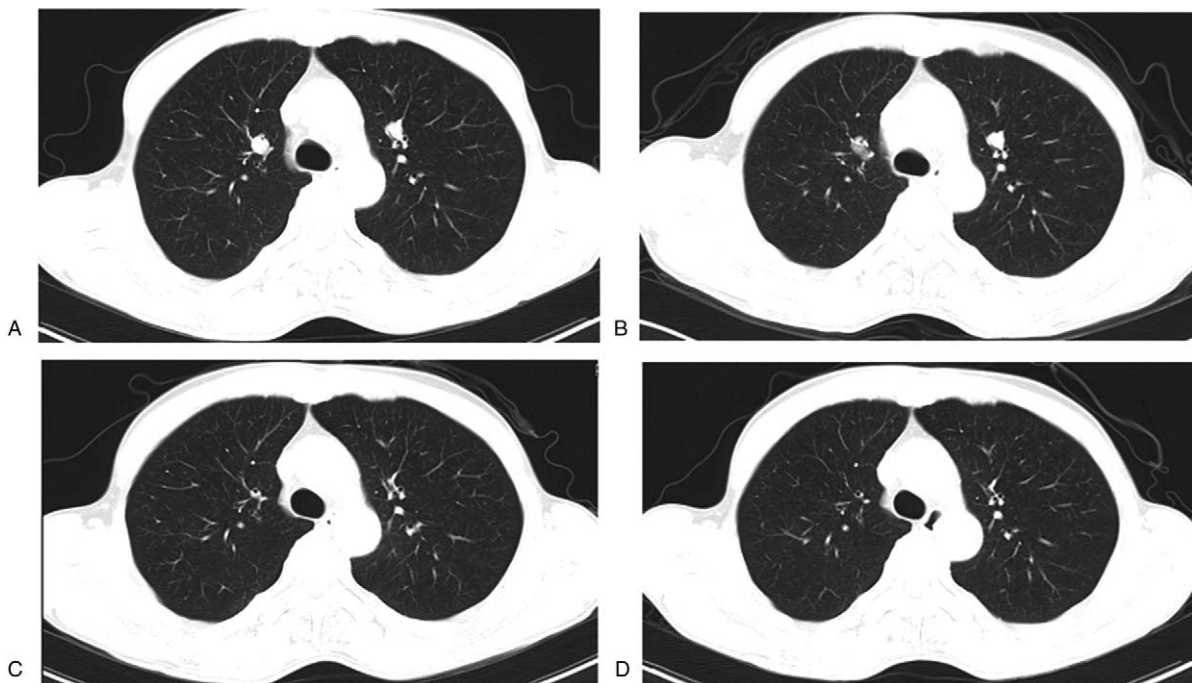


Figure 3. A, The lung metastases before Brivanib alaninate treatment (October 18, 2017). B, The lung metastases about 3 months after Brivanib alaninate treatment (January 18, 2018). C, The lung metastases 5.5 months after Brivanib alaninate treatment (April 12, 2018). D, The lung metastases about 9.5 months after Brivanib alaninate treatment (August 16, 2018).

