

CASE STUDY

Combined application of the traditional Chinese herbal medicine, Renvatinib, and Carrelizumab in a patient with primary liver cancer: A case report and literature review

Yan Zhu¹ | Yaoshui Lai¹ | Hongjie Song²

¹Department of Traditional Chinese Medicine, Beijing Electric Power Teaching Hospital, Capital Medical University, Beijing, China

²Department of Oncology, Beidahuang Industry Group General Hospital, Harbin, Heilongjiang 150088, China

Correspondence

Hongjie Song, Department of Oncology, Beidahuang Industry Group General Hospital, Harbin, Heilongjiang 150088, China.
Email: janeysong@126.com

Abstract

The patient was diagnosed with primary liver cancer featuring intrahepatic metastasis (Barcelona stage B; Stage IIB), hepatitis B infection, and post-hepatitis B cirrhosis during the period of compensated liver function. Following a 7-month regimen combining traditional Chinese herbal medicine (TCHM) with Renvatinib and Carrelizumab, the patient exhibited favorable tolerability, no bleeding risks, and stable tumor progression. The effectiveness of TCHM in this case was marked by significant symptom alleviation, reduced serum molecular markers, minimized adverse reactions, and obviated surgical intervention. Blood tests displayed alpha-fetoprotein levels ranging from 8.85 to 20.65 IU/mL, with no increase in bleeding risks.

KEYWORDS

Carrelizumab, case report, literature review, primary liver cancer, Renvatinib, traditional Chinese herbal medicine

INTRODUCTION

Traditional Chinese herbal medicine (TCHM) is increasingly recognized as an effective adjunct therapy for liver cancer. Its widespread adoption in Asian countries is attributed to its cost-effectiveness, efficacy, minimal invasiveness, and absence of adverse effects. This therapeutic modality employs Fuzheng anticancer therapy, which targets the tonification of deficiencies and the expulsion of pathogenic influences [1]. This approach revitalizes Qi, regulates vital energy, enhances circulation, and nourishes the body [2].

Clinical applications of TCHM have demonstrated its potential to alleviate symptoms, enhance life quality, and reduce the toxicity associated with conventional cancer therapies such as radiotherapy and chemotherapy [3]. Additionally, it has shown promise in

improving biochemical indices, preserving liver function, and extending survival [4]. Notably, TCHM is associated with a reduced incidence of adverse reactions and a decreased likelihood of developing drug resistance [5].

This paper presents a detailed case study of a patient with primary liver cancer, characterized by intrahepatic metastasis (Barcelona stage B; Stage IIB) and compounded by hepatitis B and post-hepatitis B cirrhosis during a period of compensated liver function. The patient underwent a 7-month integrated treatment regimen combining TCHM with the targeted therapeutic agents Renvatinib and Carrelizumab. This treatment protocol resulted in good tolerability, no significant bleeding risks, and stable tumor progression. The integration of TCHM in the treatment protocol illustrates the potential for enhancing conventional therapy

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s). *Advanced Chinese Medicine* published by John Wiley & Sons Australia, Ltd on behalf of Higher Education Press.

outcomes in managing advanced liver cancer. Written informed consent for publication of this case was obtained from the patient.

CASE REPORT

Patient's presentation and diagnosis

A 69-year-old Chinese female patient presented at our hospital on July 26, 2021, with abdominal distention and hepatic pain. Previously diagnosed with chronic hepatitis B in June 2017 at a local hospital, she had not adhered to the prescribed anti-hepatitis B medication regimen and neglected follow-up exams. In February 2021, worsening symptoms of abdominal distention and hepatic pain, scoring a pain intensity of 4, led to a computed tomography (CT) scan that revealed cirrhosis with multiple nodular lesions suggestive of malignancy, prompting her admission to our hospital. Enhanced CT scans showed an irregularly shaped

hepatic morphology with an uneven surface, accompanied by the presence of multiple circular subequal density shadows within the liver (Figure 1). The arterial phase and portal vein phase demonstrate enhancement, with an increased diameter measuring approximately 21 mm × 18 mm. Nodular high-density lesions were observed along the hepatic margins. Pathological examination on October 21, 2021 revealed dysplastic hepatocytes and the presence of well-differentiated hepatocellular carcinoma in a focal area (Figure 2). The immunohistochemistry results revealed positive staining for HepPar-1 and GPC-3, with a Ki-67 proliferation index of 30%–40%. Vascular CD34 expression was observed. Smooth muscle actin staining was also positive. Additionally, screen dyeing indicated the presence of fractures. However, CK19 staining was negative while CD10 showed positive expression.

