European Review for Medical and Pharmacological Sciences 2023; 27: 4135-4144

Evaluation of the efficacy of aparatinib and carrilizumab combined with transcatheter arterial chemoembolization in the treatment of primary hepatocellular carcinoma

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Abstract. – OBJECTIVE: **The study aimed to analyze the efficacy of aparatinib and carrilizumab combined with transcatheter arterial chemoembolization (TACE) in the treatment of primary hepatocellular carcinoma (HCC).**

PATIENTS AND METHODS: **A total of 150 patients with primary HCC admitted to our hospital from March 1, 2019, to March 1, 2022 was chosen and randomized as the control and treatment group. The control group went through TACE treatment, and the treatment group experienced apatinib + karilizumab + TACE treatment. The near and long-term efficacy of the two groups were compared. The total survival time (OS), time to progression (TTP), and hospital costs were compared between the two groups. Fasting venous blood was collected before and one month after treatment in the two groups, and liver and kidney functions were tested using automatic biochemical analyzer. The levels of CD3+, CD4+ and CD8+ were detected by flow cytometry, and CD4+/CD8+ was calculated. The levels of cysteinyl aspartate specific protease-8 (Caspase-8), vascular endothelial growth factor (VEGF) and alpha fetoprotein (AFP) were detected by enzyme-linked immunosorbent assay (ELISA). The patients' conditions were closely observed and the adverse reaction rates of diarrhea, hand foot syndrome, bone marrow suppression, proteinuria, fever and pain were compared between the two groups.**

RESULTS: **The disease control rate (DCR) of short-term treatment in the treatment group was 97.33%, which was much higher than 88.00% in the control group. The survival ratios of the treatment group in September and December were 65.33% and 42.67% respectively, which were also much higher than 48.00% and 20.00% in the control group ($p < 0.05$). The TTP and OS of patients in the treatment group were significantly longer than those in the control group ($p < 0.05$), and the hospital expenses were significantly higher than those in the control group ($p < 0.05$). The levels of liver function indicators such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TBIL) were largely decreased in both groups after treatment, and more significant difference was detected in the treatment group ($p < 0.05$). Renal function between the two groups had no significant difference after treatment ($p > 0.05$). After treatment, the levels AFP and VEGF were strongly decreased and the level of Caspase-8 was markedly increased in both groups, and the treatment group had lower levels of AFP and VEGF and higher level of Caspase-8 than the control group ($p < 0.05$). The CD3+ and CD4+/CD8+ levels in two groups were dramatically elevated after treatment, and the treatment group had much higher CD3+ and CD4+/CD8+ levels than the control group ($p < 0.05$). There was no statistically significant difference in the rates of adverse reactions such as diarrhea, hand-foot syndrome, bone marrow suppression, proteinuria, fever, and pain between the two groups ($p > 0.05$).**

CONCLUSIONS: **The combination of apatinib and carrilizumab with TACE had better near- and long-term efficacy in the treatment of primary HCC by effectively inhibiting tumor vascular regeneration, inducing tumor cell apoptosis, and improving patients' liver function and immune function with higher safety, which could be widely used in clinical practice.**

Key Words:
Apatinib, Carrilizumab, Hepatic artery interventional embolization, Primary hepatocellular carcinoma, Efficacy.

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Introduction

Primary hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world, and its incidence and mortality rate are about 4.7% and 8.2%, respectively[1]. At present, the specific pathogenesis of primary HCC has not been clarified, but research[2,3] shows that the occurrence of primary HCC is closely related to chemical carcinogens and environmental factors such as cirrhosis, viral hepatitis and aflatoxin. Because the early symptoms of primary HCC are relatively hidden, most patients missed the opportunity of surgical treatment when they were diagnosed. For such patients, chemotherapy and radiotherapy are preferred[4].