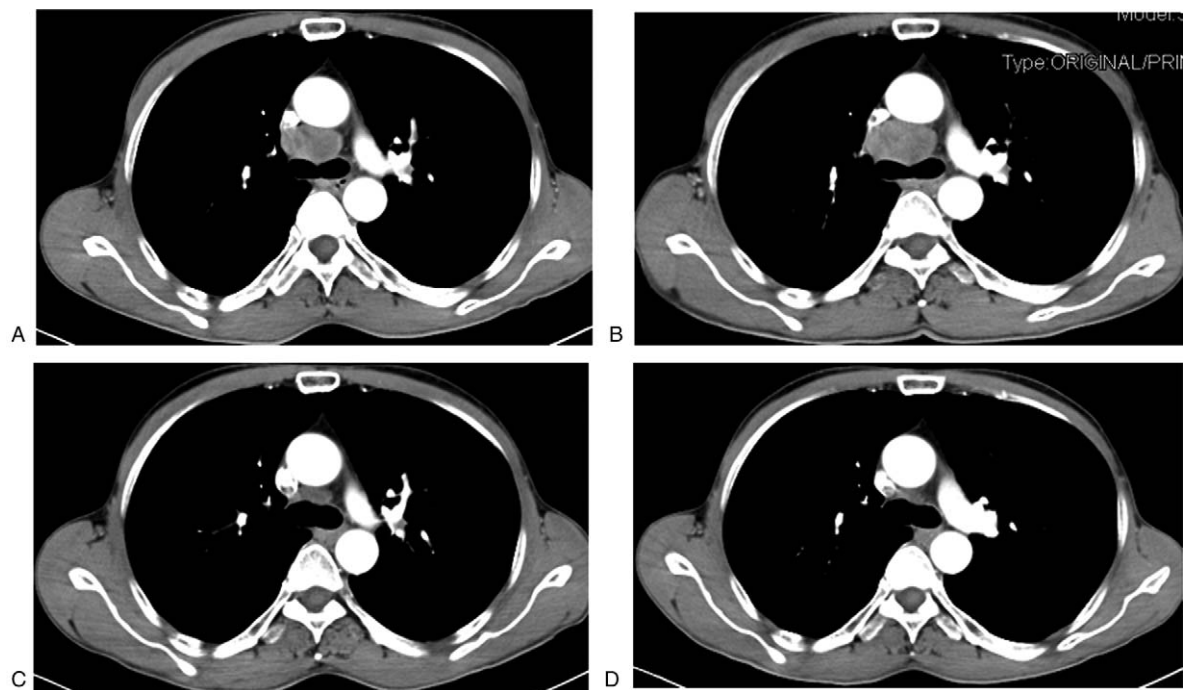


Figure 4. A, The mediastinal lymph node metastasis before Brivanib alaninate treatment (October 18, 2017). B, The mediastinal lymph node metastasis about 3 months after Brivanib alaninate treatment (January 18, 2018). C, The mediastinal lymph node metastasis 5.5 months after Brivanib alaninate treatment (April 12, 2018). D, The mediastinal lymph node metastasis about 9.5 months after Brivanib alaninate treatment (August 16, 2018).

HCC in China is HBV infection, and the prognosis of these patients is very poor.^[14]

Sorafenib, a multikinase inhibitor of Raf/MEK/ERK signaling and the tyrosine kinase receptor, is the first systemic therapeutic

agent to demonstrate efficacy in HCC in a randomized, placebo-controlled study; median time to progression (mTTP) improved from 2.8 months with placebo to 5.5 months with sorafenib, and median overall survival (mOS) improved from 7.9 to 10.7