The patient's previous medical and personal history includes a chronic gastritis diagnosis, hypersensitivity to analgesic tablets, denial of hypertension, diabetes, and tuberculosis history; there is no record of food

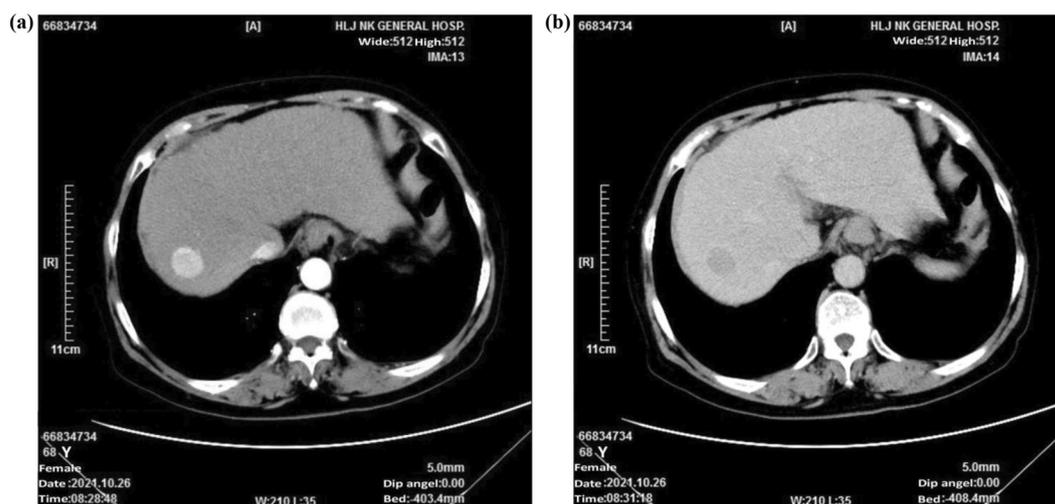


FIGURE 1 Liver enhanced computed tomography scan before treatment on October 26, 2021. (a) A size of about 21 mm × 18 mm low-density focus can be seen on the right lobe of the liver, with obvious homogeneous enhancement on arterial phase. (b) A low-density focus can be seen in the right lobe of the liver in portal phase, enhanced lower than the surrounding liver parenchyma, and boundary is still clear.

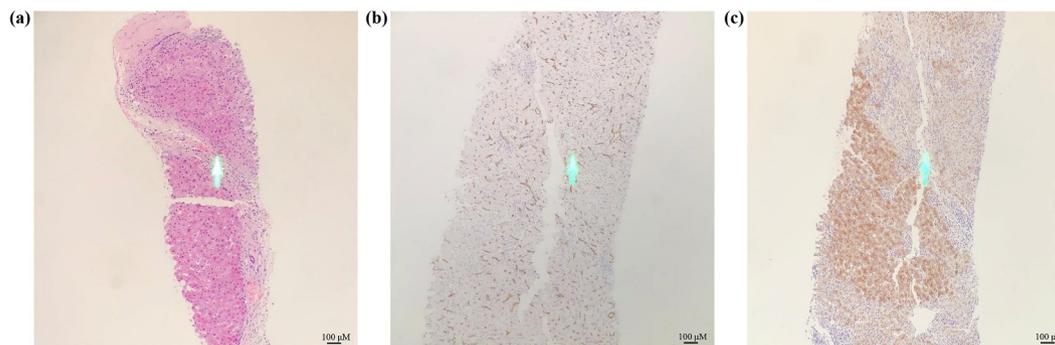


FIGURE 2 Pathological and immunohistochemistry findings by percutaneous liver puncture under CT guidance. (a) Hepatocellular carcinoma cells with HE staining. (b) Capillary network shows by CD34. (c) Heterotypic hepatocyte expression by GPC-3. CT, computed tomography; HE, Hematoxylin-eosin staining.

allergies. In June 2015, the patient underwent coronary angiography and stent implantation and has been regularly taking anticoagulant medication since then. There is no history of trauma or blood transfusion. The vaccination history is unknown. The patient denies smoking or alcohol abuse and there is no family history of infection or genetic disorders. The physical examination revealed a blood pressure reading of 123/80 mmHg, a pulse rate of 80 beats per minute, and a body temperature measuring 36.3°C. The patient's Eastern Cooperative Oncology Group score was determined to be 1. The patient had liver palms without spider nevus, and no presence of yellow mucous membranes throughout the body. Cardiopulmonary auscultation did not reveal any abnormalities. The abdomen was found to be flat and soft, with percussion pain in the liver area but negative mobile dullness; there was no enlargement observed in the liver or spleen region. Additionally, there was no evidence of edema in the lower limbs. Symptoms of traditional Chinese medicine (TCM) include anxiety, fatigue, dyspnea, hepatic discomfort and pain, and loose stools. The tongue appears pale red with a thin white coating, while the pulse is weak. The patient was diagnosed with primary liver cancer accompanied by intrahepatic metastasis (Barcelona stage B; Stage IIB), hepatitis B infection, and post-hepatitis B cirrhosis during the period of compensated liver function. TCM diagnosis are liver depression and spleen deficiency; Qi deficiency and blood stasis.

Treatment and clinical course

Radiofrequency ablation treatment was considered for her, along with daily oral administration of 8 mg Renvatinib and intravenous drip of Carrelizumab at a dosage of 200 mg every 21 days. Additionally, TCHM was administered (Table 1). The herbal solution was subjected to two rounds of boiling and thorough mixing, followed by daily administration during the time intervals of 9:00–10:00 a.m. and 15:00–16:00 p.m. During the treatment period, the herbal solution was administered biweekly at our medical facility, with a total duration of 6 months. Abdominal distension added *Toosendan Fructus* 10 g, *Citri Reticulatae Semen* 15 g; Insomnia added *Ziziphi Spinosae Semen* 15 g, *Platycladi Semen* 15 g; Dry mouth and short breath removed *Codonopsis Radix*, and added *Pseudostellariae Radix* 15 g; White sputum added *Citri Reticulatae Pericarpium* 12 g, *Platycodonis Radix* 8 g and *Pinelliae Rhizoma* 10 g; Hot flushes and sweating added *Moutan Cortex* 10 g and *Lycii Cortex* 20 g.

