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Original Article

Efficacy and safety analysis of PD-1 combined with regorafenib in the treatment of advanced hepatocellular carcinoma

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Abstract: Objective: To investigate the therapeutic efficacy and safety of programmed death-1 (PD-1) inhibitors combined with regorafenib in the treatment of advanced hepatocellular carcinoma (HCC). Methods: A retrospective analysis was performed on 82 patients diagnosed with advanced HCC at Lanzhou Petrochemical General Hospital and the Second People's Hospital of Lanzhou City from October 2021 to October 2022. Patients were divided into two groups: the observation group (42 patients) received combined therapy with regorafenib and a PD-1 inhibitor, while the control group (40 patients) received only regorafenib monotherapy. Treatment efficacy, changes in serum tumor markers pre- and post-treatment, incidence of adverse reactions, progression-free survival (PFS), 1-year survival rate, and independent prognostic factors were evaluated for both groups. Results: The treatment efficacy in the observation group was significantly better than that in the control group ($P<0.05$). Post-treatment levels of VEGF, sIL-2R, and CEA were significantly lower in the observation group compared to the control group (all $P<0.05$). The incidence of adverse reactions was similar between the two groups ($P>0.05$). However, the observation group demonstrated a significantly higher median PFS and 1-year survival rate than the control group (both $P<0.05$). Vascular invasion, degree of differentiation, and treatment regimen were identified as independent prognostic factors affecting outcomes (all $P<0.05$). Conclusion: For patients with advanced HCC, integrating PD-1 inhibitors with regorafenib treatment not only enhances clinical efficacy but also maintains safety. This combination therapy significantly improves progression-free survival and 1-year survival rates, supporting its further clinical application.

Keywords: Programmed death-1, regorafenib, advanced hepatocellular carcinoma, prognosis

Introduction

Primary liver cancer, with hepatocellular carcinoma (HCC) as its major subtype (accounting for approximately 90% of cases), is the fourth leading cause of cancer-related deaths worldwide [1]. The often asymptomatic nature of HCC leads to late diagnoses, with many patients presenting at advanced stages, which limits surgical treatment options and contributes to a poor prognosis with a five-year survival rate under 20% [2, 3]. By 2030, it is estimated that liver cancer will cause over one million deaths annually [4]. In cases where surgical options are not viable, systemic therapy becomes crucial. However, HCC typically shows low responsiveness to traditional cytotoxic chemotherapy due to the overexpression of drug-resistance genes and such treatments may aggravate hepatitis, exacerbate cirrhosis, and induce severe side effects [5]. Consequently, improving survival while reducing treatment-related adverse effects remain a critical clinical challenge.

In recent years, anti-angiogenic and molecular-targeted therapies have emerged as pivotal in managing HCC. For instance, regorafenib, a multi-targeted tyrosine kinase inhibitor, has shown efficacy in inhibiting tumor growth and proliferation [6]. Nonetheless, the overall res-

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ponse rates (ORR) to such therapies are modest and offer limited extension of survival [7]. Innovations in monoclonal antibodies targeting the programmed death-1 (PD-1)/programmed death-Ligand 1 (PD-L1) pathway have introduced promising avenues for liver cancer treatment [8]. Notable are ongoing clinical trials like the Phase I/II study of regorafenib with Nivolumab (NCT04170556) and the Phase II study of regorafenib with Atezolizumab (NCT04183088), which explore the efficacy of these combinations in advanced HCC treatment [9]. Although results from many of these studies are still pending, their potential in improving outcomes for HCC patients is significant.

This study retrospectively analyzes clinical data to compare the efficacy and safety of combining regorafenib with PD-1 inhibitors against regorafenib alone in the second-line treatment of advanced HCC.

Materials and methods

Clinical data

A retrospective analysis was conducted on 82 patients with advanced HCC treated at Lanzhou Petrochemical General Hospital and the Second People's Hospital of Lanzhou City from October 2021 to October 2022. Patients were divided into two groups: the observation group (42 patients) received combination therapy with regorafenib and PD-1 inhibitors, while the control group (40 patients) received regorafenib monotherapy.

