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Peer Review of *World Journal of Gastrointestinal Oncology*, Jihwan Ko, MD, FRSPH, Director, Baekyang Jeil Internal Medicine Clinic, Busan 47181, South Korea. jihwanko65@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

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ORIGINAL ARTICLE

Retrospective Study

Clinical observation of nivolumab combined with cabozantinib in the treatment of advanced hepatocellular carcinoma

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a particularly serious kind of liver cancer. Liver cancer ranks third in terms of mortality rate worldwide, putting it among the leading causes of deaths from cancer. HCC is the primary kind of liver cancer and makes up the vast majority of cases, accounting for approximately 90% of occurrences. Numerous research have verified this information. the progress of fatty liver, alcohol induced cirrhosis, smoking habits, obesity caused by overweight, and metabolic diseases such as diabetes. The treatment strategies for HCC can be divided into two categories: One is curative treatment, including liver transplantation, surgical resection, and ablation therapy or selective arterial radiation embolization, aimed at completely eliminating the lesion; Another type is non curative treatment options, including transarterial chemoembolization and systemic therapy, which focus on controlling disease progression and prolonging patient survival. The majority of HCC patients are found to be in an advanced stage and need systemic therapy. Sorafenib and lenvatinib are frequently used as first-line medications in traditional HCC treatment to slow the disease's progression. For second-line treatment, regorafenib, cabozantinib, or remdesizumab are used to inhibit tumors through different mechanisms and prolong survival. In recent years, with the in-depth exploration of the pathogenesis and progression mechanism of HCC, as well as the rapid progress within the domain of tumor immunotherapy, the treatment prospects for advanced HCC patients have shown a positive transformation. This transformation is reflected in the fact that more and more patients are gradually gaining significant and considerable therapeutic advantages from advanced immunotherapy regimens, bringing unprecedented improvements to their treatment outcomes. In order to enable activated T cells to attack tumor cells, immune checkpoint inhibitors interfere with the inhibitory.

AIM
To evaluate the effects of nivolumab in combination with cabozantinib on patient tumor markers and immune function, as well as the therapeutic efficacy of this combination in treating advanced HCC, a study was conducted.

METHODS
In all, 100 patients with advanced HCC who were brought to our hospital between July 2022 and July 2023 and who did not match the requirements for surgical resection had their clinical data thoroughly analyzed retrospectively in this study. Among them, half of the patients (50 cases) only received oral cabozantinib as a single treatment regimen (set as the control group), while the other half of the patients (50 cases) received intravenous infusion of nivolumab in addition to oral cabozantinib (set as the observation group). The objective of the probe is to examine the variations in disease control rate (DCR) and objective response rate (ORR) between two groups; At the same time, changes in the levels of T lymphocyte subsets (CD3+, CD4+, CD8+) and tumor markers, including AFP, GP-73, and AFP-L3, were evaluated; In addition, changes in liver and kidney function indicators and adverse reactions during treatment were also monitored. For patients with advanced HCC, this research also calculated and analyzed the progression free survival of two patient groups throughout the course of a 12-month follow-up to assess the effectiveness and safety of this therapeutic approach.

RESULTS
Upon comparing baseline information for both groups of subjects before treatment, it was found that no statistically significant alterations had occurred ($P > 0.05$). After the therapeutic intervention, the observation group and control group's ORR and DCR differed statistically significantly ($P < 0.05$). The observation group's scores significantly improved. Subsequent examination revealed that the observation group's T lymphocyte subset levels had significantly changed, mostly exhibiting an increase in CD3+, CD4+, and CD4+/CD8+ levels while CD8+ levels had comparatively dropped. There was a significant difference ($P < 0.05$) between these changes and those in the control group. The observation group also showed positive improvements in tumor markers; AFP, GP-73, and AFP-L3 levels were considerably lower in the group under observation than in the control group, with statistically significant differences ($P < 0.05$). When liver function was assessed, total bilirubin and alanine aminotransferase were found to be considerably lower in the observation group than in the control group ($P < 0.05$). The incidence of adverse responses was not statistically significant ($P > 0.05$), indicating that the incidence of adverse responses did not differ significantly between the two groups.