Enhanced CT scan of the liver conducted on November 25, 2021, revealed (Figure 3) an irregularly shaped liver with a non-uniform surface texture. Multiple aberrant angiographic enhancements are observed

TABLE 1 The herbs and dose used in the formula used in the case.

Herbs	Chinese name	Dose (g)
<i>Trionycis Carapax</i>	Bie Jia	30
<i>Paeoniae Radix Alba</i>	Bai Shao	10
<i>Curcumae Rhizoma</i>	E'Zhu	10
<i>Radix Actinidia root</i>	Tengli Gen	10
<i>Codonopsis Radix</i>	Dang Shen	6
<i>Astragali Radix</i>	Huang Qi	30
<i>Notoginseng Radix</i>	Sanqi Powder	3
<i>Amomi Fructus</i>	Sha Ren	10
<i>Bupleuri Radix</i>	Chai Hu	10
<i>Coicis Semen</i>	Yiyi Ren	30
<i>Poria</i>	Fu Ling	20
<i>Citrus Tangerina</i>	Ju Ye	10
<i>Glycyrrhizae Radix</i>	Gan Cao	3
<i>Ganoderma</i>	Ling Zhi	10
<i>Dioscoreae Rhizoma</i>	Shan Yao	20
<i>Aucklandiae Radix</i>	Mu Xiang	10

in the liver. The CT attenuation values of the arterial phase, portal phase, and equilibrium phase were approximately 40, 44, and 45 HU respectively. Additionally, the true dimensions of the larger entity measured approximately 2 mm × 28 mm. The balance period revealed a relatively low-density lesion measuring approximately 5 mm in diameter located in the parietal region of the liver; the arterial and portal phase exhibit suboptimal visualization, while a nodular high-density lesion is observed at the periphery of the liver. The liver enhanced CT scan (Figure 4) conducted on May 25, 2022 was reassessed, revealing an irregular shape of the liver with an uneven surface. Additionally, multiple quasi-circular mixed density lesions were observed within the liver. The lesions on the enhanced scan did not exhibit any apparent enhancement, and the larger lesion measured approximately 18 mm × 29 mm in size. The blood surveillance revealed a range of alpha-fetoprotein (AFP) levels from 8.85 to 20.65 IU/mL (Table 2), with no observed increase in the risk of bleeding (Table 3).

DISCUSSION

Liver cancer poses significant challenges due to limited treatment options

According to global cancer statistics [6], primary liver cancer has emerged as the sixth most prevalent malignancy and the fourth leading cause of cancer-related

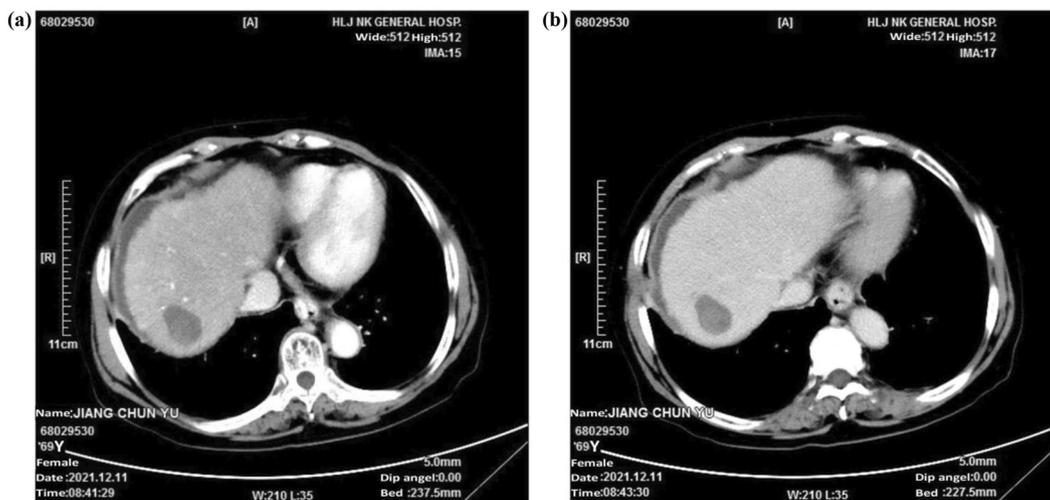


FIGURE 3 Liver enhanced computed tomography scan after treatment on December 11, 2021. (a) A size of about 21 mm × 28 mm low-density focus can be seen on the right lobe of the liver, larger than before, with slight enhancement in arterial phase which is significantly lower than the surrounding liver parenchyma. (b) Slight patchy enhancement can be seen in the low-density focus of the right lobe of the liver in the portal phase.