Transcatheter arterial chemoembolization (TACE) is the best treatment for unresectable primary HCC. TACE effectively kills tumor cells by introducing chemotherapy drugs into the lesions through catheters, and selectively embolizing blood vessels to prevent blood supply to tumor sites. The short-term effective rate of TACE can be as high as 70%, but the long-term effect is not satisfactory. Simple TACE treatment has the shortcomings of incomplete tumor inactivation and collateral circulation regeneration, and the 5-year survival rate of patients is only 8%-43%[5]. Therefore, TACE is often used clinically in combination with other treatments to maximize tumor inactivation. Apatinib, an anti-angiogenesis drug, is an independently developed anti-tumor drug in China, which can effectively inhibit tumor angiogenesis and tumor growth by suppressing the vascular endothelial growth factor receptor, thus effectively improve the survival of tumor patients[6]. Carrilizumab, an anti-programmed death-1 (PD-1) antibody, is an immune checkpoint PD-1 inhibitor, which can expose tumor cell antigens by competing for PD-1 receptors, thus helping immune cells recognizing tumor cells and kill them with good tolerability and tumor activity. However, there are few studies on the efficacy of apatinib and carrilizumab combined with TACE in the treatment of primary HCC.

In this study, 150 patients with primary HCC admitted to our hospital from March 1, 2019 to March 1, 2022 were chosen to analyze the efficacy of aparatinib and carrilizumab combined with TACE in the treatment of primary HCC, thereby providing effective treatment strategies for liver cancer clinically.

Patients and Methods

Patients

A total of 150 patients with primary HCC admitted to our hospital from March 1, 2019, to March 1, 2022 was chosen. Inclusive criteria: (1) Patients were diagnosed as primary HCC through pathological examination and could not receive operation due to limited conditions. (2) Patients' age ranged from 18 to 80. (3) The Barcelona Clinic Liver Cancer (BCLC) stage of HCC was B or C, and the Child-Pugh grade of liver function was A or B. (4) The estimated survival time of patients was over 3 months. (5) Patients and their family members signed an informed consent form and could cooperate with the examination and treatment with good compliance. Exclusion criteria: (1) Patients with TACE contraindication. (2) Patients with other malignant tumors. (3) Patients with serious dysfunction in important organs. (4) Patients during lactating or pregnant period. (5) Patients with radiotherapy and chemotherapy history. The patients were randomized as the control and treatment group. The control group consisted of 42 males and 33 females, with an average age of (53.16 ± 8.85) years. The treatment group consisted of 38 males and 37 females, with an average age of (53.28 ± 9.04) years. There was no significant difference in age and gender between groups ($p > 0.05$). The operation of this experiment was approved by the Hospital Ethics Committee of Affiliated Hospital of Hebei Engineering University and the written informed consents were obtained from patients [Ethics approval: 2019(K)003].

Methods

The control group went through TACE treatment: (1) Before operation: all patients were examined for routine blood test, liver function, kidney function, blood coagulation, tumor markers and Electrocardiogram (ECG). The location, size, boundary and blood supply of the tumor were determined by CT examination. Patients were forbidden to eat and drink within 8 hours before operation and received intravenous nutrition support. Preoperative skin preparation was conducted at groin. After ensuring that the patients had no history of iodine allergy, we provided preoperative education for patients. (2) TACE: patients were instructed to use supine position, and routine disinfection was carried out in the groin and perineum. The puncture was performed in the right lower or left groin, and 1% lidocaine was given for local anesthesia. The femoral artery was threaded by Seldinger method, and the vascular sheath was ful-

ly implanted. The tube was sealed using heparin saline, and the contrast agent was added into the proper hepatic artery, splenic artery, left gastric artery and duodenum. The specific location, size and blood supply of the tumor were determined by full radiography with iohexol. The tumor blood supply vessel was selected and the chemical drug lobaplatin 50 mg was fully injected into it. The dosage of chemotherapy drugs shall be adjusted according to the tumor size, blood supply and actual situation of the patients during the operation. After the operation, the catheter shall be pulled out and then pressure bandaged. (3) Postoperative: according to the general situation of the patient, support treatment such as liver protection, pain relief, gastric acid inhibition and vomiting prevention was given.

The treatment group experienced apatinib + carrelizumab + TACE treatment: (1) TACE treatment was the same as the control group. (2) Drug treatment was carried out within 7 days after TACE treatment. Oral administration of apatinib mesylate tablets (Itan) (manufacturer: Jiangsu Hengrui Pharmaceutical Co., Ltd.; Jiangsu, China, approval number/production license number: GYZZ H20140103), 250 mg/once, once/day. Apatinib was discontinued 3 days before TACE treatment. Intravenous drip of carrelizumab (Erika) (manufacturer: Suzhou Shengdiya Biomedical Co., Ltd.; Suzhou, China, approval number/production license number: GYZZ S20190027) 200 mg/time, once/3 weeks. The patients' condition changes and adverse reactions were closely observed, and the treatment dose and time of taking medicine were adjusted in time.

