Tropical Journal of Pharmaceutical Research September 2022; 21 (9): 1973-1978
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i9.22

Original Research Article

Concomitant administration of lenvatinib and camrelizumab for the treatment of hepatocellular carcinoma, and its effect on hepatocellular carcinoma control

Ruibao Liu, Xiaolei Zhang, Wei Wei, Xing Wang*
Department of Oncology, The People's Hospital of Dongying, Dongying, Shandong Province, China

For correspondence:* ***Email:* *wangxingliuweixin@163.com*

Sent for review: 18 May 2022 *Revised accepted: 31 August 2022*

Abstract

Purpose: *To study the efficacy of combined use of lenvatinib and camrelizumab in hepatocellular carcinoma (HCC) therapy, and its impact on disease control rate (DCR).*
Methods: *The medical records of 92 HCC patients treated at the Oncology Department of The People's Hospital of Dongying, Dongying, China (April 2019-April 2020), were chosen for analysis, and assigned into study group (SG, n = 46) and reference group (RG, n = 46) based on odd and even hospital admission no. All patients received specific routine treatments. In addition, SG was treated with lenvatinib in combination with camrelizumab. After treatment, liver function and levels of serum tumor markers were determined.*
Results: *Compared with RG, SG had significantly lower levels of liver function indices {alanine aminotransferase (ALT), total bilirubin (TBiL), and aspartate aminotransferase (AST)} and lower levels of serum tumor markers {alpha-fetoprotein (AFP), alpha-fetoprotein variant (AFP-L3) and Golgi protein 73 (GP73)} ($p < 0.001$); higher DCR ($p < 0.05$), lower score in Eastern Cooperative Oncology Group (ECOG), and higher Karnofsky (KPS) score ($p < 0.001$).*
Conclusion: *The combined use of lenvatinib and camrelizumab may be a reliable strategy for reducing serum tumor marker levels in HCC patients, improving liver function and patients' performance status, and enhancing DCR.*

Keywords: *Lenvatinib, Camrelizumab, Hepatocellular carcinoma (HCC), Serum tumor markers*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Hepatocellular carcinoma (HCC), a malignant tumor which occurs within the intrahepatic cholangiocytes or hepatocytes, seriously threatens human health, and it results in high morbidity and mortality [1]. With the current rise in incidence of HCC, nearly half of HCC occurs in Chinese people, mostly as a result of viral infection. Since HCC has an insidious onset, majority of the patients have no abnormal physical manifestations in the early stage, such that most times, it is only at the middle and late

stages of the disease that they feel great discomfort [2].

Investigations have revealed that about 80 % of HCC patients are medically unfit for radical resection at the time of diagnosis. At present, the use of molecular level-targeted drugs is one of the reliable methods for treating middle and advanced HCC [3]. Lenvatinib is a multi-targeted tyrosine kinase inhibitor (TKI) which not only inhibits tumor proliferation but also selectively suppresses the kinase activity of vascular endothelial growth factor (VEGF) receptors [4]. This drug obtained the approval of the U.S. Food and Drug Administration (USFDA) for first-line use in the treatment of liver cancer in 2018 [5].

A recent clinical study showed that camrelizumab, an independently-developed PD-1 inhibitor in China with sustained antitumor effects, has achieved remarkable results in treating diseases such as refractory NSCLC and primary liver cancer with lung metastasis [6]. However, not much is known about the treatment of HCC in China using a combination of lenvatinib and camrelizumab. This study was aimed at investigating the clinical effect of combined use of lenvatinib and camrelizumab in treating HCC, and its effect on disease control rate (DCR).

METHODS

Patients' profiles

The medical records of 92 HCC patients treated in the Oncology Department of The People's Hospital of Dongying, Dongying, China (April 2019 - April 2020) were chosen for retrospective analysis, and they were assigned to study group (SG, n = 46) and reference group (RG, n = 46), based on odd and even hospital admission no.

Ethical approval

Approved by the ethics committee of The People's Hospital of Dongying, Dongying (approval no. 20190144), this study followed the guidelines of the 2013 World Medical Association Declaration of Helsinki [7].