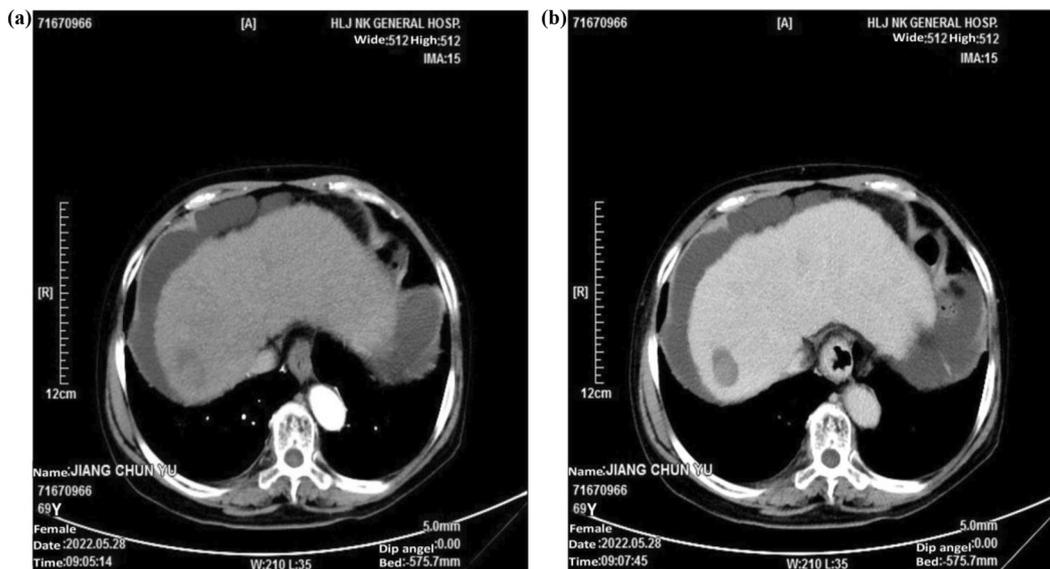


FIGURE 4 Liver enhanced computed tomography scan after treatment on May 28, 2022. (a) A size of about 18 mm × 29 mm low-density focus can be seen on the right lobe of the liver, with mild homogeneous enhancement in the arterial phase. (b) Slight patchy enhancement can be seen in the low-density focus in the liver portal phase, significantly lower than the surrounding liver parenchyma.

mortality worldwide, posing a significant threat to human life and well-being. Among the newly reported cases of liver cancer deaths in China, there were a total of 326,000 fatalities (242,000 males and 84,000 females). The age-standardized mortality rates for males and females were recorded as 15.33 per 100,000 and 15.09 per 100,000 respectively [7], based on both Chinese standard population and World Segi's population.

Currently, the diagnosis of hepatocellular carcinoma primarily relies on [8] imaging modalities including ultrasound, CT/magnetic resonance imaging, digital subtraction angiography, nuclear medicine imaging

techniques, and hematological molecular markers. Serum AFP serves as a crucial and prevalent biomarker for the diagnosis of hepatocellular carcinoma and its therapeutic monitoring. Moreover, puncture biopsy of liver lesions for diagnostic purposes is generally not recommended in patients exhibiting typical imaging features and meeting the clinical diagnostic criteria of hepatocellular carcinoma.

The current therapeutic modalities for primary liver cancer [9] encompass surgical intervention, local ablation techniques, transcatheter arterial chemo-embolization, radiotherapy, pharmacotherapy, and immunotherapy. In the early stages of hepatocellular

carcinoma, the best outcomes are achieved through tumor resection, transcatheter arterial chemo-embolization, or radiofrequency ablation. However, due to the disease's insidious onset and the absence of typical clinical manifestations in the early stages, most patients are diagnosed in the middle or late stages with obvious cirrhosis and poor liver function. For such patients, comprehensive treatment measures should be taken.

Currently, clinical practice commonly uses a combination of TCHM and other treatment methods to reduce the side effects of combined treatment and improve patients' prognosis and quality of life [10]. Targeted drugs inhibit primary liver cancer's development by anti-angiogenesis and anti-cell proliferation. However, drug resistance and adverse reactions are common problems that can affect patient medication compliance and clinical efficacy. Combining TCHM and targeted drugs can enhance the efficacy of targeted drugs, alleviate their adverse reactions, prolong survival cycles, and increase survival rates. This combination treatment reduces targeted drug resistance and gives new hope for patients with primary liver cancer.

The Chinese herbs used in this particular case have shown varying degrees of effectiveness in fighting cancer

Astragali Radix is recognized as a Qi and deficiency tonic in traditional medicine. The application of this treatment primarily focuses on addressing bodily deficiencies, excessive perspiration, gastrointestinal disorders,

uterine prolapse, chronic nephritis, neoplastic conditions, and edematous states. The chemical composition of *Astragali Radix* [11] primarily comprises saponins, flavonoids, nitrogenous compounds, and aminophenols. The extracts of *Astragali Radix* have demonstrated the ability to impede tumor cell proliferation and facilitate tumor cell apoptosis. The administration of *Astragali Radix* enhances the non-specific functions of the immune system, including both humoral and cellular immunity. The administration of *Astragali Radix* extract resulted in a significant reduction in liver index parameters and a decrease in the secretion levels of Alanine Transaminase (ALT), Aspartate Transaminase, Serum total cholesterol, and Triglyceride [12]. The polysaccharides, saponins, and flavonoids of *Astragali Radix* have been extensively documented for their anticancer effects in preclinical studies. Moreover, the whole extract of *Astragali Radix* has shown promising potential as an adjunctive cancer therapeutics due to its immunomodulatory properties, anti-proliferative activity, and ability to mitigate adverse events associated with cytotoxic therapy [13].