CONCLUSION
When treating advanced HCC, nivolumab and cabozantinib together have the ability to increase T lymphocyte numbers, reduce tumor marker levels, effectively prolong survival time, and have better efficacy than simple control treatment, with good safety.

Key Words: Nivolumab; Cabozantinib; Hepatocellular carcinoma; Tumor markers; Immune function

Core Tip: The combination therapy of cabozantinib and nivolumab in advanced hepatocellular carcinoma can upregulate T lymphocyte levels, reduce tumor marker levels, effectively prolong survival time, and has better efficacy than simple control treatment, with good safety.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a particularly serious kind of liver cancer. Liver cancer ranks third in terms of mortality rate worldwide, putting it among the leading causes of deaths from cancer. HCC is the primary kind of liver cancer and makes up the vast majority of cases, accounting for approximately 90% of occurrences. Numerous research have verified this information[1,2]. The progress of fatty liver, alcohol induced cirrhosis, smoking habits, obesity caused by overweight, and metabolic diseases such as diabetes[3]. The treatment strategies for HCC can be divided into two categories: One is curative treatment, including liver transplantation, surgical resection, and ablation therapy or selective arterial radiation embolization, aimed at completely eliminating the lesion; Another type is non curative treatment options, including transarterial chemoembolization (TACE) and systemic therapy, which focus on controlling disease

progression (PD) and prolonging patient survival[4]. The majority of HCC patients are found to be in an advanced stage and need systemic therapy[5]. Sorafenib and lenvatinib are frequently used as first-line medications in traditional HCC treatment to slow the disease's progression. For second-line treatment, regorafenib, cabozantinib, or remdesizumab are used to inhibit tumors through different mechanisms and prolong survival. In recent years, with the in-depth exploration of the pathogenesis and progression mechanism of HCC, as well as the rapid progress within the domain of tumor immunotherapy, the treatment prospects for advanced HCC patients have shown a positive transformation. This transformation is reflected in the fact that more and more patients are gradually gaining significant and considerable therapeutic advantages from advanced immunotherapy regimens, bringing unprecedented improvements to their treatment outcomes. In order to enable activated T cells to attack tumor cells, immune checkpoint inhibitors interfere with the inhibitory signals that tumor cells provide to immune effector cells[6]. For the first time, checkpoint inhibitors and VEGF antibodies have been demonstrated to be more effective than sorafenib in prior research[7]. HCC treatment has advanced significantly in the last few years due to the switch from single control medications (like sorafenib and lenvatinib) to combinations of checkpoint inhibitors and control medications (like atezolizumab plus bevacizumab). There are still a lot of therapy obstacles because only a small percentage of patients can benefit over the long run, even with the notable therapeutic outcomes. In recent years, various emerging treatment methods such as molecular controlled drugs (such as donafenib), immune oncology monotherapy (such as durvalumab), and innovative combination therapies (such as durvalumab combined with trastuzumab) have emerged, with significant clinical trial results[8]. A member of the CD28 family of immunological checkpoint molecules is called PD-1. By attaching to its ligand, PD-L1 or PD-L2, it blocks T cell receptor activation signals, lowering T cell activity during the immune response and averting autoimmune damage. Consequently, a major part of the immunosuppressive microenvironment of HCC is mediated by the PD-1/PD-L1 pathway[9]. Navulimumab, an immunoglobulin G4 subclass molecule, can precisely interfere with the interaction chain between activated T cell surface PD-1 and the ligands PD-L1 and PD-L2, which relate to it, effectively inhibiting T cell inactivation[10]. Nivolumab has great tolerability and a prolonged tumor response in advanced HCC patients undergoing sorafenib therapy in addition to initial treatment, as previous research has shown[11]. As a multi-kinase inhibitor of the VEGF receptors VEGFR-2, AXL, and c-MET[12], cabotinib is engaged in a number of cellular pathways related to angiogenesis and controlling immune cells[13]. The combination of cabozantinib and nivolumab as a single antibody has demonstrated significant clinical efficacy in the population of HCC patients in prior studies, and its toxicity has been deemed tolerable[14]. These findings suggest that the use of this combination as a first line of treatment is reasonable from a scientific standpoint. The aim of this study is to evaluate and validate the therapeutic efficacy and potential of neoadjuvant therapy for HCC patients in critical resectable or locally advanced stages.