Inclusion and exclusion criteria

Inclusion criteria

The enrolled subjects were those meeting the diagnostic criteria for HCC in the *Specification for Diagnosis and Treatment of Hepatocellular Carcinoma* (2019 version) [8]: patients who had basic well-enough conditions and could accept targeted therapy, those who were not given any other cancer treatments and who had the entire treatment in *The People's Hospital of Dongying*, patients with normal functions in vital organs such as heart, and those with normal bone marrow hematopoiesis.

Exclusion criteria

The excluded patients were those with severe hemorrhagic tendency or abnormal hemogram, patients suffering from refractory massive ascites, dyscrasia or active infection, those who could not cooperate with treatment or follow-up due to disturbance of consciousness, and those with bleeding from esophageal varices 1 month before treatment.

Treatments

All patients received specific routine treatments such as liver protection therapy with glycyrrhizin injection (CSPC Ouyi Pharmaceutical Co. Ltd.; NMPA approval no. H20065475; specification: 20 mL), and symptomatic and supportive treatment with ceftriaxone sodium injection (Shanghai Roche Pharmaceuticals Ltd.; NMPA approval no. H10983036; specification: 1 g×1 bottle/box), and compound amino acid injection (Sichuan Kelun Pharmaceutical Co. Ltd.; NMPA approval no. H19993590; specification: 500 mL: 25 g/bottle). In addition, patients in SG received lenvatinib in combination with camrelizumab. Lenvatinib (Beacon Pharmaceuticals Limited; NMPA approval no. H20180052; specification: 4 mg x 10 pills x 3 plates) was orally administrated at a dose of 12 mg/day for patients with body mass ≥ 60 kg, and at a dose of 8 mg/day for patients with body mass < 60 kg. In addition, 3 mg/kg camrelizumab (Suzhou Shengdiya Biomedicine Co. Ltd.; NMPA approval no. S20190027; specification: 200 mg/bottle) was administered once every two weeks via intravenous drip. The treatment dose and interval of administration were adjusted properly based on patients' adverse drug reactions. Each patient's blood pressure was monitored daily until the disease condition progressed or the patient asked for drug withdrawal.

Evaluation of parameters/indices

Liver function and serum tumor markers

After treatment, fasting venous blood (5 mL) was drawn from each patient in each group, and was centrifuged to obtain the supernatant (serum). The serum levels of alanine aminotransferase (ALT), total bilirubin (TBiL), and aspartate aminotransferase (AST) were measured using

automatic biochemical analyzer model iChem-540 (Shenzhen iCubio Biomedical Technology Co. Ltd). The levels of serum tumor markers i.e., alpha-fetoprotein (AFP), alpha-fetoprotein variant (AFP-L3) and golgi protein 73 (GP73) were measured with chemiluminescence, microcentrifuge column method, and ELISA, respectively.

Treatment efficacy

All patients received MRI imaging examination before treatment for the determination of tumor status, and were reviewed with the same examination method after treatment. Treatment efficacy was divided into complete response (CR, i.e., complete disappearance of lesions and no new lesions after treatment), partial response [PR, ≥ 30 % decrease in the sum of the longest diameters of target lesions (SUM)], stable disease (SD, < 30 decrease in the SUM, or < 20 increase in the SUM), and progressive disease (PD, ≥ 20 % increase in the sum of the longest diameters of target lesions, or new lesions). Disease control rate (DCR) was calculated as shown in Eq 1:

$$DCR = \frac{(CR + PR + SD)}{T} \times 100 \quad \ldots\ldots\ldots (1)$$

where *DCR* = Disease control rate; *CR* = number of patients with complete response; *PR* = number of patients with partial response; *SD* = number of patients with stable disease; *T* = total number of patients.

Performance status

Each patient's performance status after treatment was assessed using the Eastern Cooperative Oncology Group (ECOG) [9]. The specific scoring criteria are shown in Table 1.

Physical condition

The patients' physical condition after treatment was assessed with Karnofsky (KPS) score (0-100 points), with a higher score demonstrating better physical condition [10].