Trionycis Carapax (Soft-Shell Turtle [SST]) is a well-established functional food in TCM, known for its immune-boosting properties through mechanisms that are yet to be fully understood. Feng et al. [14] discovered that oral administration of the SST powder exhibits potential in suppressing solid tumor growth by stimulating the host immune system. Recent studies have demonstrated [15] that SST peptides possess the ability to modulate cancer-related pathways by regulating miRNA expression in gastric cancer (GC) cells. The application of SST [16] has been employed to enhance the prognostic outcomes of cancer patients undergoing radiotherapy and chemotherapy.

Bupleuri Radix is recognized for its ability to alleviate Qi and relieve depression. The primary bioactive constituents of *Bupleuri Radix* contain triterpenoid saponins, flavonoids, and essential oil. Polysaccharides present in Vinegar-baked *Bupleuri Radix* were found by Wu et al. [17] to enhance liver targeting. The underlying mechanism was associated with the up-regulation of OCT1 and HNF4 α expression, accompanied by down-regulation of Mrp2. Hang et al. [18] discovered that the aqueous extracts of *Bupleuri Radix* exhibit the potential to augment 5-fluorouracil-induced cytotoxicity in

TABLE 2 Progress of α -fetoprotein (AFP) throughout the course of the case.

Date	AFP (0–5.500 IU/mL)
Jul 26, 2021	19.95
Oct 22, 2021	14.4
Dec 25, 2021	9.981
Jan 13, 2022	11.85
Mar 7, 2022	20.65
May 25, 2022	8.85

TABLE 3 Monitoring results of blood coagulation items.

Date	D-dimer (0–0.50)	Antithrombin (80%–120%)	Prothrombin time (11–15.0 s)	Prothrombin activity (70–150.00)
Oct 22, 2021	0.87	64	16.4	60.47
Dec 25, 2021	1.21	38	19	46.43
Jan 13, 2022	1.11	66	16.4	60.47
Mar 7, 2022	0.96	70	22.0	55.32
May 25, 2022	4.13	58	18.3	49.52

HepG2 hepatoma cells by inducing cellular arrest at the late G1/early S phase, while concurrently safeguarding normal blood lymphocytes. The active constituents of *Bupleuri Radix* exhibited remarkable efficacy against the HepG2 cell line, with an IC₅₀ value of 12.5 mg/mL [19]. The mechanism underlying cytotoxicity is believed to involve the activation of caspase-3 and caspase-7, leading to subsequent cleavage of poly-ADP-ribose polymerase (PARP), thereby inducing apoptosis. The study conducted by Hou et al. [20] demonstrated that the active constituents of *Bupleuri Radix* exerted their antitumor effects on the human hepatocellular carcinoma cell line SMMC-7721 through modulation of the HIF-1 α /COX-2 pathway. The combination of *Paeoniae Radix Alba* and *Bupleuri Radix* exhibits hepatoprotective properties and has been traditionally employed in China for the management of depression.

The antioxidant and antifatigue effects of *Paeoniae Radix Alba* have been scientifically demonstrated [21]. The study conducted by Bae et al. revealed that *Paeoniae Radix Alba* exerts an inhibitory effect on cancer cachexia through the down-regulation of NF- κ B signaling in skeletal muscles and muscle-specific E3 ubiquitin ligases [22]. Wu et al. [23] reported the combined administration of *Paeoniae Radix Alba* and *Astragali Radix* induces apoptosis and inhibits the proliferation, migration and invasion of human hepatoma cells.

Curcumae Rhizoma is extensively prescribed in TCHM for its broad-spectrum antineoplastic activities, making it a valuable candidate for anticancer therapy. Terpenoids derived from the essential oil of *Curcumae Rhizoma* constitute an integral component in cancer research and are widely acknowledged as a promising candidate for anticancer therapy [24]. Terpenoids derived from the essential oil of *Curcumae Rhizoma* constitute an integral component in cancer research and are widely acknowledged as a promising candidate for anticancer therapy. The anti-cancer effects of these terpenoids [25] are associated with the delay in cell cycle arrest, induction of apoptosis, and inhibition of metastasis or tissue invasion. The key drug targets of *Curcumae Rhizoma* acting on HBV-Related Hepatocellular carcinoma (HCC) are mainly enriched in cell cycle checkpoint, DNA integrity checkpoint, and peptidyl-serine modification [26]. *Curcumae Rhizoma* is used in combination with *Astragali Radix* in a certain ratio, mainly for the treatment of digestive tract-related inflammation and tumors [27].

Radix Actinidia root is used primarily for the treatment of tumors of the digestive tract based on TCHM theory. Ethanol extracted from *Radix Actinidia root* [28] may be a promising anti-Cholangiocarcinoma agent and could be beneficial in the treatment of Cholangiocarcinoma through the targeting of Mcl-1. Hu et al. [29] also found that *Radix Actinidia root* effectively

inhibits human colon tumor through inhibiting Notch-signaling pathway. Crosolic Acid [30] isolated from *Radix Actinidia root* induces apoptosis of human GC cell line BGC823 in vitro via down-regulation of the NF- κ B pathway.