Outcome Measurements

The short-term efficacy was graded as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), in which CR meant that the lesions disappeared completely, tumor markers returned to normal, no new lesions appeared, and the maintenance time was over 4 weeks. PR meant that the sum of the maximum diameters of the lesions decreased by ≥ 30%, and the duration was > 4 weeks. SD was between PR and PD. PD meant that the sum of the maximum diameters of the lesions increased by ≥ 20%, or new lesions were found. The disease control rate (DCR) = CR + PR + SD.

Long term efficacy: the patients' condition was closely observed. Outpatient or telephone follow-up was performed in June, September and December respectively. The survival of patients in each group in June, September and December was recorded and compared.

Survival time: Survival time included overall survival (OS) and time to progression (TTP). OS was defined as the time interval between the patients' surgical treatment and death or last follow-up. TTP was defined as the time interval between the time a patient undergoes surgery and the radiographic discovery of liver parenchymal tumor progression.

Liver and kidney functions: The levels of liver function indicators such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), blood urea nitrogen (BUN) and blood creatinine (Crea) of the two groups of patients were measured by automatic biochemical analyzer before and after treatment.

Serum indicators: The fasting venous blood of patients before treatment and one month after treatment was collected, centrifuged at 3000 r/min for 10 min. The supernatant was carefully separated and stored at -80°C. The levels of CD3+, CD4+and CD8+ were measured by flow cytometry, and CD4+/CD8+ was calculated.

Enzyme-linked immunosorbent assay (ELISA): The levels of Cysteinyl aspartate specific protease-8 (Caspase-8), vascular endothelial growth factor (VEGF) and alpha fetoprotein (AFP) were measured by ELISA. The kits were purchased from Shanghai Fusheng Biotechnology Co., Ltd (Yangpu, Shanghai, China). Detection steps: The kits and serum were equilibrated to room temperature and then all reagents were mixed thoroughly. After equilibrating at room temperature for 20 min, the desired strips were removed from the foil bag. The blank, standard and sample wells were set up, and 50 μL of standard solutions of different concentrations were added into the standard wells. 10 μL of sample and 40 μL of sample diluent were added into the sample well, while no wells were added in the blank group. The horseradish peroxide was added into each well of the standard well and sample well, except for the blank well. In addition to the blank wells, 100 μL of HRP-labeled antibody was added into the standard and sample wells, then the reaction wells were sealed with a sealing membrane and incubated for 60 min in a 37°C incubator. The cardboard is washed in the washing machine, the liquid is discarded, the absorbent paper is patted dry. We filled each hole with detergent, let stand for 1 min, threw away the detergent, and repeated the wash 5 times. 50 μL of substrate A and substrate B were added into each well and incubated for 15 min in a 37°C incubator protected from light. 50 μL of stop solution was added into each well and the OD value of each well was measured at a wavelength of 450 nm within 15 min.

Adverse reactions: The patients' conditions were closely observed and the adverse reaction rates of diarrhea, hand foot syndrome, bone marrow suppression, proteinuria, fever and pain were compared between the two groups.

Statistical Analysis

SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used to analyze the experimental data. The measurement data such as age, AFP, VEGF were presented as ($\bar{x} \pm s$), and compared using t. Enumeration data including gender, short-term and long-term efficacy, adverse reactions were expressed in (%) and compared using χ^2 text. $p < 0.05$ indicated that the statistical results were statistically significant.

Results

Analysis of General Data Between Two Groups

A total of 200 patients with primary HCC admitted to our hospital was chosen. According to the inclusion and exclusion criteria, 15 patients were excluded, 17 patients with incomplete clinical data were excluded, and 18 patients with incomplete follow-up data were excluded. Finally, 150 cases were included and grouped as the control and treatment group according to different treatment methods. General clinical data of the two groups are shown in Table I, and the inclusion process of general data are shown in Figure 1.

