Clinical Case Report

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Efficacy of anti-PD-1 antibody SHR-1210 as second-line treatment in hepatocellular carcinoma patient with sorafenib resistance

A case report

Hong Zhu, MD*, Xi Yang, MD, Yaqin Zhao, MD, Cheng Yi, MD

Abstract

Rationale: Hepatocellular carcinoma (HCC), one of the most common cancers worldwide, is an aggressive tumor with very poor prognosis. Regorafenib was the first agent to show a survival benefit over placebo in patients who showed progression while being treated with sorafenib, but it remains an unsatisfactory agent owing to its serious side effects. Therefore, more efficient and milder therapies are needed.

Patient concerns: Herein, we report a patient with advanced HCC with many lung metastases who showed progression during sorafenib treatment.

Diagnoses: HCC with lung metastases (stage IVB).

Interventions: SHR-1210 alone was used as second-line treatment.

Outcomes: Although the lung metastases did not decrease 3 months after the treatment, they decreased significantly at 6 months after the treatment and partially disappeared. The tumor response indicated partial response. Furthermore, all of the lung metastases continued to decrease at about 17 months after treatment. The alpha-fetoprotein levels showed a similar trend. After a follow up of 19 months, the patient remains in good health.

Lessons: SHR-1210 alone as a second-line treatment for a patient with HCC showed excellent antitumor effects. We think that SHR-1210 may exert its antitumor effects through a late-onset model, which persist for a long time. The side effects were mild and well tolerated.

Abbreviations: AFP = alpha-fetoprotein, CT = computed tomography, HCC = hepatocellular carcinoma, PD-1 = programmed cell death protein 1, PD-L1 = programmed death ligand 1.

Keywords: excellent effect, HCC, late onset, second line, SHR-1210

1. Introduction

Hepatocellular carcinoma (HCC), one of the most common cancers worldwide, is an aggressive tumor with a very poor prognosis.[1] Most patients with HCC are localized to Asia-Pacific areas. In China, over 394,000 cases of HCC are diagnosed every year, resulting in 383,000 deaths, with a mortality rate of over 97%.[2] Sorafenib was the first systemic therapeutic agent to be approved for the first-line treatment of HCC after a landmark study revealed improvements in median time to progression and overall survival.[3,4] However, the therapeutic impact of sorafenib remains limited, and patients often acquire resistance soon after treatment.[5] Thus, the second-line treatment for HCC is very important. Regorafenib was the first agent to show a survival benefit over placebo in patients who showed progression while on sorafenib, but this therapy remains unsatisfactory, with serious side effects.[6] More efficient and milder therapies are needed.

In recent years, breakthroughs in immune treatment have offered new therapeutic options for many malignancies.[7] The inhibition of the programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) pathway has emerged as a promising therapeutic strategy in a variety of cancers, such as melanoma, lung cancer, renal cell carcinoma, and head and neck squamous cell carcinoma.[7,8] One anti-PD-1 antibody, nivolumab, showed promising efficacy in patients with HCC and a manageable safety profile in a phase 1/2 dose escalation and expansion trial.[9] However, no investigation of anti-PD-1 antibody treatment for HCC has been reported.

SHR-1210 (Jiangsu Hengrui Medicine Co. Ltd, Lianyungang, Jiangsu Province, China) is a selective, humanized, high-affinity immunoglobulin G4-kappa monoclonal antibody against PD-1 that has shown antitumor effects and tolerable side effects when

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Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, P.R. China.

** Correspondence: Hong Zhu, Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China (e-mail: 441695131@qq.com).*

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used for treatment of esophageal squamous cell carcinoma and recurrent or metastatic nasopharyngeal carcinoma in prior studies.[10,11] Here, we report a patient with HCC who was treated with SHR-1210, which showed promising antitumor effects. To our knowledge, this is the first report on the treatment efficacy and side effects of SHR-1210 in a patient with HCC. The report was approved by the West China Hospital institutional review board (2017 TRAIL No. 28), and informed written consent was obtained from the patient for publication of this case report and accompanying images.