Codonopsis Radix have shown activities against several types of cancer [31]. Lobetyolin, isolated from the roots of *Codonopsis Radix*, down-regulated the glutamine metabolism, contributing to drug-induced apoptosis and tumor growth inhibition. Lobetyolin markedly reduces both mRNA and protein expression of the amino acid transporter alanine-serine-cysteine transporter 2. In Liu's study [32], 12 differentially expressed genes (5 upregulated and 7 downregulated) of *Codonopsis pilosula* treating HepG2 cells (a kind of HCC cell) were identified. Ko et al. [33] showed that two genes, GDF15 and HMOX1, could serve as biomarkers in liver cells for identifying responses after treatment with *Codonopsis Radix* and *Astragali Radix*. Acidic polysaccharide (CPPA) from the roots of *Codonopsis Radix* may be a potential candidate compound for the prevention of tumor metastasis [34], presumably by inhibiting invasion, migration, and adhesion of tumor cells, as well as the CD44 expression on the tumor cells.

Ganoderma, also known as Ling-zhi, is a type of mushroom generally cultivated on oak trees and plum trees, are commonly used in Chinese medicine, with the thought that they are effective in energy enhancement, stimulation of the immune system, and prolongation of life [35]. *Ganoderma lucidum* polysaccharides is the main bioactive component in the water-soluble extracts of this mushroom. There are laboratory and animal studies that show the immunomodulatory, anti-inflammatory, hepatoprotective, anti-metastatic and anti-angiogenic effects of *G. lucidum* extract [36–42]. *Ganoderma lucidum* could be administered as an alternative adjunct to conventional treatment in consideration of its potential of enhancing tumor response and stimulating host immunity [43]. No major toxicity was observed across the studies.

Notoginseng Radix attracts attention and interest due to its potential therapeutic effects not only on blood diseases, but also other kinds of human chronic disorders [44]. *Notoginseng Radix* is a multi-targeted agent with anti-inflammatory properties in the adjuvant and alternative treatment of chronic diseases in humans. Zhong et al. [45] found that *Notoginseng Radix* saponins promote liver regeneration through activation of the PI3K/AKT/mTOR cell proliferation pathway and upregulation of the AKT/Bad cell survival pathway in mice. Liu et al. [46] found that Neutral Polysaccharide from *Notoginseng Radix* has a potential antitumor activity for the treatment of liver cancer combined with cyclophosphamide.

CONCLUSION

TCHM can effectively improve the patient's symptoms and reduce adverse reactions

This case underscores the potential of integrating TCHM with contemporary oncological therapies in treating primary liver cancer. By utilizing TCHM, we observed not only an improvement in clinical symptoms and biochemical markers but also a reduction in the adverse effects commonly associated with conventional cancer treatments. The potential principles [9, 10] are that TCHM inhibits the proliferation and induces apoptosis of liver cancer cells by blocking the cell cycle, decreasing telomerase activity, affecting mitogen-activated protein kinase, phosphatidylinositol-3-hydroxykinase/protein kinase B (PI3K/Akt), signal transduction and transcription activation factor 3, and activating caspase containing cysteine. It can inhibit the invasion and metastasis of liver cancer cells, reverse the drug resistance of liver cancer cells, and enhance the immunity of the body by affecting the vascular endothelial growth factor pathway, matrix metalloproteinases pathway, and reactive oxygen species.

To sum up, TCHM has shown to have multi-level, multi-targets, and coordinated intervention effects in treating liver cancer. It is expected to become a promising pharmaceutical agent for hepatocellular carcinoma treatment in the near future. Future research should focus on elucidating the mechanisms of action of TCHM, exploring its potential synergies with other treatments, and defining strategies to minimize toxicity, thereby enhancing the therapeutic landscape for liver cancer.

AUTHOR CONTRIBUTIONS

Yan Zhu: Conceptualization; project administration; writing – original draft. **Yaoshui Lai:** Writing – original draft. **Hongjie Song:** Project administration.

CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data and materials used during the paper are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Beidahuang Industry Group General Hospital (reference number BDAJTZY-2022-002-LW).

PATIENT CONSENT FOR PUBLICATION

Patient consent for publication of material in oncology letters was obtained.