MATERIALS AND METHODS

General information

The clinical information of one hundred patients with advanced, those with incurable HCC who were brought to our facility between July 2022 and July 2024 was examined retrospectively in this study. These 100 patients were split into two groups at random: One group was the control group (n = 50), receiving only oral cabozantinib as the treatment regimen; The other group was the observation group (n = 50), who received intravenous infusion of nivolumab in addition to oral cabozantinib. The inclusion criteria include: (1) Compliance with internationally recognized diagnostic criteria for HCC; (2) Confirm the presence of at least one assessable tumor lesion through computed tomography (CT) or magnetic resonance imaging (MRI) imaging examination; (3) The staging of liver cancer should be defined as stage III; (4) The patient's liver function needs to be maintained within the range of grade A to B; (5) The physical activity status score should be between 0 and 1 point; (6) Age between 18 and 75 years old; and (7) Participants participated in this study based on their personal wishes and continued to receive regular follow-up monitoring after completing hospitalization. Exclusion criteria include: (1) Individuals suffering from severe renal or cardiac problems; (2) Individuals with coagulation dysfunction; and (3) Individuals who also suffer from other types of malignant tumors. Table 1 displays the main characteristics of the two patient groups. This study has strictly followed the relevant regulations of the hospital ethics committee and obtained formal approval.

Methods

Control group: Oral Cabotinib, 0.06 g/time, once daily.

Observation group: On the basis of the control group, 160 mg (3 mg/kg) of nivolumab was given intravenously once every 2 weeks.

Observation indicators

Clinical efficacy evaluation: Continuous tracking and monitoring of the target lesion are performed through routine CT or MRI imaging examinations, and the treatment efficacy is evaluated using the mRECIST standard. (1) Complete response (CR): Manifested as no significant enhancement signs of the target lesion during the vascular enhancement phase; (2) Partial response (PR): A minimum 30% decrease in the target lesion's diameter from its pre-treatment size; (3) Disease stability (SD): The target lesion's diameter decreases by less than 30% or increases by no more than 20%; (4) PD: The diameter of the target lesion increases by at least 20 %, or new lesions appear objective response rate (ORR)= (CR + PR)/total cases × 100%; and (5) Disease control rate (DCR)= (CR + PR + SD)/total cases × 100%.

Table 1 Comparison of general information (mean ± SD)

Project	Observation group (*n* = 50)	Control group (*n* = 50)	χ^2/t	*P* value
Gender, *n* (%)				
Male	21 (42.00)	28 (64.00)	1.961	0.161
Female	29 (58.00)	22 (36.00)		
Age (years), mean ± SD	57.84 ± 6.37	56.49 ± 6.15	1.007	0.316
Hepatitis B virus positive, *n* (%)	45 (90.00)	47 (94.00)	0.543	0.461
Cirrhosis, *n* (%)	36 (72.00)	39 (78.00)	0.480	0.488
Tumor length (cm), *n* (%)				
≥ 5	37 (74.00)	39 (78.00)	0.219	0.640
< 5	13 (26.00)	11 (22.00)		
Multiple tumors, *n* (%)	7 (14.00)	9 (18.00)	0.298	0.585
TNM staging, *n* (%)				
Stage I to II	19 (38.00)	15 (30.00)	0.713	0.398
Stage III	31 (62.00)	35 (70.00)		
Child-Pugh liver function grade, *n* (%)				
A-level	23 (46.00)	20 (40.00)	0.545	0.367
Class B	27 (54.00)	30 (60.00)		
Physical activity status score, *n* (%)				
0	29 (58.00)	32 (66.00)	0.378	0.539
1	21 (42.00)	18 (34.00)		

Immune and tumor marker detection: Venous blood samples were collected on an empty stomach before and after three months of treatment in patients. Using flow cytometry to measure the T lymphocyte subgroup levels (CD3+, CD4+, CD8+); At the same time, the ELISA method was employed to measure the quantities of AFP, GP73, and AFP-L3 in serum to evaluate changes in tumor related marker levels.