2. Case presentation

A 45-year-old male patient was brought to the outpatient department of our hospital more than 1 year ago. He had a liver mass and was clinically diagnosed with primary hepatic cancer in April 2016. His alpha-fetoprotein (AFP) levels were greater than 1210 ng/mL. He underwent transcatheter arterial chemoembolization twice, on May 31, 2016 and July 9, 2016. On August 20, 2016, he underwent a right hemihepatectomy, cholecystectomy, portal vein repair, and left hepatic hemangioma resection. The postoperative pathological examination showed that the tumor was 7 cm × 5.8 cm × 4 cm in size, with moderate differentiation, and invaded the hepatic capsule. The incisal edge was not invaded; the peripheral liver tissue showed nodular cirrhosis with mild hepatitis, and the tumor stage was stage I. The patient had a history of hepatitis B virus infection, and entecavir treatment was started from August 2016. Unfortunately, he was found to have lung metastases in November 2016 (stage IVB disease). His AFP level was 4401.00 ng/mL, so treatment was started with sorafenib 400 mg twice daily, from November 24, 2016 to July 22, 2017. On July 23, 2017, computer tomography (CT) indicated that the liver was out of tumor lesion (Fig. 1A), but there were new lung metastases (Figs. 2A, 3A, 4A, 5A, and 6A). Progressive disease, as defined by the Response Evaluation Criteria in Solid Tumors 1.1,[9] was observed. The tumor stage remained IVB, and his AFP level was 10486.00 ng/mL. Then, SHR-1210 treatment was started on August 18, 2017, at a dose of 3 mg/kg, intravenously, administered over 60 minutes, every 3 weeks. Three months later, CT examination (November 29, 2017) showed nearly no change of the lung metastases (Figs. 2B, 3B, 4B, 5B, and 6B), and the liver was out of tumor too (Fig. 1B). The tumor response indicated stable disease, and his AFP level was 17896.00 ng/mL. Six months later, CT examination (February 26, 2018) showed that all the lung metastases had begun to decrease significantly, and some metastases had disappeared (Figs. 2C, 3C, 4C, 5C, and 6C). The liver did not show any tumor lesions (Fig. 1C), and the AFP level was 6420.00 ng/mL. The result of the treatment indicated a partial response. Until the recent CT examination on January 18, 2019, the lung metastases have continued to decrease (Fig. 2D, 3D, 4D, 5D, and 6D). The patients' AFP level was 3556.00 ng/mL, and his liver has remained tumor free (Fig. 1D). At his last follow-up, 19 months after initiating SHR-1210 treatment, he was observed to be in a very good condition, without evidence of disease progression.

During the treatment process, the patient developed grade 2 hemangioma cutis and grade 3 rashes, as defined by the Common Terminology Criteria for Adverse Events 4.0.[12] However, there was no itching or pain, and the grade 3 rashes resolved spontaneously. Furthermore, bone marrow suppression, hand–foot syndrome, hypertension, alopecia, diarrhea, or other adverse events did not occur.

3. Discussion

HCC is the most common malignant primary liver cancer and affects more than half a million patients annually.[1,13] The prognosis is extremely poor, and the treatments for advanced