Statistical analysis

In this study, data were processed using the professional statistical software SPSS24.0. Graphs were prepared with GraphPad Prism 7 (GraphPad Software, San Diego, USA). Enumeration data are expressed as numbers and percentages [n (%)], and were tested with χ^2 test, while measurement data are presented as mean ± SD, and were tested with t-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

General patients' data

Table 2 presented no statistical differences between the two groups with respect to general patient data such as mean age, Child-Pugh grade, blood platelet count, and degree of education ($p > 0.05$).

Liver function

After treatment, there were markedly lower levels of various liver function indicators in SG than in RG ($p < 0.001$; Table 3).

Changes in tumor characteristics

Table 4 showed a higher DCR in SG than in RG ($p < 0.05$).

ECOG and KPS scores

After treatment, ECOG scores of SG and RG were 2.11 ± 0.88 and 2.83 ± 0.85, respectively, while the corresponding KPS scores were 70.67 ± 1.47 and 64.80 ± 3.88, respectively. Compared with RG post-treatment, SG showed significantly lower ECOG score ($t = 3.991$, $p < 0.001$) and higher KPS score ($t = 9.595$, $p < 0.001$).

Levels of serum tumor markers

After treatment, the levels of various serum tumor markers were lower in SG than in RG ($p < 0.001$; Table 5).

Table 1: ECOG scoring criteria

Grade	Performance status
0	Fully active, able to carry out all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a lighter or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activity. Up and about more than 50 % of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.
4	Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Table 2: Clinical data (n = 46)

Parameter	SG	RG	χ^2/t	*P*-value
Gender			0.396	0.529
Male/female	24/22	27/19		
Mean age (years)	51.83±9.31	51.30±7.65	0.298	0.776
Child-Pugh grade			0.183	0.669
B	27 (58.70)	29 (63.04)		
C	19 (41.30)	17 (36.96)		
Albumin (**g/L)**	60.07±4.54	61.25±1.83	1.635	0.106
AFP (**ug/L)**	41.74±1.84	42.18±1.58	1.230	0.222
Leukocytes (**×** 10^9/L)	6.92±0.85	7.07±0.76	0.892	0.375
Blood ammonia (μmol/L)	22.21±2.34	22.91±2.38	1.422	0.158
TBiL (μmol/L)	23.06±2.56	22.73±3.01	0.566	0.573
Blood platelet count (**×** 10^9/L)	433.42±68.11	433.84±54.92	0.033	0.974
Cause of disease			0.047	0.828
Hepatitis	29 (63.04)	30 (65.22)		
Cirrhosis	17 (36.96)	16 (34.78)		
Educational degree				
College	3 (6.52%)	3 (6.52%)	0.000	1.000
Middle school	29 (63.04%)	27 (58.70%)	0.183	0.669
Primary school	14 (30.43%)	16 (34.78%)	0.198	0.656
Place of residence			0.198	0.656
Urban area	18 (39.13%)	17 (36.96%)		
Rural area	28 (60.87%)	29 (63.04%)		

Table 3: Levels of liver function indicators after treatment (mean ± SD, n = 46)

Group	ALT (U/L)	TBiL (μmol/L)	AST (U/L)
SG	44.25±3.90	19.01±2.33	48.83±3.29
RG	50.32±7.45	27.23±3.37	56.70±5.46
t	4.896	13.608	8.373
P-value	< 0.001	< 0.001	< 0.001

Table 4: Changes in tumor characteristics

Group	CR	PR	SD	PD	DCR
SG	13 (28.26)	21 (45.65)	9 (19.57)	3 (6.52)	93.48% (43/46)
RG	8 (17.39)	16 (34.78)	11 (23.91)	11 (23.91)	76.09% (35/46)
χ^2					5.392
P-value					< 0.05

Note: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; DCR = disease control rate

Table 5: Levels of various serum tumor markers (mean ± SD, n = 96)

Group	GP73 (μg/L)	AFP-L3 (%)	AFP (ng/ml)
SG	84.41±6.96	9.22±2.13	34.19±2.30
RG	109.17±7.97	12.25±1.78	44.99±4.67
t	15.871	7.403	14.071
P-value	< 0.001	< 0.001	< 0.001

DISCUSSION

Hepatocellular carcinoma (HCC) is a malignant neoplastic disease with high morbidity and mortality worldwide [11]. The disease, which is related to hepatic viral infections (HCV and HBV), occurs mainly in Asia, with nearly half of the cases in China. Therefore, diagnosis and treatment of HCC constitute a major challenge for healthcare workers [12]. There are limited treatments and a poor prognosis for HCC patients, with a median survival of about 1 year. Surveys have found that about 50 % of patients are in the late stage at diagnosis and are unable to undergo surgical treatment, thereby making systemic therapy the primary modality [13]. Since sorafenib was approved for HCC treatment in November 2007, no breakthrough or progress has been observed in related therapeutic agents until an international multi-center and randomized controlled study in 2018 introduced the new option, lenvatinib [14].