Safety monitoring: During the treatment process, patients' liver and kidney function indicators are regularly monitored, and various adverse reactions such as diarrhea, decreased appetite, abnormal liver function, proteinuria, and hand foot syndrome are recorded in detail.

Statistical analysis

The statistical analysis step of the data was carried out using SPSS 23.0. $P < 0.05$ was regarded as statistically significant. The measurement data were represented as mean ± SD; the *t*-test or repeated measures analysis of variance were utilized.

RESULTS

Clinical efficacy evaluation

All evaluation indicators in the comparison study showed that the observation group performed much better than the control group; this difference was statistically significant, with the observation group's ORR and DCR being significantly higher ($P < 0.05$; Table 2). The results showed that the therapeutic effect of the observation group was better than that of the control group.

Immune and tumor marker indicators

The comparison of immune indexes between the two groups before treatment did not reach a significant level ($P > 0.05$), and the difference was not statistically significant. However, after treatment, the levels of CD3+, CD4+ and CD4+/CD8+ in the observation group were significantly higher than those in the control group ($P < 0.05$), while the level of CD8+ was significantly decreased ($P < 0.05$; Table 3). For the comparative analysis of the content of tumor markers between the two groups, no statistically significant difference was found before treatment intervention ($P > 0.05$). However, after treatment, the measured values of AFP, GP-73 and AFP-L3 in the observation group were significantly lower than those in the control group, and the difference was statistically significant ($P < 0.05$; Table 4). The above results show that the

Table 2 Comparison of clinical efficacy, *n* (%)

Group	CR	PR	SD	PD	ORR	DCR
Control group (n = 50)	0 (0.00)	8 (16.00)	10 (20.00)	30 (60.00)	8 (16.00)	18 (36.00)
Observation group (n = 50)	2 (4.00)	18 (34.00)	9 (18.00)	22 (44.00)	20 (40.00)	29 (58.00)
χ^2	-	-	-	-	7.143	4.857
P value	-	-	-	-	0.008	0.028

CR: Complete response; PR: Partial response; SD: Disease stability; PD: Disease progression; ORR: Objective response rate; DCR: Disease control rate.

Table 3 Comparison of immune indicators (mean ± SD)

Group	CD3+ (%)		CD4+ (%)		CD8+ (%)		CD4+/CD8+ (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 50)	54.65 ± 4.32	58.16 ± 4.83	33.54 ± 3.98	38.09 ± 4.62	27.89 ± 3.65	25.16 ± 3.84	1.28 ± 0.51	1.63 ± 0.27
Observation group (n = 50)	54.02 ± 4.54	61.98 ± 5.16[a]	32.97 ± 4.08	40.65 ± 4.84[a]	28.06 ± 3.94	21.55 ± 3.17[a]	1.24 ± 0.49	1.92 ± 0.35[a]
t value	0.711	3.821	0.708	2.708	0.222	5.126	0.402	4.632
P value	0.478	< 0.001	0.481	0.008	0.825	< 0.001	0.688	< 0.001

[a]P < 0.05 compared with the control group.

Table 4 Comparison of tumor markers (mean ± SD)

Group	AFP (μg/L)		GP-73 (μg/L)		AFP-L3 (μg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 50)	84.61 ± 5.34	33.94 ± 6.24	89.17 ± 5.27	63.08 ± 6.62	151.99 ± 31.64	117.43 ± 34.94
Observation group (n = 50)	85.17 ± 5.18	17.49 ± 4.16[a]	90.82 ± 6.04	47.67 ± 6.15[a]	154.94 ± 30.48	81.43 ± 27.95[a]
t value	0.532	15.510	1.456	12.050	0.474	5.689
P value	0.596	< 0.001	0.149	< 0.001	0.636	< 0.001

[a]P < 0.05 compared with the control group.

combination of nivolumab and cabozantinib can improve the immune indexes of patients and reduce the expression of tumor markers.