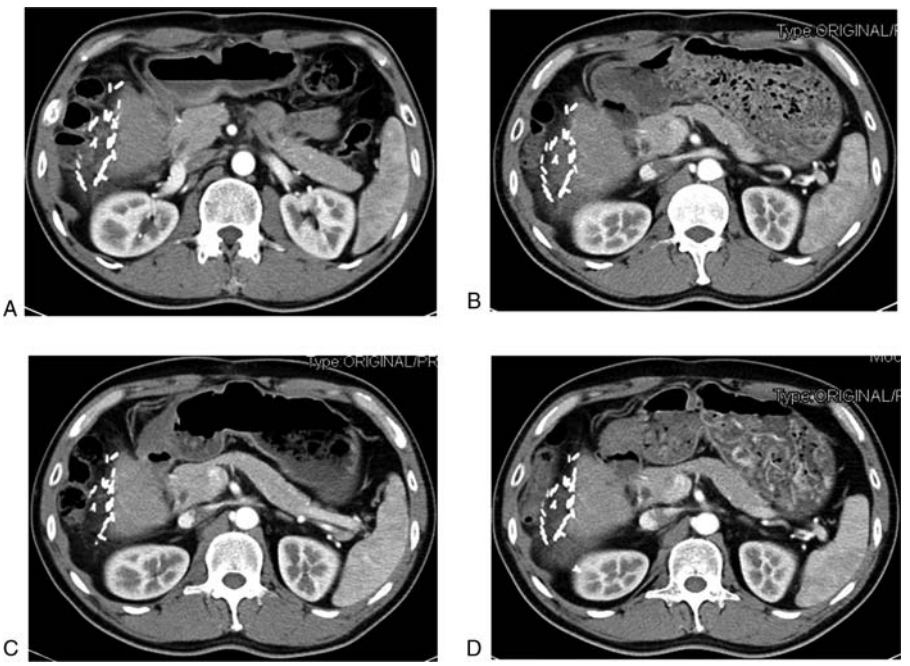

Figure 1. (A) The liver before SHR-1210 treatment (July 23, 2017). (B) The liver 3 months after SHR-1210 treatment (November 29, 2017). (C) The liver 6 months after SHR-1210 treatment (February 26, 2018). (D) The liver about 17 months after SHR-1210 treatment (January 18, 2019).

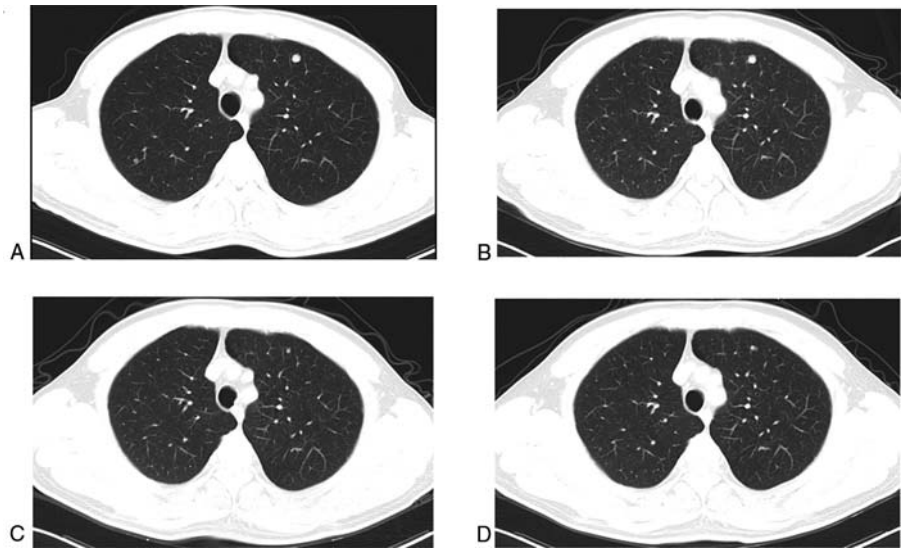

Figure 2. (A) The lung metastases before SHR-1210 treatment (July 23, 2017). (B) The lung metastases 3 months after SHR-1210 treatment (November 29, 2017). (C) The lung metastases 6 months after SHR-1210 treatment (February 26, 2018). (D) The lung metastases about 17 months after SHR-1210 treatment (January 18, 2019).

HCC are very limited.[1,2] Although regorafenib has been approved as a second-line treatment for patients with advanced HCC who show progression after sorafenib therapy, the treatment efficacy remains insufficient, and the side effects are intolerable for many patients.[1,6] With the development of immune therapy, the treatment effects on HCC need to be urgently explored.