An oral multi-target inhibitor for the treatment of cancer, lenvatinib not only counteracts tumor angiogenesis and promotes vascular normalization [15], it also improves immune function. Clinically, it is effective in treating locally recurrent or metastatic and progressive,

radioiodine, intractable differentiated thyroid cancer, as well as treating renal cancer patients who have received VEGF-targeted therapy [16].

Currently, camrelizumab is approved for treating relapsed or refractory lymphoma. In a study in which camrelizumab was clinically applied in the treatment of advanced HCC patients, the results showed a DCR (44.2 %) [17]. Although the overall incidence of adverse effects was high, the reactions due to camrelizumab were mild, with only 13.2 % of severe adverse events of grade 3 and above. These results suggest that camrelizumab has promising antineoplastic activity and controllable toxicity, and may serve as a novel treatment option for HCC patients [18].

Based on a previous clinical treatment experience, this study applied lenvatinib in combination with camrelizumab to HCC patients, showing a higher DCR in SG than in RG (93.48 % vs 76.09 %). Thus, the combined therapy effectively enhanced the DCR for HCC patients and exerted positive effects on the prognosis of patients. Serum tumor markers are important indices for diagnosing diseases and assessing prognosis in the clinic [19]. For example, AFP-L3, a marker unique to HCC cells, accurately reflects the degrees of intravascular invasion and metastasis in patients, and its levels are positively correlated with the degree of tumor deterioration. In addition, GP73, a transmembrane protein on the Golgi body, is lowly expressed in biliary epithelial cells and hepatic cells of healthy people, but it is highly expressed in disease conditions [20]. The present study demonstrated lower post-treatment levels of AFP-L3 and GP73 in SG than in RG. This confirms that the combined treatment lowered the serum levels of tumor markers in HCC patients.

Limitations of the study

Due to short follow-up time and small sample size, this retrospective study lacks the confirmation derivable from clinical controlled trials. Moreover, some hidden adverse reactions in patients were not monitored. These deficiencies may lead to some bias in the results obtained in this study. Therefore, more studies with longer follow-up times and larger sample sizes are needed to verify the findings in this study.

CONCLUSION

The combination of lenvatinib and camrelizumab produces significant clinical efficacy in the treatment of HCC patients through improvement of physical health status, reduction in serum levels of tumor markers, enhancement of patients' recovery, and improvement of prognosis.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Ruibao Liu and Xing Wang conceived and designed the study, and drafted the manuscript. Ruibao Liu, Xiaolei Zhang, Wei Wei and Xing Wang collected, analyzed and interpreted the experimental data. Xiaolei Zhang, Xing Wang revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