Comparison of liver and kidney function

The liver and renal function indicators of the two patient groups were examined prior to therapy, and no significant changes (P > 0.05) were seen in creatinine, uric acid, albumin, alanine aminotransferase (ALT), aspartate aminotransferase, and total bilirubin (TBIL). The levels of TBIL and ALT in the observation group were statistically significantly lower after the therapy intervention than in the control group (P < 0.05; Table 5). The results indicate that the combination therapy of nivolumab and cabozantinib can improve the levels of TBIL and ALT in patients.

Comparison of adverse reactions

Table 6 demonstrates that there was no statistically significant difference (P > 0.05) in the occurrence of adverse reactions between the two groups.

DISCUSSION

HCC is a primary malignant tumor originating from liver parenchymal cells. Its global incidence ranks sixth, and it is the

Table 5 Comparison of liver and kidney function indicators (mean ± SD)

Group	Before treatment				After treatment			
	Control group (*n* = 50)	Observation group (*n* = 50)	*t* value	*P* value	Control group (*n* = 50)	Observation group (*n* = 50)	*t* value	*P* value
TBIL (μmol/L)	22.07 ± 5.94	23.19 ± 6.05	0.933	0.353	18.74 ± 7.29	15.26 ± 6.02[a]	2.604	0.01
ALB (μmol/L)	36.56 ± 6.07	35.79 ± 6.18	0.628	0.532	35.29 ± 6.07	33.94 ± 6.67	1.059	0.292
ALT (μmol/L)	42.93 ± 7.85	41.05 ± 7.94	1.19	0.237	35.17 ± 8.93	26.88 ± 7.49[a]	5.03	< 0.001
AST (μmol/L)	59.41 ± 8.53	56.98 ± 9.04	1.383	0.17	50.87 ± 6.94	51.46 ± 6.53	0.438	0.662
Cr (μmol/L)	57.94 ± 11.97	57.04 ± 1 1.86	0.377	0.707	52.37 ± 6.94	51.86 ± 7.08	0.364	0.716
UA (μmol/L)	285. 67 ± 25.86	281.96 ± 32.45	0.632	0.529	273.49 ± 35.37	268.51 ± 30.46	0.755	0.452

[a]*P* < 0.05 compared with the control group.

TBIL: Total bilirubin; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Table 6 Comparison of adverse reactions, *n* (%)

Group	Control group (*n* = 50)	Observation group (*n* = 50)	χ^2	*P* value
Diarrhea	3 (6.00)	4 (8.00)	0.154	0.695
Loss of appetite	10 (20.00)	8 (16.00)	0.271	0.603
ALT elevation	11 (22.00)	8 (16.00)	0.585	0.444
Proteinuria	3 (6.00)	2 (4.00)	0.211	0.646
Hand-foot syndrome	1(2.00)	3 (6.00)	1.042	0.307

fourth leading cause of cancer-related death, posing a major challenge to public health[15]. According to the United States SEER database, the overall 5-year survival rate of HCC patients was 19.6%. However, in patients with advanced metastatic disease, the ratio decreased significantly to 2.5%[16]. Recent studies have shown that the reduction of adiponectin levels in adolescent men may be a key factor in the increased risk of HCC in men[17]. There are a wide range of risk factors for HCC, including chronic hepatitis B virus and hepatitis C virus infection, alcoholic liver disease, nonalcoholic fatty liver disease and other metabolic liver diseases, as well as exposure to carcinogens such as aflatoxin in food[18]. The treatment of HCC is diverse, including surgical resection, liver transplantation, radiofrequency ablation and other local treatment methods[19]. For advanced HCC that cannot be surgically removed, systemic therapy has become the main choice, involving traditional cytotoxic chemotherapy, targeted therapy, and immune checkpoint inhibitors[20]. Over the past decade, sorafenib, a multi-kinase inhibitor, has been the first-line systemic treatment for advanced HCC, but its efficacy is limited, with drug resistance and low response rate. Therefore, the current research focus has shifted to the development of combined treatment strategies in order to improve the therapeutic effect.