PD-1 is expressed by activated T lymphocytes and is a pivotal immune checkpoint receptor that mediates immunosuppression upon binding to the PD-L1 expressed by tumor cells.[8] In recent years, the immunotherapies that target PD-1 and PD-L1 have shown the most promising results for treating a variety of cancers.[7] They have unexpectedly shown good efficacy for the treatment of melanoma, nonsmall cell lung cancer, renal cell carcinoma, and so on.[7,8] However, the literature on PD-1 treatment for HCC is very limited.

SHR-1210 is a high-affinity, fully humanized anti-PD-1 monoclonal antibody.[10,14] SHR-1210 has shown promising antitumor activity and a manageable toxicity profile in extensively pretreated patients with recurrent or metastatic esophageal squamous cell carcinoma, with an overall response rate of 33.3%, a disease control rate of 56.7%, and a median

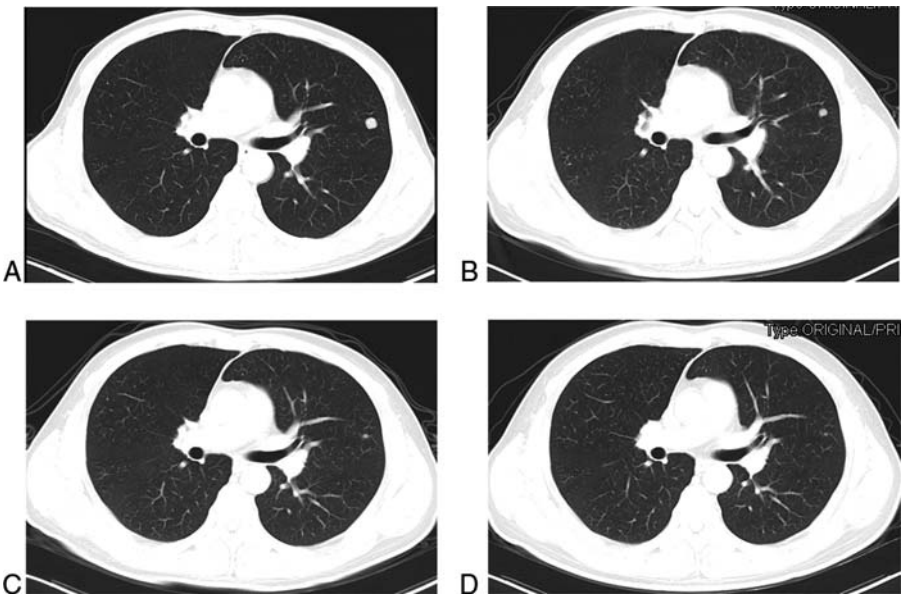

Figure 3. (A) The lung metastases before SHR-1210 treatment (July 23, 2017). (B) The lung metastases 3 months after SHR-1210 treatment (November 29, 2017). (C) The lung metastases 6 months after SHR-1210 treatment (February 26, 2018). (D) The lung metastases about 17 months after SHR-1210 treatment (January 18, 2019).