REFERENCES

- Liao YH, Lin CC, Lai HC, Chiang JH, Lin JG, Li TC. Adjunctive traditional Chinese medicine therapy improves survival of liver cancer patients. *Liver Int.* 2015;35(12):2595-2602.
- Li HM. Microcirculation of liver cancer, microenvironment of liver regeneration, and the strategy of Chinese medicine. *Chin J Integr Med.* 2016;22(3):163-167.
- Dong S, Zhuang X, Yangyang L, et al. Efficacy and safety of acupuncture combined with Chinese herbal medicine in the treatment of primary liver cancer: a protocol for systematic review and meta-analysis. *Medicine (Baltim).* 2021;100(40):e27497.
- Li M, Qiao C, Qin L, Zhang J, Ling C. Application of traditional Chinese medicine injection in treatment of primary liver cancer: a review. *J Tradit Chin Med.* 2012;32(3):299-307.
- Zhang RR, Shao MY, Fu Y, et al. Network meta-analysis of oral Chinese patent medicine for adjuvant treatment of primary liver cancer. *Zhongguo Zhongyao Zazhi.* 2021;46(9):2333-2343 (in Chinese).
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):1-31.
- An L, Zeng HM, Zheng RS, et al. Liver cancer epidemiology in China. *Zhonghua Zhongliu Zazhi.* 2019;41(10):721-727 (in Chinese).
- Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53(3):1020-1022.
- He S, Liao CX. Research progress on the mechanism of traditional Chinese medicine in the treatment of liver cancer. *Chin Pat Med.* 2017;39(1): 155-160 (in Chinese).
- Zhang Y, Chen HG, Zhao C, et al. Research progress on anti-hepatoma mechanism of effective components of traditional Chinese medicine. *Chin J Tradit Chin Med.* 2020;45(14):3395-3406 (in Chinese).
- Zhang CH, Yang X, Wei JR, et al. Ethnopharmacology, phytochemistry, pharmacology, toxicology and clinical applications of *Radix Astragali*. *Chin J Integr Med.* 2021;27(3):229-240.
- Wang Y, Liu QG, Wang SS, et al. Progress in treatment of kidney disease with *Astragalus*. *J Agric Sci Yanbian Univ (Chin).* 2016;38:105-108, 138.
- Jung YH, Jerng U, Lee SY. A systematic review of anticancer effects of *Radix Astragali*. *Chin J Integr Med.* 2016;22(3):225-236.
- Feng H, Yamazaki M, Matsuki N, Saito H. Anti-tumor effects of orally administered soft-shelled turtle powder in mice. *Biol Pharm Bull.* 1996;19(3):367-368.
- Wu YC, Liu X, Wang JL, et al. Soft-shelled turtle peptide modulates microRNA profile in human gastric cancer AGS cells. *Oncol Lett.* 2018;15(3):3109-3120.
- Fu JJ, Tan SL, Li YG, Lv H, Zhu WF, Liu HN. Adjuvant effects of snapping turtle co-peptide (STCP) on radiotherapy for cancer. *J Jiangxi Uni Trad Chin Med.* 2015;27:68-71 (in Chinese).
- Wu Y, Liu L, Zhao Y, Zhao R. Polysaccharides of vinegar-baked *radix bupleuri* promote the hepatic targeting effect of oxymatrine by regulating the protein expression of HNF4 α , Mrp2, and OCT1. *J Ethnopharmacol.* 2021;267:113471.
- Hang SJ, Lee YJ, Kim BM, et al. Effect of *Bupleuri Radix* extracts on the toxicity of 5-fluorouracil in HepG2 hepatoma cells and normal human lymphocytes. *Basic Clin Pharmacol Toxicol.* 2008;103(4):305-313.