Comparison of Short-Term Efficacy Between Two Groups

The DCR of short-term treatment in the treatment group was 97.33%, which was much higher than 88.00% in the control group ($p < 0.05$, Table II and Figure 2).

Analysis of the Long-Term Efficacy Between Two Groups

The survival ratios of the treatment group in September and December were 65.33% and 42.67% respectively, which were also much higher than 48.00% and 20.00% in the control group ($p < 0.05$, Table III).

Comparison of Survival and Hospital Costs Between the Two Groups

The TTP and OS of patients in the treatment group were significantly longer than those in the control group ($p < 0.05$, Table IV), and the hospital costs were significantly higher than that in the control group ($p < 0.05$, Table IV).

Comparison of Liver and Kidney Function Between Two Groups Before and After Treatment

There was no significant difference in liver and kidney function between the two groups before treatment ($p > 0.05$). The levels of liver function indexes, including AST, ALT and TBIL were largely decreased in both groups after treatment, and more significant difference was detected in the treatment group ($p < 0.05$). Renal function between the two groups had no significant difference after treatment ($p > 0.05$, TableV).

Comparison of Serum Indexes Before and After Treatment Between Two Groups

After treatment, the levels of AFP and VEGF were strongly decreased and the level of Caspase-8 was markedly increased in both groups, and the treatment group had lower levels of AFP and VEGF and higher level of Caspase-8 than the control group ($p < 0.05$, Table VI).

Table I. Comparison of general data ($\bar{x}$±s, %).

General data		Control group (n = 75)	Treatment group (n = 75)	t/χ^2	p
Gender	Male	42 (56.00)	38 (50.67)	0.429	0.513
	Female	33 (44.00)	37 (49.33)		
Age (year)		53.16 ± 8.85	53.28 ± 9.04	0.082	0.935
Tumor size (cm)		7.52 ± 1.32	7.12 ± 1.26	1.898	0.060
KPS score (score)		80.23 ± 6.78	78.56 ± 5.34	1.676	0.096
Child-Pugh grade	A	50 (66.67)	45 (60.00)	0.718	0.397
	B	25 (33.33)	30 (40.00)		
Clinical stages	B	53 (70.67)	58 (77.33)	0.866	0.352
	C	22 (29.33)	17 (22.67)		