REFERENCES

1. Pu Z, Wang Y, Ge F, Zhu S, Cheng Y, Liu H, Dai Q, Hua H. Matrine induces cell cycle arrest and apoptosis in hepatocellular carcinoma cells via miR-122 mediated CG1/livin/survivin signal axis. Trop J Pharm Res 2021; 20(2): 263-268.
2. Marchio A, Cerapio JP, Ruiz E, Cano L, Casavilca S, Terris B, Deharo E, Dejean A, Bertani S, Pineau P. Early-onset liver cancer in South America associates with low hepatitis B virus DNA burden. Sci Rep 2018; 8(1): 12031.
3. Cai L, Luo L, Tang Z, Meng X. Combined antitumor effects of 1,25 - dihydroxy vitamin D3 and Notch inhibitor in liver cancer. Oncol Rep 2018; 40(3): 1515-1524.
4. Pineau P, Ruiz E, Deharo E, Bertani S. On hepatocellular carcinoma in South America and early-age onset of the disease. Clin Res Hepatol Gastroenterol 2019; 43(5): 522-526.
5. Huan HB, Chen XJ, Xia F. Liver cancer immunotherapy in the context of precision medicine. Zhonghua Gan Zang Bing Za Zhi 2020; 28(11): 910-914.
6. Couri T, Pillai A. Goals and targets for personalized therapy for HCC. Hepatol Int 2019; 13(2): 125-137.
7. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.
8. Kosaka Y, Kawaoka T, Aikata H, Suehiro Y, Yamaoka K, Ando Y, Namba M, Takeuchi Y, Fujii Y, Uchikawa S, et al. A case of advanced HCC treated with lenvatinib after hepatic arterial infusion chemotherapy combined with radiation therapy treatment for portal vein tumor thrombosis in the main trunk. Clin J Gastroenterol 2020; 13(5): 839-843.
9. Hui VW, Chan SL, Wong VW, Liang LY, Yip TC, Lai JC, Yuen BW, Luk HW, Tse YK, Lee HW, et al. Increasing antiviral treatment uptake improves survival in patients with HBV-related HCC. JHEP Rep 2020; 2(6): 100152.
10. Cho HJ, Kim B, Kim HJ, Huh J, Kim JK, Lee JH, Seo CW, Ahn HR, Eun JW, Kim SS, et al. Liver stiffness measured by MR elastography is a predictor of early HCC recurrence after treatment. Eur Radiol 2020; 30(8): 4182-4192.
11. Tan AT, Schreiber S. Adoptive T-cell therapy for HBV-associated HCC and HBV infection. Antiviral Res 2020; 176: 104748.
12. Allaire M, El Hajj W, Brichler S, Diallo K, Fanica D, Blaise L, Nkontchou G, Grando V, Arbadi F, Nahon P, et al. Prior surveillance and antiviral treatment improve the prognosis of HCC developed in HBV patients in the West. Clin Res Hepatol Gastroenterol 2021; 45(1): 101436.
13. Zhao Z, Wang B, Mu L, Wang H, Luo J, Yang Y, Yang H, Li M, Zhou L, Tao C. Long-term exposure to ceftriaxone sodium induces alteration of gut microbiota accompanied by abnormal behaviors in mice. Front cell infect Microbiol 2020; 10: 258.
14. Fujita M, Yamaguchi R, Hasegawa T, Shimada S, Arihiro K, Hayashi S, Maejima K, Nakano K, Fujimoto A, Ono A, et al. Classification of primary liver cancer with immunosuppression mechanisms and correlation with genomic alterations. EBioMedicine 2020; 53: 102659.
15. Ma C, Zhang Q, Greten TF. MDSCs in liver cancer: A critical tumor-promoting player and a potential therapeutic target. Cell Immunol 2021; 361: 104295.
16. Shi JF, Cao M, Wang Y, Bai FZ, Lei L, Peng J, Feletto E, Canfell K, Qu C, Chen W. Is it possible to halve the incidence of liver cancer in China by 2050? Int J Cancer 2021; 148(5): 1051-1065.
17. Liu Z, Jiang Y, Yuan H, Fang Q, Cai N, Suo C, Jin L, Zhang T, Chen X. The trends in incidence of primary liver cancer caused by specific etiologies: Results from the Global burden of disease study 2016 and implications for liver cancer prevention. J Hepatol 2019; 70(4): 674-683.
18. Song J, Zhao W, Lu C, Shao X. Spliced X-box binding protein 1 induces liver cancer cell death via activating the Mst1-JNK-mROS signalling pathway. J Cell Physiol 2020; 235(12): 9378-9387.
19. Zhen H, Qian X, Fu X, Chen Z, Zhang A, Shi L. Regulation of Shaoyao Ruangan mixture on intestinal flora in mice with primary liver cancer. Integr Cancer Ther 2019; 18: 1534735419843178.
20. Celsa C, Cabibbo G, Pagano D, di Marco V, Cammà C, Gruttadauria S. Sicily network for liver cancer: A multidisciplinary network model for the management of primary liver tumors. J Laparoendosc Adv Surg Tech A 2020; 30(10): 1048-1053.