19. Chiang LC, Ng LT, Liu LT, Shieh DE, Lin CC. Cytotoxicity and anti-hepatitis B virus activities of saikosaponins from *Bupleurum* species. *Planta Med.* 2003;69(8):705-709.
20. Hou HL, He SX, Zhu ZF, et al. The role of saikosaponin d in regulating HIF-1 α /COX-2 signal transduction pathway in human hepatocellular carcinoma cells. *J Xi'an Jiaot Univ.* 2011;32:80-84.
21. Kwon DA, Kim YS, Kim SK, Baek SH, Kim HK, Lee HS. Antioxidant and antifatigue effect of a standardized fraction (HemoHIM) from *Angelica gigas*, *Cnidium officinale*, and *Paeonia lactiflora*. *Pharm Biol.* 2021;59(1):391-400.
22. Bae T, Jang J, Lee H, et al. *Paeonia lactiflora* root extract suppresses cancer cachexia by down-regulating muscular NF- κ B signalling and muscle-specific E3 ubiquitin ligases in cancer-bearing mice. *J Ethnopharmacol.* 2020;246:112222.
23. Wu JJ, Sun WY, Hu SS, Zhang S, Wei W. A standardized extract from *Paeonia lactiflora* and *Astragalus membranaceus* induces apoptosis and inhibits the proliferation, migration and invasion of human hepatoma cell lines. *Int J Oncol.* 2013;43(5):1643-1651.
24. Chen Y, Zhu Z, Chen J, et al. Terpenoids from *Curcuma Rhizoma*: their anticancer effects and clinical uses on combination and versus drug therapies. *Biomed Pharmacother.* 2021;138:111350.
25. Lu JJ, Dang YY, Huang M, Xu WS, Chen XP, Wang YT. Anticancer properties of terpenoids isolated from *Rhizoma Curcuma*—a review. *J Ethnopharmacol.* 2012;143(2):406-411.
26. Zhao M, Fu Y, Liu L, et al. Identification of key drug targets and molecular mechanisms of *Curcuma Rhizoma* acting on HBV-related HCC: weighted correlation network and network pharmacological analyses. *Evid Based Complement Alternat Med.* 2022;2022:5399766.
27. Sun RL, Tang DC, Gu JF. Study on intervention effect of *Astragali Radix-Curcuma Rhizoma* on growth and metastasis of colon cancer in orthotopic transplantation mice model of colon cancer. *Zhongguo Zhongyao Zazhi.* 2021;46(9):2267-2275 (in Chinese).
28. Zhao X, Wen F, Wang W, Lu Z, Guo Q. *Actinidia arguta* (Hardy Kiwi) root extract exerts anti-cancer effects via Mcl-1-mediated apoptosis in cholangiocarcinoma. *Nutr Cancer.* 2019;71(2):246-256.
29. Hu W, Wu C, Yuan C, Chen M, Jin C, Zheng C. Ethanol extracted from *Radix of Actinidia chinensis* inhibits human colon tumor through inhibiting Notch-signaling pathway. *J Cancer.* 2021;12(3):622-629.
30. Cheng QL, Li HL, Li YC, Liu ZW, Guo XH, Cheng YJ. CRA (Crosolic Acid) isolated from *Actinidia valvata* Dunn. Radix induces apoptosis of human gastric cancer cell line BGC823 in vitro via down-regulation of the NF- κ B pathway. *Food Chem Toxicol.* 2017;105:475-485.
31. Bailly C. Anticancer properties of lobetyolin, an essential component of *Radix Codonopsis* (Dangshen). *Nat Prod Bioprospect.* 2021;11(2):143-153.
32. Liu Z, Sun Y, Zhen H, Nie C. Network pharmacology integrated with transcriptomics deciphered the potential mechanism of *Codonopsis pilosula* against hepatocellular carcinoma. *Evid Based Complement Alternat Med.* 2022;2022:1340194.
33. Ko PH, Huang CW, Chang HH, Chuang EY, Tsai MH, Lai LC. Identifying the functions and biomarkers of *Codonopsis pilosula* and *Astragalus membranaceus* aqueous extracts in hepatic cells. *Chin Med.* 2019;14(1):10.
34. Xin T, Zhang F, Jiang Q, et al. The inhibitory effect of a polysaccharide from *Codonopsis pilosula* on tumor growth and metastasis in vitro. *Int J Biol Macromol.* 2012;51(5):788-793.
35. Unlu A, Nayir E, Kirca O, Ozdogan M. *Ganoderma lucidum* (Reishi mushroom) and cancer. *J BUON.* 2016;21(4):792-798.
36. Joseph S, Sabulal B, George V, Antony KR, Janardhanan KK. Antitumor and anti-inflammatory activities of polysaccharides isolated from *Ganoderma lucidum*. *Acta Pharm.* 2011;61(3):335-342.
37. Jin H, Jin F, Jin JX, et al. Protective effects of *Ganoderma lucidum* spore on cadmium hepatotoxicity in mice. *Food Chem Toxicol.* 2013;52:171-175.
38. Chen HS, Tsai YF, Lin S, et al. Studies on the immuno-modulating and anti-tumor activities of *Ganoderma lucidum* (Reishi) polysaccharides. *Bioorg Med Chem.* 2004;12(21):5595-5601.
39. Gao Y, Zhou S, Wen J, Huang M, Xu A. Mechanism of the antiulcerogenic effect of *Ganoderma lucidum* polysaccharides on indomethacin-induced lesions in the rat. *Life Sci.* 2002;72(6):731-745.
40. Hsu MJ, Lee SS, Lin WW. Polysaccharide purified from *Ganoderma lucidum* inhibits spontaneous and Fas-mediated apoptosis in human neutrophils through activation of the phosphatidylinositol 3 kinase/Akt signaling pathway. *J Leukoc Biol.* 2002;72(1):207-216.
41. Shieh YH, Liu CF, Huang YK, et al. Evaluation of the hepatic and renal-protective effects of *Ganoderma lucidum* in mice. *Am J Chin Med.* 2001;29(03n04):501-507.
42. Sohretoglu D, Huang S. *Ganoderma lucidum* polysaccharides as an anti-cancer agent. *Anti Cancer Agents Med Chem.* 2018;18(5):667-674.
43. Jin X, Ruiz Beguerie J, Sze DM, Chan GC. *Ganoderma lucidum* (Reishi mushroom) for cancer treatment. *Cochrane Database Syst Rev.* 2016;4(4):CD007731.
44. Xu Y, Tan HY, Li S, Wang N, Feng Y. *Panax notoginseng* for inflammation-related chronic diseases: a review on the modulations of multiple pathways. *Am J Chin Med.* 2018;46(5):971-996.
45. Zhong H, Wu H, Bai H, et al. *Panax notoginseng* saponins promote liver regeneration through activation of the PI3K/AKT/mTOR cell proliferation pathway and upregulation of the AKT/Bad cell survival pathway in mice. *BMC Compl Alternative Med.* 2019;19(1):122.
46. Liu YH, Qin HY, Zhong YY, et al. Neutral polysaccharide from *Panax notoginseng* enhanced cyclophosphamide antitumor efficacy in hepatoma H22-bearing mice. *BMC Cancer.* 2021;21(1):37.

How to cite this article: Zhu Y, Lai Y, Song H. Combined application of the traditional Chinese herbal medicine, Renvatinib, and Carrelizumab in a patient with primary liver cancer: a case report and literature review. *Adv Chin Med.* 2024;1(2):128-135. <https://doi.org/10.1002/acm4.20>