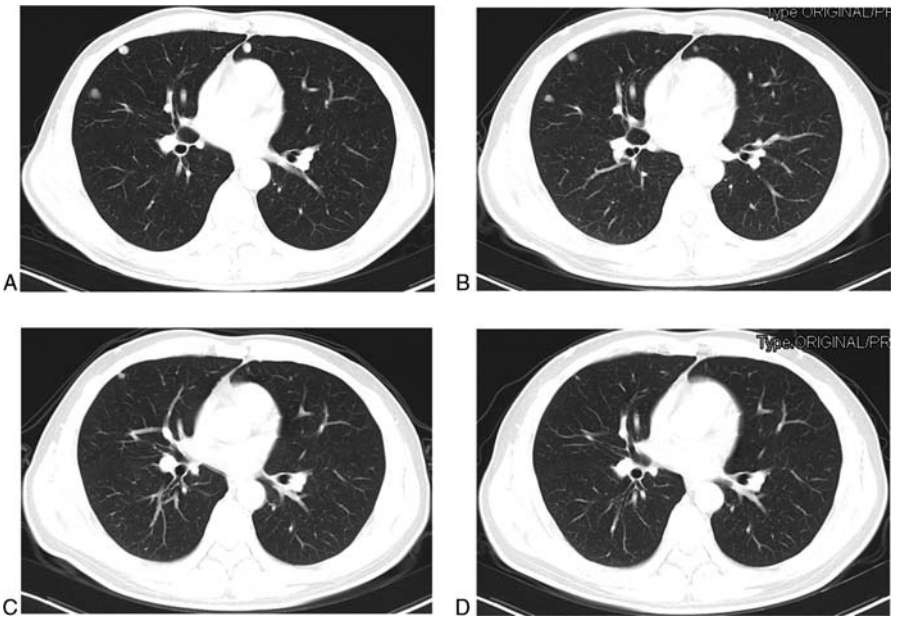

Figure 4. (A) The lung metastases before SHR-1210 treatment (July 23, 2017). (B) The lung metastases 3 months after SHR-1210 treatment (November 29, 2017). (C) The lung metastases 6 months after SHR-1210 treatment (February 26, 2018). (D) The lung metastases about 17 months after SHR-1210 treatment (January 18, 2019).

patient-free survival of 3.6 months.[10] SHR-1210 alone or combined with chemotherapy has also shown manageable toxicity profiles and promising preliminary antitumor activity in the treatment of nasopharyngeal carcinoma.[11] As regorafenib showed limited efficacy and high side effects, the patient in this study wanted to use PD-1 treatment. However, the nivolumab was too expensive, and SHR-1210 showed promising effects on some other cancer patients, so the patient chose to use SHR-1210 for a try. In this case, we found that the lung metastases did not decrease 3 months after the treatment. However, all of the lung metastases decreased significantly 6 months after treatment and continue to decrease. Furthermore, the patient's AFP levels showed a similar trend. Therefore, we think that SHR-1210 has late-onset and lasting antitumor effects in patients with HCC.

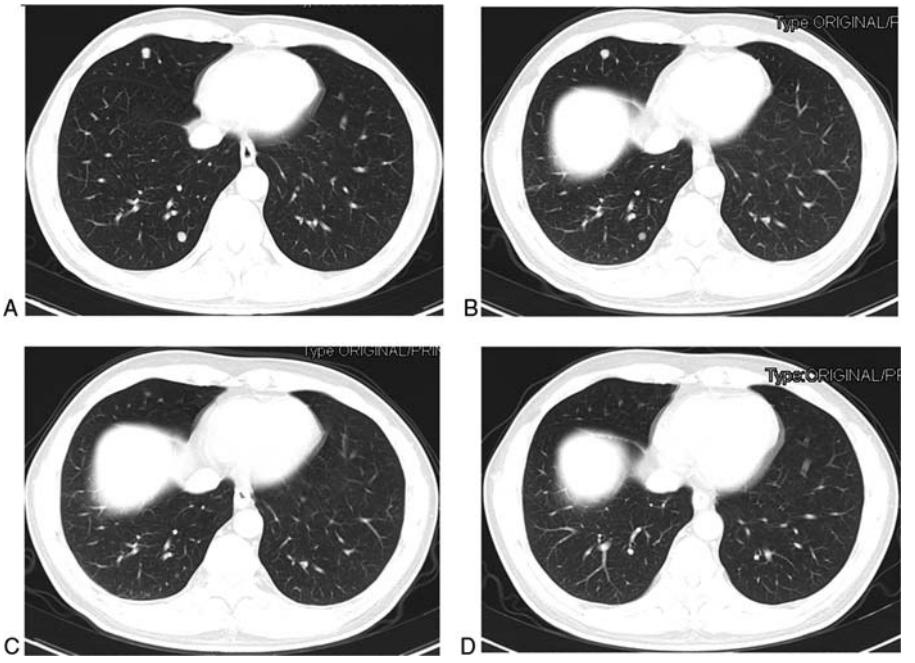

Figure 5. (A) The lung metastases before SHR-1210 treatment (July 23, 2017). (B) The lung metastases 3 months after SHR-1210 treatment (November 29, 2017). (C) The lung metastases 6 months after SHR-1210 treatment (February 26, 2018). (D) The lung metastases about 17 months after SHR-1210 treatment (January 18, 2019).