The inclusion criteria were: (1) Diagnosis of primary HCC confirmed through imaging and pathological examinations, according to the World Health Organization diagnostic criteria [10]; (2) TNM stage III B or IV; (3) Failure of prior first-line treatment with Sorafenib or Lenvatinib; (4) Availability of complete medical records. Exclusion criteria included: (1) Prior treatment with immunomodulatory agents; (2) Psychiatric disorders or impaired consciousness; (3) Language, cognitive, or communication disabilities; (4) Significant systemic diseases; (5) Previous treatment with other targeted therapies; (6) Life expectancy less than 6 months; (7) Abnormal liver or kidney function tests; (8) Lactating or pregnant women; (9) Presence of other concurrent tumors.

Ethical approval for this study was obtained from the Second People's Hospital of Lanzhou City ethics committee, and the study conforms to the ethical guidelines of the Helsinki Declaration.

Treatment methods

Both cohorts were administered regorafenib (Bayer Healthcare, Germany, National Medical Products Administration Approval No.: HJ20-171300) at a dosage of 80-160 mg daily for a 21-day cycle, followed by a 7-day drug-free interval, comprising a 28-day treatment cycle. In addition to the control protocol, the intervention group received the PD-1 inhibitor camrelizumab (Innovent Biologics, Suzhou, China, National Medical Products Administration Approval No.: S20190027) at a dosage of 200 mg every 3 weeks. Patients were instructed to report any discomfort or adverse reactions promptly to their attending physicians for appropriate management. Tumor assessments were conducted every 2-3 cycles using computed tomography or magnetic resonance imaging and evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified RECIST criteria until disease progression or treatment modification.

Outcome measures

(1) Treatment efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) [11]. Response categories included: Complete Response (CR): complete disappearance of lesions maintained for at least four weeks; Partial Remission (PR): at least a 30% reduction in the sum of diameters of measurable lesions, maintained for at least 4 weeks without new lesions; Stable Disease (SD): insufficient shrinkage for PR and insufficient increase for Progressive Disease (PD); PD: at least a 20% increase in the sum of diameters of target lesions or the appearance of new lesions. The ORR was calculated as (CR + PR)/total number of patients × 100%. (2) Serum tumor markers, including vascular endothelial growth factor (VEGF), soluble interleukin-2 receptor (sIL-2R), and carcinoembryonic antigen (CEA), were measured before and after treatment using ELISA (Shanghai Yaji Biotechnology Co., Ltd.). Blood samples were collected in the morning and centrifuged at 3000 rpm for 15 minutes. (3) Progression-free survival (PFS) and

Table 1. Comparison of general data [n (%)]

Variable	Observation Group (n = 42)	Control Group (n = 40)	t/X^2	P
Gender			0.001	0.991
Male	22 (52.38)	21 (52.50)		
Female	20 (47.62)	19 (47.50)		
Age (years)			0.001	0.974
≤65	18 (42.86)	17 (42.50)		
>65	24 (57.14)	23 (57.50)		
Body mass index (kg/m^2)			0.042	0.837
≤23	23 (54.76)	21 (52.50)		
>23	19 (45.24)	19 (47.50)		
Smoking history			0.002	0.965
Yes	25 (59.52)	24 (60.00)		
No	17 (40.48)	16 (40.00)		
Vascular cancer thrombus			0.004	0.946
Yes	27 (64.29)	26 (65.00)		
No	15 (35.71)	14 (35.00)		
First-line treatment drugs			0.046	0.829
Sorafenib	20 (47.62)	20 (50.00)		
Lenvatinib	22 (52.38)	20 (50.00)		

1-year survival rates were compared between the groups, with regular follow-ups through hospital revisits, telephone, text messages, and home visits until October 31, 2023. (4) Safety evaluations were based on the Common Terminology Criteria for Adverse Events 5.0 [12] with a scale from 1 to 5. Grade 1 is mild, presenting as asymptomatic or mild symptoms, with only clinical or diagnostic findings, and no treatment required. Grade 2 is moderate, necessitating minor, local, or non-invasive treatment and possibly causing limitations in instrumental activities of daily living such as cooking, shopping, using the phone, or managing finances. Grade 3 is considered serious or medically significant but not immediately life-threatening, often resulting in hospitalization or prolonged hospital stay, disability, or significant limitations in independent daily activities like bathing, dressing, eating, and taking medications, although not to the extent of being bedridden. Grade 4 involves life-threatening conditions requiring emergency intervention, and Grade 5 corresponds to death related to an adverse event. (5) Prognostic factors were analyzed using a logistic regression model.