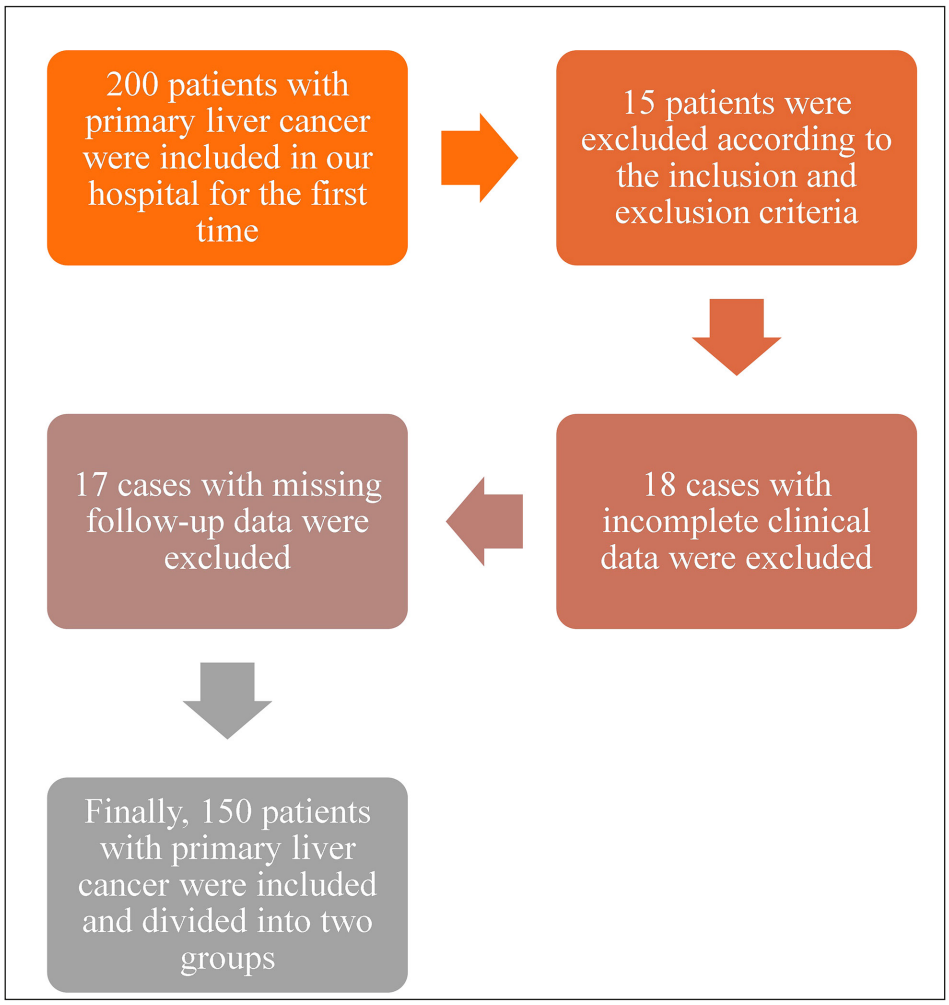

Figure 1. The inclusion process of general data.

Comparison of Immune Function Before and After Treatment Between Two Groups

The CD3+ and CD4+/CD8+ levels in two groups were dramatically elevated after treatment, and the treatment group had higher CD3+ and CD4+/CD8+ levels than the control group ($p < 0.05$, Table VII).

Comparison of Adverse Reactions Between Two Groups

There was no statistically significant difference in the rates of adverse reactions such as diarrhea, hand-foot syndrome, bone marrow suppression, proteinuria, fever and pain between the two groups ($p > 0.05$, Table VIII and Figure 3).

Table II. Comparison of short-term efficacy (cases, %).

Groups	cases	CR	PR	SD	PD	DCR
Control group	75	5 (6.67%)	23 (30.67%)	38 (50.67%)	9 (12.00%)	66 (88.00%)
Treatment group	75	12 (16.00%)	36 (48.00%)	25 (33.33%)	2 (2.67%)	73 (97.33%)
χ^2						4.807
p						0.028

Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), disease control rate (DCR).

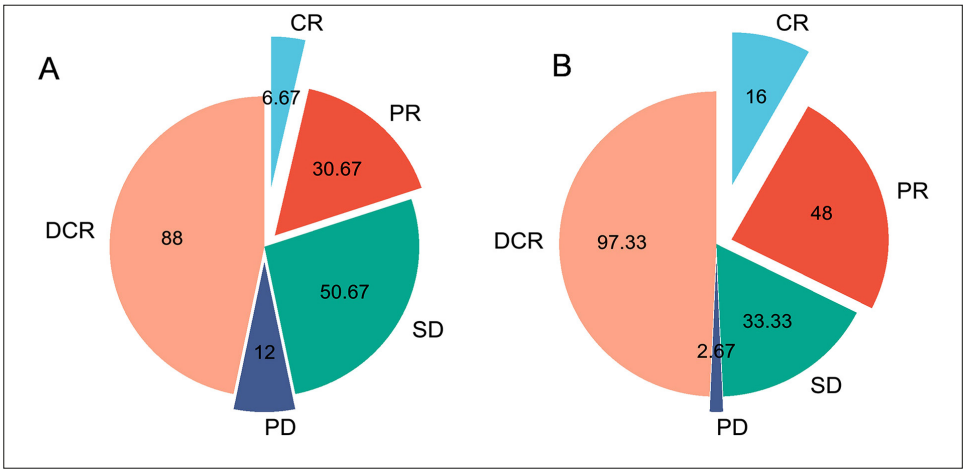

Figure 2. Comparison of short-term efficacy between two groups. **A**, Distribution of short-term clinical efficacy in the control group. **B**, Distribution of short-term clinical efficacy in the treatment group. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table III. Long-term efficacy comparison of two groups (cases, %).

Groups	Cases	DCR of June	DCR of September	DCR of December
Control group	75	53 (70.67%)	36 (48.00%)	15 (20.00%)
Treatment group	75	62 (82.67%)	49 (65.33%)	32 (42.67%)
χ^2		3.019	4.588	8.955
p		0.082	0.032	0.003

Disease control rate (DCR).