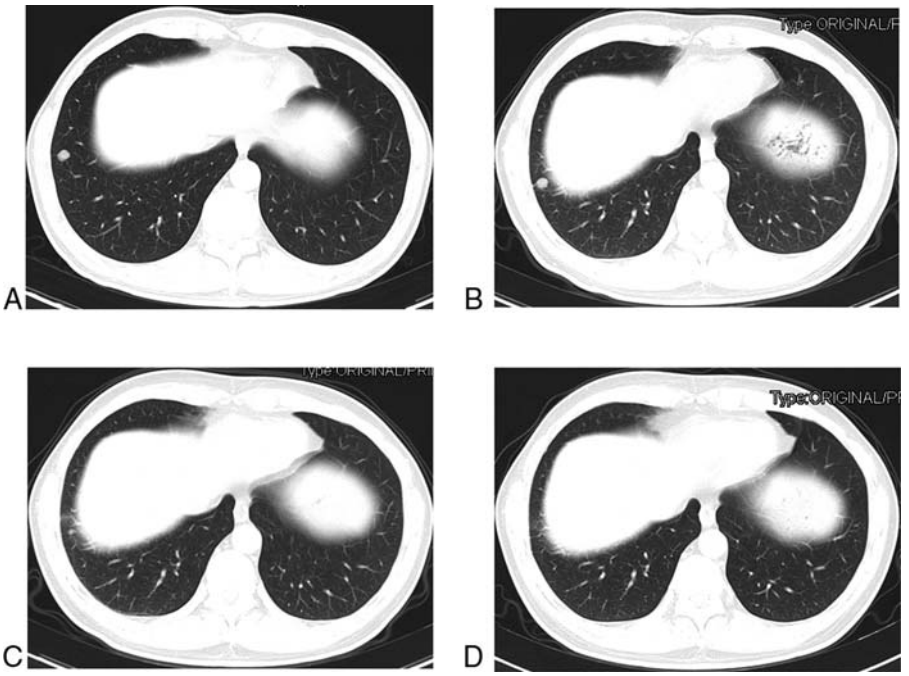

Figure 6. (A) The lung metastases before SHR-1210 treatment (July 23, 2017). (B) The lung metastases 3 months after SHR-1210 treatment (November 29, 2017). (C) The lung metastases 6 months after SHR-1210 treatment (February 26, 2018). (D) The lung metastases about 17 months after SHR-1210 treatment (January 18, 2019).

The toxicities were very mild, and the treatment was very well tolerated. Although hemangioma cutis and rashes occurred during the treatment, they did not affect the patient's life quality and improved spontaneously.

SHR-1210 alone as a second-line treatment for HCC showed excellent antitumor effects in our patient. Although the lung metastases did not decrease 3 months after treatment, they decreased significantly after 6 months, and some disappeared. Moreover, all of the lung metastases continued to decrease at about 17 months after treatment. The AFP levels showed a similar trend; therefore, SHR-1210 may exert its antitumor effects through a late-onset model, and its effects appear to persist for a long time. The side effects were mild and well tolerated.

Author contributions

Conceptualization: Hong Zhu.
Data curation: Xi Yang, Yaqin Zhao, Cheng Yi.
Investigation: Hong Zhu.
Supervision: Hong Zhu.
Validation: Hong Zhu, Yaqin Zhao, Cheng Yi.
Writing – original draft: Hong Zhu, Xi Yang.
Writing – review and editing: Hong Zhu.

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