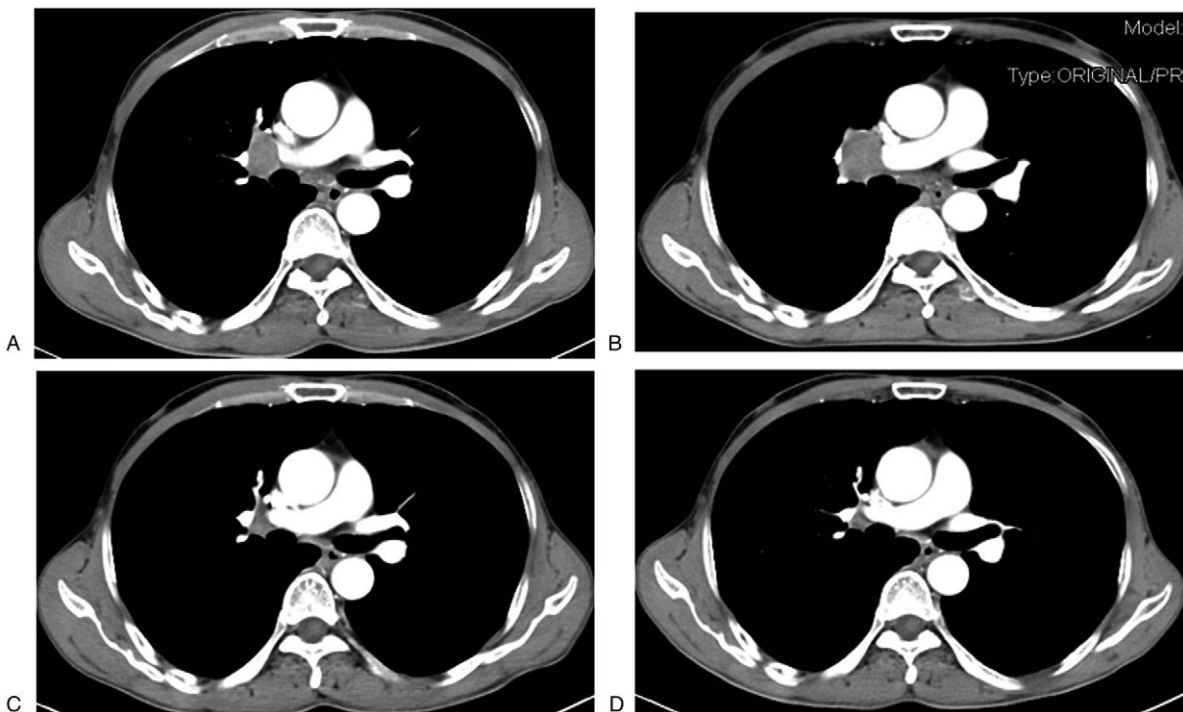


Figure 5. A, The pulmonary portal lymph node metastasis before Brivanib alaninate treatment (October 18, 2017). B, The pulmonary portal lymph node metastasis about 3 months after Brivanib alaninate treatment (January 18, 2018). C, The pulmonary portal lymph node metastasis 5.5 months after Brivanib alaninate treatment (April 12, 2018). D, The pulmonary portal lymph node metastasis about 9.5 months after Brivanib alaninate treatment (August 16, 2018).