Table IV. Comparison of survival and hospital expenses between the two groups ($\bar{x}$±s).

Groups	Cases	TTP (Month)	OS (Month)	Hospital costs
Control group	75	4.25 ± 1.39	15.38 ± 2.44	7,452.85 ± 247.13
Treatment group	75	7.47 ± 3.22	11.24 ± 3.57	10,452.44 ± 485.26
t		7.951	8.291	47.703
p		< 0.001	< 0.001	< 0.001

Overall survival (OS), time to progression (TTP)

Table V. Comparison of liver and kidney function between two groups before and after treatment ($\bar{x}$±s).

Liver and kidney function	Time	Control group (n = 75)	Treatment group (n = 75)	t	p
AST (U/L)	Before treatment	108.52 ± 10.49	109.72 ± 10.83	0.689	0.492
	After treatment	64.23 ± 6.25	38.42 ± 4.52	28.979	< 0.001
ALT (U/L)	Before treatment	115.70 ± 10.24	116.85 ± 11.79	0.638	0.525
	After treatment	70.70 ± 6.42	46.53 ± 6.21	23.435	< 0.001
TBIL (μmol/L)	Before treatment	100.54 ± 10.49	101.42 ± 10.11	0.523	0.602
	After treatment	79.53 ± 6.42	58.34 ± 5.52	21.674	< 0.001
Crea (μmol/L)	Before treatment	45.23 ± 10.19	46.34 ± 11.14	0.637	0.525
	After treatment	45.35 ± 9.66	48.12 ± 12.35	1.530	0.128
BUN (mmol/L)	Before treatment	3.49 ± 0.12	3.52 ± 0.30	0.804	0.423
	After treatment	3.42 ± 0.43	3.30 ± 0.34	1.896	0.060

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), blood urea nitrogen (BUN), blood creatinine (Crea).

Table VI. Comparison of short-term efficacy (cases, %).

Groups		Caspase-8 (pg/l)	AFP (ng/ml)	VEGF (ng/L)
Before treatment	Control group (n = 75)	80.12 ± 16.59	876.39 ± 75.23	220.16 ± 23.15
	Treatment group (n = 75)	78.95 ± 16.38	881.46 ± 84.12	224.85 ± 19.64
	t	0.435	0.389	1.338
	p	0.665	0.698	0.183
After treatment	Control group (n = 75)	89.45 ± 20.15[a]	378.29 ± 25.96[a]	174.96 ± 15.86[a]
	Treatment group (n = 75)	112.56 ± 20.18[ab]	235.46 ± 20.14[ab]	130.45 ± 26.96[ab]
	t	7.018	130.925	11.479
	p	< 0.001	< 0.001	< 0.001

[a]$p < 0.05$ compared with the same group before treatment; [b]$p < 0.05$ compared with control group at the same treatment time. Vascular endothelial growth factor (VEGF), alpha fetoprotein (AFP).

Table VII. Comparison of immune function before and after treatment ($\bar{x}$±s).

Groups		CD3+	CD4+/CD8+
Before treatment	Control group (n = 75)	48.52 ± 4.96	1.08 ± 0.12
	Treatment group (n = 75)	50.12 ± 6.39	1.12 ± 0.15
	t	1.713	1.803
	p	0.089	0.073
After treatment	Control group (n = 75)	56.12 ± 9.56[a]	1.36 ± 0.15[a]
	Treatment group (n = 75)	63.58 ± 10.45[ab]	1.75 ± 0.26[ab]
	t	4.562	11.252
	p	< 0.001	< 0.001

[a]$p < 0.05$ compared with the same group before treatment; [b]$p < 0.05$ compared with control group at the same treatment time.

Table VIII. Comparison of adverse reactions (cases, %).