Statistical analysis

Data analysis was conducted using SPSS version 20.0, and graphical data processing was performed with GraphPad Prism version 8. Quantitative data were expressed as mean ± standard deviation and group comparisons were made using independent and paired sample t-tests as appropriate. Categorical data were presented as cases (%) and analyzed using the chi-square test. Kaplan-Meier analysis was used to evaluate PFS and one-year overall survival. Statistical significance was set at $P<0.05$.

Results

Comparison of general data

There were no significant differences between the two groups in terms of gender, age, smoking history, etc. (all $P>0.05$), indicating comparability. See **Table 1**.

Comparison of treatment efficacy

The ORR was significantly higher in the observation group at 95.24%, compared to 62.50% in the control group (**Table 2**).

Comparison of serum tumor markers before and after treatment

Initially, there were no significant differences in serum tumor marker levels between the groups ($P>0.05$). Post-treatment, both

Table 2. Comparison of efficacy between two groups of patients [n (%)]

Efficacy	Observation Group n = 42	Control Group n = 40	X^2	P
Complete response	0	0	-	-
Partial remission	18 (42.86)	10 (25.00)	-	-
Stable disease	22 (52.38)	15 (37.50)	-	-
Disease progression	2 (4.76)	15 (37.50)	-	-
Overall response rate	40 (95.24)	25 (62.50)	13.36	0.001