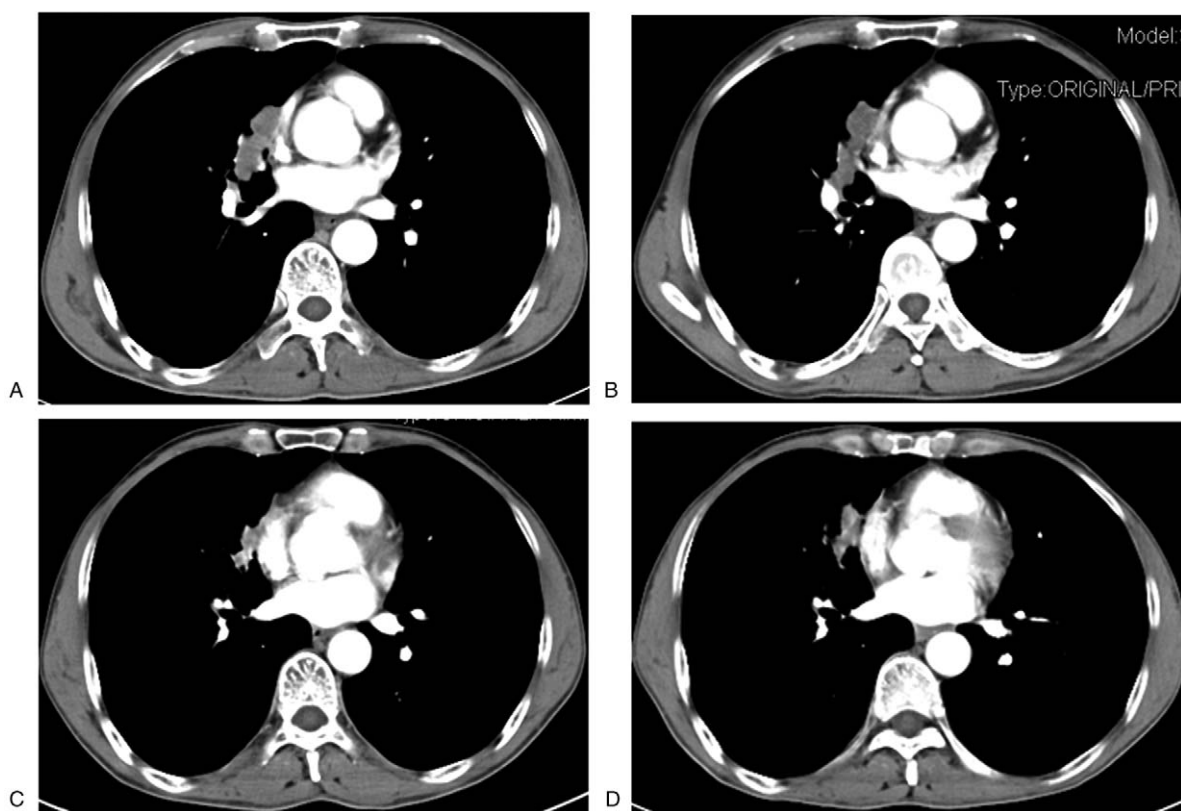


Figure 6. A, The lung metastases before Brivanib alaninate treatment (October 18, 2017). B, The lung metastases about 3 months after Brivanib alaninate treatment (January 18, 2018). C, The lung metastases 5.5 months after Brivanib alaninate treatment (April 12, 2018). D, The lung metastases about 9.5 months after Brivanib alaninate treatment (August 16, 2018).

months.^[15] Sorafenib also showed survival benefits in HCC patients of the Asia-Pacific region, with mTTP improving from 1.4 to 2.8 months, and mOS improving from 4.2 to 6.5 months.^[4] However, in clinical practice, we have found the response rate of sorafenib to be low, with resistance developing early after treatment. In the case reported here, the patient took sorafenib for approximately 1 year. Nevertheless, he developed disease progression 3 months after initiation, and the disease continued to progress thereafter. Another systemic treatment was urgently needed.

The patient then received brivanib alaninate as a second-line treatment. Three months after initiation, the tumors continued to increase slightly in size, and the AFP level continued to increase. However, all the lung metastases decreased in size significantly 2.5 months later, and some metastases disappeared. The pulmonary portal, and mediastinal lymph node metastases also decreased in size. Nine and a half months after brivanib alaninate was initiated, the pulmonary portal, and mediastinal lymph node metastases nearly disappeared and the lung metastases continued to decrease in size. The AFP level sequentially decreased at each of the 5.5- and 9.5-month follow-up evaluations, eventually to a very low level (24.94 ng/mL). Fifteen months after brivanib alaninate initiation, the patient remained in very good condition without evidence of disease progression.

As previously mentioned earlier, brivanib alaninate as first- or second-line treatment failed to meet the endpoint in both of 2 phase III clinical trials in HCC patients, but it did show similar antitumor activity as brivanib and sorafenib.^[9,10] In preclinical

studies, brivanib alaninate showed strong antitumor effects on tumor cells across a range of tumor types, including liver, colon, lung, and breast.^[16] In 2 phase II clinical studies of HCC patients, brivanib alaninate seemed to be a promising therapy that resulted in median overall survival rates of 10 and 9.79 months, respectively.^[7,8] Very surprisingly, in the report presented here, brivanib alaninate was shown to be ineffective approximately 3 months after initiation; however, it showed very good antitumor effects at 5.5 and 9.5 months. Therefore, we hypothesize that brivanib alaninate may exert its antitumor effects in a delayed onset fashion, and suggest that HCC patients receive it for a long duration to fully determine its efficacy.

The side effects of brivanib alaninate were tolerable. Although he showed repeated grade 2 thrombocytopenia, no bleeding or other related complications occurred. All adverse effects were easily relieved by appropriate treatment. More importantly, the patient did not show any sign of hand-foot syndrome, which has been the dose-limiting toxicity for many other molecular-targeted agents.^[2]

Brivanib alaninate alone as a second-line therapy showed excellent antitumor efficacy for an HCC patient with numerous lung and lymph node metastases. All lung metastases decreased in size significantly, and some disappeared. The pulmonary portal, and mediastinal lymph node metastases nearly disappeared as well. The side effects were tolerable. Brivanib alaninate may exert its antitumor effects in a delayed onset fashion. We suggest that patients receive brivanib alaninate for a long duration to fully determine its efficacy.

Author contributions

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Writing – review & editing: Hong Zhu.

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