Groups	Cases	Diarrhea	Hand-foot syndrome	Bone marrow suppression	Proteinuria	Fever	Pain
Control group	75	32 (42.67%)	47 (62.67%)	38 (50.67%)	51 (68.00%)	15 (20.00%)	32 (42.67%)
Treatment group	75	40 (53.33%)	52 (69.33%)	41 (54.67%)	50 (66.67%)	12 (16.00%)	29 (38.67%)
χ^2		1.709	0.743	0.241	0.030	0.406	0.249
p		0.191	0.389	0.624	0.862	0.524	0.618

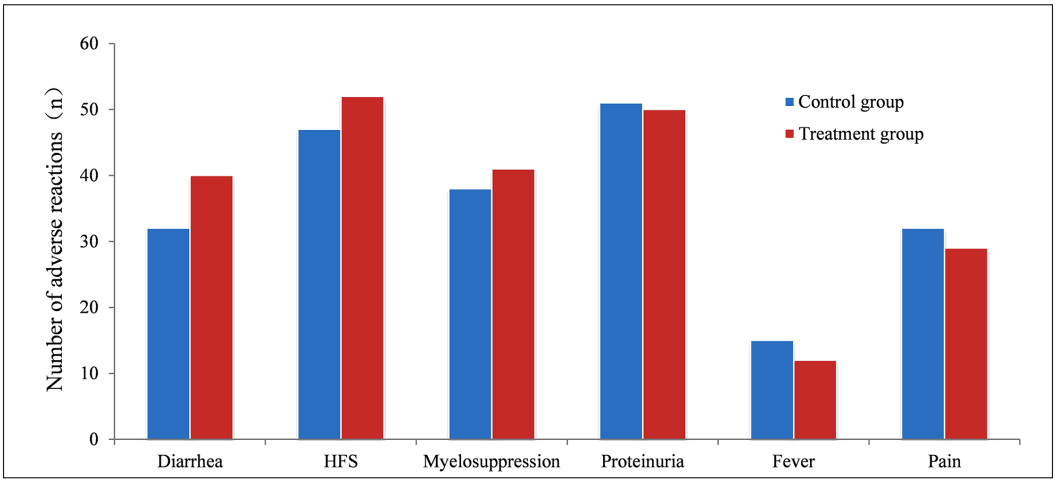

Figure 3. Comparison of adverse reactions between two groups.

Discussion

Primary HCC is one of the most common malignant tumors in China with a high incidence rate and mortality[7], and it has become a key topic in clinical research. The early symptoms of primary liver cancer are not typical and cannot attract the attention of patients. Most patients were in the middle and late stages of treatment due to obvious symptoms and missed the best opportunity for surgical treatment[8], so they had to choose palliative treatment. The etiology of HCC is related to various factors, including liver cirrhosis, hepatitis B virus, hepatitis C virus, and the intake of yellow mold toxin, etc. Among them, liver cirrhosis is a key part of the increasing incidence and mortality of HCC[9]. Liver cirrhosis-related HCC survival rate was 33%. Hepatitis virus, especially hepatitis B, and hepatitis C, are the main causes of HCC. According to a previous survey[10], the median survival period of patients with hepatitis B virus-related hepatocytosis group was 15 months, and the survival rates of 1, 3, 5, and 7 years were 71.0%, 34.0%, 30.7%, 11.53%. The survival period of the hepatitis C virus-related HCC group was 19 months, and the survival rates at 1, 3, 5, and 7 years were 90.3%, 68.2%, 41.9%, and 31.41%, respectively. The overall prognosis of hepatitis C virus-related HCC was better than hepatitis B virus-related liver cell carcinoma. Aflatoxin is a fungal toxin with high genetic toxicity and carcinogenicity. Survival analysis confirms that cyclooxygenase toxin exposure was associated with HCC prognosis. The total survival rate to high exposure is 12.59%, and the total survival rate to the low exposure group is 28.13%. The higher the degree of exposure, the worse the prognosis[11]. Thus, the survivals of HCC patients with different etiology are slightly different, and the occurrence of HCC is a very complicated process. With the rapid development of cancer treatment, how to prolong the survival time and improve the quality of life of patients with primary HCC has become the focus of medical scholars.