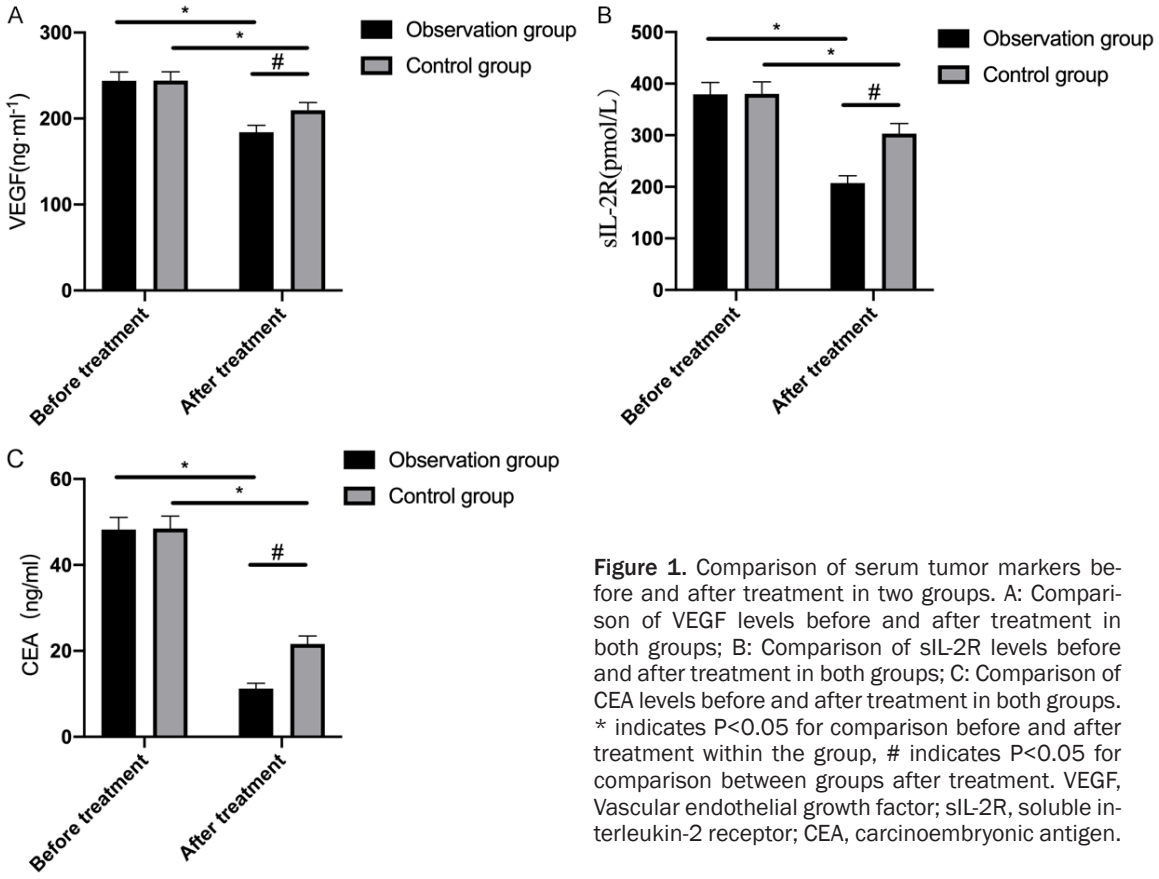

Figure 1. Comparison of serum tumor markers before and after treatment in two groups. A: Comparison of VEGF levels before and after treatment in both groups; B: Comparison of sIL-2R levels before and after treatment in both groups; C: Comparison of CEA levels before and after treatment in both groups. * indicates P<0.05 for comparison before and after treatment within the group, # indicates P<0.05 for comparison between groups after treatment. VEGF, Vascular endothelial growth factor; sIL-2R, soluble interleukin-2 receptor; CEA, carcinoembryonic antigen.

groups showed reduced levels of VEGF, sIL-2R, and CEA. However, reductions were significantly greater in the observation group, indicating substantial differences (P<0.05; **Figure 1**).

Comparison of survival

During the follow-up period, tumor progression was observed in 70.8% of the observation group and 86.7% of the control group. The median PFS was notably longer in the observation group at 9.5 months, compared to 3.0 months in the control group (P<0.001). The one-year survival rate was also higher in the observation group at 36.90%, compared to 64.10% in the control group, showing a statistically significant improvement (P<0.001; **Figure 2**).

Comparison of treatment adverse reactions

Adverse reactions occurred in all patients; however, there were no treatment-related deaths. The number of patients experiencing grade 1, 2, and 3 adverse reactions was 18, 11, and 11 in the observation group, and 20, 12, and 8 in the control group, respectively, with no significant differences between the groups (all P>0.05; **Table 3**).

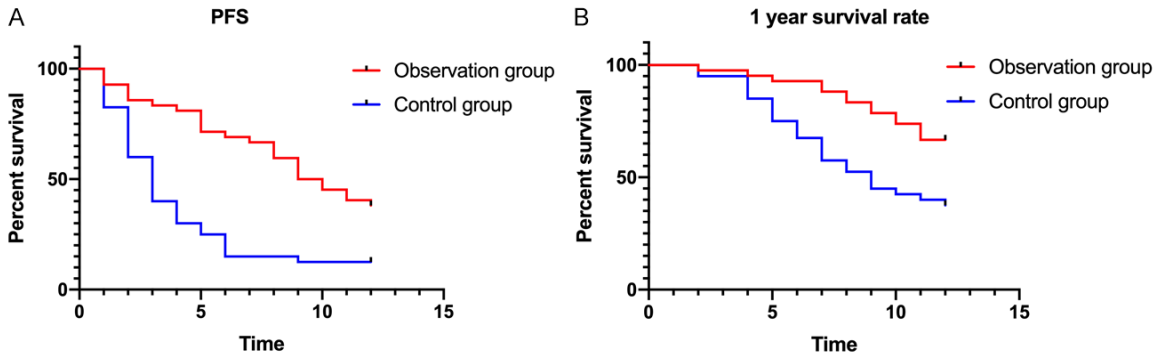

Figure 2. Comparison of survival conditions between the two groups of patients. A: Comparison of PFS between the two groups of patients; B: Comparison of the 1-year survival rates of the two groups of patients. PFS, Progression-free survival.