Immunotherapy represents the forefront of HCC treatment, and the combination of PD-L1 CPI and vascular endothelial growth factor blockade has been approved for the first-line treatment of unresectable HCC[21]. Cabotinib, an oral multi-kinase inhibitor targeting VEGFR1-3, TAM kinase family, KIT, RET, FLT3 and MET, has been approved for patients with advanced HCC after sorafenib treatment failure in Europe since November 2018 and in the United States in January 2019 due to the key role of these targets in angiogenesis and tumorigenesis and their correlation with HCC progression and sorafenib acquired resistance[22,23]. CPI, as a monoclonal antibody, enhances anti-tumor immune response by blocking checkpoint proteins such as PD-1[24]. For example, nivolumab, a PD-1 blocking antibody[25], showed significant efficacy in this study. The ORR and DCR of the observation group reached 40.00 % and 58.00 %, respectively, which were much higher than those of the control group (16.00% and 36.00%). This result is consistent with previous literature[26,27], indicating that the combined treatment regimen has a positive effect in delaying HCC progression and prolonging survival. The results are attributed to the fact that cabozantinib, as an efficient small molecule tyrosine kinase antagonist, can specifically block key signaling pathways and effectively inhibit tumor neovascularization, which is essential for preventing tumor recurrence, and significantly improves the quality of life and prolongs survival time of patients.

This study also explored the effects of this treatment regimen on T lymphocyte subsets and tumor-specific markers in patients. The results showed that the levels of CD3+, CD4+ and CD4+/CD8+ in the observation group increased significantly after treatment, while the level of CD8+ decreased. This change indicated that the combination regimen could effectively improve the overall activity of T lymphocytes, alleviate the immunosuppressive state in the tumor

microenvironment, enhance the ability of the immune system to recognize and remove HCC cells, and promote the enhancement of anti-tumor effect and the continuous inhibition of tumor development[28]. In addition, this study also found that the levels of AFP, GP-73 and AFP-L3 in the observation group were significantly lower than those in the control group after treatment. As a glycoprotein closely related to growth and development, AFP is a key indicator in the evaluation of liver cancer[29]. AFP-L3 has become an important auxiliary method for HCC diagnosis with its high specificity of 90.0%-92.0%[30]; gP73 is abnormally highly expressed in HCC tissues and is regarded as a potential serum biomarker for HCC diagnosis[31]. This suggests that the regimen can effectively reduce the level of tumor markers in HCC patients, reflecting a significant inhibitory effect on tumor growth. The significant improvement of the above markers in the observation group further supported the effectiveness of the combination regimen in the treatment of HCC. The reasons are as follows: On the one hand, synergistic drugs may stimulate and restore the activity of impaired T lymphocytes in tumor patients by optimizing the immunosuppressive environment, and then promote these cells to release efficient tumor suppressor factors to achieve effective clearance of HCC cells; on the other hand, this regimen may also block PD-1-related signaling pathways and affect the expression of PD-1 inhibitor checkpoints, thereby further enhancing the anti-tumor ability of the immune system.

It has been pointed out that low-dose nivolumab may have a lower toxicity burden while maintaining efficacy, providing new treatment options for patients with advanced HCC who cannot afford high-cost immune checkpoint inhibitors for economic reasons[32]. In terms of safety, this study observed that the levels of TBIL and ALT in the observation group were lower than those in the control group after treatment, and there was no significant difference in the incidence of adverse reactions between the two groups. It shows that the treatment method has good safety, and its side effects are within the controllable and tolerable range.

Finally, individuals with advanced HCC might profit from combination therapy consisting of cabozantinib and nivolumab since it has the ability to improve immune function, lower levels of tumor-specific markers, and extend survival. Additionally, this treatment regimen has shown good safety aspects. This finding not only provides a new choice for the treatment of advanced HCC, but also may guide future research to explore more strategies for the combination of immunotherapy and targeted drugs in order to further improve the prognosis and quality of life of patients.

CONCLUSION

When treating advanced HCC, nivolumab and cabozantinib together have the ability to increase T lymphocyte numbers, reduce tumor marker levels, effectively prolong survival time, and have better efficacy than simple control treatment, with good safety.

FOOTNOTES

Author contributions: Liang LW and Tang LN designs research; Huang ZL conducts case collection; Luo RH guide the research.

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