TACE is the first palliative treatment for primary HCC, which can be contrapuntally used for tumor focus treatment by suppressing tumor growth. However, simple TACE treatment requires multiple cycles of treatment in a short time, and the tumor cells are not completely inactivated, thus inducing high recurrence and metastasis rate in patients. At the same time, TACE treatment may lead to ischemia and hypoxia in the embolic tissue, thus inducing the formation of tumor blood vessels and promoting tumor growth and metastasis due to increased VEGF and other growth factors[12,13]. Recent studies[14] have found that TACE combined with targeted drugs and immunotherapy are helpful for improving the therapeutic effect. As a small molecule tyrosine kinase inhibitor, apatinib has good efficacy for the treatment of thyroid cancer and other malignant tumors. On the one hand, it blocks tumor metastasis and invasion by mediating angiogenesis factors such as VEGF, and on the other hand, it inactivates tumor cell by mediating tumor cell cycle change[15,16]. Immunotherapy is a new treatment method in recent years and the main immunosuppressive points include PD-L1, PD-1 and cytotoxic T lymphocyte-associated antigen (CTLA-4). Carrelizumab is a PD-1 inhibitor, which effectively delays the invasion and migration of tumor cells by improving the immune capacity of the body and inhibiting the immune escape of tumor cells, which has achieved good efficacy in the treatment of breast cancer, glioma and other tumors[17]. In this experiment, the short-term total effective rate of the treatment group received with apatinib and carrelizumab in combined with TACE was 97.33%, much higher than 88.00% of the control group. The survival rates of treatment group in September and December were 65.33% and 42.67% respectively, which were much higher than 48.00% and 20.00% of the control group. Moreover, TTP and OS in the treatment group were significantly longer than those in the control group. There was no significant difference in adverse reaction rate between the two groups. It is suggested[18] that the combination of apatinib, carrelizumab and TACE has better short-term and long-term efficacy and higher safety in the treatment of primary HCC, and can significantly increase patient survival, suggesting that they have better clinical application prospects than TACE monotherapy.

The recurrence and metastasis of tumor is the main reason for the failure of chemotherapy. As an angiogenesis factor, VEGF mediates tumor angiogenesis and participates in tumor metastasis and invasion. At the same time, as an important target of appatinib, the change of VEGF level reflects the therapeutic effect of tumor drugs[19]. Caspase-8 is an apoptosis factor commonly used in clinical tumor research, and elevated Caspase-8 expression induces tumor cell apoptosis, so as to effectively control the disease[20]. AFP is one of the most important tumor markers for clinical diagnosis of primary HCC, and changed expression of AFP is closely related to tumor size, differentiation and therapeutic effect. The progression of tumors is closely related to the immune function of the body. Tumor cells cut down

the immune capacity of the body by inhibiting the production of CD3+, inducing immunosuppressive active substances such as CD8+, thereby changing the tumor microenvironment, inducing tumor cells to invade and metastasize, promoting angiogenesis and immune escape, and finally achieving tumor metastasis[21]. In this study, the CD3+ and CD4+/CD8+ levels in two groups were dramatically elevated and the levels of AFP and VEGF greatly decreased after treatment, and the treatment group had higher CD3+ and CD4+/CD8+ levels and lower AFP and VEGF levels than the control group. It is suggested that the combination of apatinib, carrelizumab and TACE may exert an anti-tumor role by inhibiting tumor angiogenesis and inducing tumor apoptosis, and effectively improve patients' immune function and life quality, which is similar to the research results of Li et al[22].

Conclusions

In general, the combination of apatinib and carrilizumab with TACE had better near- and long-term efficacy in the treatment of primary HCC by effectively inhibiting tumor vascular regeneration, inducing tumor cell apoptosis, improving patients' liver function and immune function with higher safety, which could be widely used in clinical practice. However, due to the limited time of this study, some patients had not enough time to reach the endpoint of treatment. In addition, in-depth study on the time and dose of targeted and immune-drug therapy was not explored. In our following study, the experimental objects and research time will be expanded for in-depth exploration.

Informed Consent

Written informed consents were obtained from patients.

Ethics Approval

The operation of this experiment was approved by the Hospital Ethics Committee of Affiliated Hospital of Hebei Engineering University [Ethics approval number: 2019(K)003].

Authors' Contributions

C. Chen edited the manuscript and performed the experiment. X.-J. Hao collected data. W.-L. Wang and Y.-F. Shen processed the data and the statistics. S.-H. Zhang gave the support for everything we needed. X.-T. Duan and G.-Y. Li designed the research, provided critical comments and revised the manuscript. All authors contributed to the article and approved the submitted version.

Availability of Data and Materials

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

Funding

This study was funded by Medical Science Research Project Program of Hebei Provincial Health Commission (20190960).

Conflict of Interest

The authors declare that they have no competing interests.

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