Table 3. Comparison of treatment adverse reactions

Grading	Observation Group n = 42	Control Group n = 40	X^2	P
1	18 (42.86)	20 (50.00)	0.420	0.517
2	11 (26.19)	12 (30.00)	0.147	0.701
3	11 (26.19)	8 (20.00)	0.441	0.507

Analysis of prognostic factors affecting patients' outcomes

Patients were divided into a survival group (43 cases) and a deceased group (39 cases) based on one-year survival status. Single-factor analysis identified vascular invasion, degree of differentiation, and treatment regimen as influential prognostic factors (**Table 4**). Subsequently, through assigning values (**Table 5**), logistic regression analysis further confirmed these factors as independent risk factors for adverse outcomes (**Table 6**; all P<0.05).

Discussion

Anti-angiogenic targeted therapy has become an established and effective treatment for advanced HCC, especially as a second-line intervention, using approved drugs such as regorafenib, apatinib, and cabozantinib [13]. Despite its benefits, challenges in clinical outcomes, drug resistance, and patient tolerability continue, driving ongoing efforts to develop innovative therapeutic strategies [14, 15]. Recent advances in tumor immunotherapy, particularly immune checkpoint inhibitors [8], have shown promise, although issues with delayed responses and limited effectiveness in specific patient groups restrict their broader use. Consequently, there is growing interest in exploring combination therapies that integrate PD-1 inhibitors with anti-angiogenic agents.

Regorafenib, known for its broad anti-angiogenic effects, favorable influence on macrophage polarization, and enhancement of CD8+ lymphocyte cytotoxicity, has been identified as a potential candidate for combination therapy with PD-1 inhibitors in second-line treatment [16]. However, research on the combined efficacy and safety of regorafenib with PD-1 inhibitors in advanced HCC remains limited. In this study, we observed a significantly higher overall response rate in the observation group, which received both PD-1 inhibitors and regorafenib, compared to the control group, which received only regorafenib. This finding suggests enhanced short-term efficacy of the combination therapy in advanced HCC patients, particularly those who did not respond to first-line treatments like sorafenib or lenvatinib. Notably, the combination therapy resulted in an increase in median PFS from 3.0 to 9.5 months and a significantly improved 1-year survival rate.

In examining the factors contributing to the enhanced efficacy of combination therapy, it is noteworthy that regorafenib upregulates hypoxia-inducible factor 1 (HIF-1), which increases the expression of PD-L1 on myeloid-derived suppressor cells and consequently inhibits T cell proliferation. However, PD-1 inhibitors can counteract the resistance induced by the anti-angiogenic actions mediated by HIF-1 [17, 18]. Additionally, regorafenib suppresses the JAK1/2-STAT1 and MAPK signaling pathways,

Table 4. Univariate analysis

Factor	Survival group (n = 43)	Death group (n = 39)	X^2	P
Gender			0.040	0.842
Male (n = 43)	23 (53.49)	20 (51.28)		
Female (n = 39)	20 (46.51)	19 (48.72)		
Age			0.083	0.773
≤65 (n = 35)	19 (44.19)	16 (41.03)		
>65 (n = 47)	24 (55.81)	23 (58.97)		
Body mass index			0.169	0.681
≤23 kg/m^2 (n = 44)	24 (55.81)	20 (51.28)		
>23 kg/m^2 (n = 38)	19 (44.19)	19 (48.72)		
Smoking history			0.584	0.445
Yes (n = 49)	24 (55.81)	25 (64.10)		
No (n = 33)	19 (44.19)	14 (35.90)		
Vascular cancer Thrombus			4.914	0.027
Yes (n = 53)	23 (53.49)	30 (76.92)		
No (n = 29)	20 (46.51)	9 (23.08)		
Degree of differentiation			7.851	0.005
Low (n = 62)	36 (67.92)	36 (92.31)		
Mid and High (n = 20)	17 (32.08)	3 (7.69)		
Treatment programs			6.988	0.008
Regorafenib monotherapy (n = 40)	15 (34.88)	25 (64.10)		
PD-1 inhibitor combined with regorafenib (n = 42)	28 (65.12)	14 (36.90)		

Table 5. Assignment table

Variable	Assignment
Vascular cancer thrombus	Yes = 1, no = 0
Degree of differentiation	Low = 1, Mid and High = 0
Treatment programs	Regorafenib monotherapy = 1, PD-1 inhibitor combined with regorafenib = 0

PD-1, Programmed death-1.

Table 6. Multivariate analysis

Variable	B	S.E.	Wals	P	Exp (B)	95% C.I.	
						Lower limit	Upper limit
Vascular cancer Thrombus	2.688	0.745	11.711	0.005	11.992	3.155	50.723
Degree of differentiation	1.625	0.681	5.669	0.023	4.891	1.323	18.291
Treatment programs	3.211	0.855	14.171	0.004	25.913	5.082	120.323

leading to decreased PD-L1 expression in tumors, inhibits Colony-stimulating factor 1 receptor to disrupt tumor-associated immunosuppression, and targets VEGFR2/3 to modulate macrophages, thereby enhancing CD8+ T cell proliferation and activation [19-21]. These mechanisms collectively enhance the efficacy of PD-1 inhibitors.

VEGF, a critical proangiogenic factor in primary liver cancer, includes several family members that mediate distinct biological functions through various receptors. It is essential for promoting endothelial cell proliferation and facilitating neovascularization in and around tumor tissues [22, 23]. The significant prognostic and therapeutic implications of VEGF in HCC

are well-documented [24]. sIL-2R, produced by activated T lymphocytes and monocytes, is markedly elevated in the serum of patients with autoimmune diseases and cancer, and is closely associated with disease progression, treatment response, and prognosis [25]. CEA, an acidic glycoprotein primarily expressed in luminal organs such as the respiratory and digestive tracts, is composed of sugar and peptide chains. Found in macrophages, monocytes, and multinucleated giant cells, CEA contains human embryonic antigen determinant clusters and functions as a tumor-associated antigen, relevant for monitoring tumor recurrence [26].

The findings of this study reveal that after treatment, the levels of VEGF, SIL-2R, and CEA decreased in both groups, with the observation group exhibiting significantly lower levels than the control group. This underscores the efficacy of PD-1 inhibitors combined with regorafenib in treating advanced HCC, yielding better outcomes compared to regorafenib monotherapy. Subsequently, an assessment of adverse reactions between the groups demonstrated similar rates across various grades, with a lower incidence of grade 3 adverse events. These findings suggest that the adjunctive use of PD-1 inhibitors with regorafenib does not substantially escalate the occurrence of adverse reactions, highlighting the favorable tolerability of this combination therapy in patients with advanced HCC. Previous retrospective studies also support that regorafenib combined with a PD-1 inhibitor improves overall survival more than regorafenib alone and is generally well-tolerated by patients, aligning with our observations [27]. Furthermore, we conducted an analysis of independent risk factors affecting patient prognosis, revealing that pathological staging, degree of differentiation, and treatment plan are independent risk factors influencing unfavorable patient prognosis. These insights are crucial for developing tailored treatment strategies for individual patients in future clinical interventions.

However, this study still has certain shortcomings. Firstly, the long-term follow-up time of this study is relatively short, rendering the overall survival data somewhat preliminary. A longer follow-up period is necessary to provide more definitive OS insights. Secondly, the study's small sample size may limit the generalizability of the findings. Future studies with larger sample sizes are essential to validate these results.

In summary, the incorporation of PD-1 inhibitors into regorafenib therapy represents a promising strategy for patients with advanced HCC. This combined approach not only improves clinical efficacy and patient survival but also maintains manageable safety profiles, thereby extending the therapeutic benefits of regorafenib. Given these encouraging findings, the adoption of this combination regimen warrants consideration in clinical practice, as it offers a balance between treatment safety and improved therapeutic outcomes for patients with advanced HCC.

Disclosure of conflict of interest

None.

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