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Effect of Apatinib Mesylate on Clinical Remission Rate and Adverse Reactions in Patients with Advanced Primary Hepatocellular Carcinoma

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Abstract: Objective: To investigate the effect of apatinib mesylate on the clinical remission rate and adverse reactions in patients with advanced primary hepatocellular carcinoma. Methods: A total of 60 patients with advanced primary hepatocellular carcinoma admitted to our hospital from January 2021 to September 2022 were selected. They were divided into two groups using a random number table. The control group (n=30) underwent drug-eluting beads transarterial chemoembolization (DEB-TACE), while the observation group (n=30) was treated with apatinib mesylate in combination with the treatment method of the control group. The short-term clinical effects, adverse reaction rates, pre- and post-treatment serum levels of Vascular Endothelial Growth Factor (VEGF) and Hypoxia-Inducible Factor-1α (HIF-1α), and survival times were compared between the two groups. Results: The short-term clinical efficacy in the observation group was significantly better than in the control group (P<0.05). The incidence rates of fever, abdominal pain, nausea and vomiting, and bone marrow suppression were comparable between the two groups (P>0.05). The observation group had a higher incidence of general fatigue, hypertension, proteinuria, hand-foot syndrome, and rash than the control group (P<0.05). Before treatment, the levels of VEGF and HIF-1α were comparable between the two groups (P>0.05). After treatment, the VEGF and HIF-1α levels in the observation group were lower than those in the control group (P<0.05). The survival time of patients in the observation group was longer than that of the control group (P<0.05). Conclusion: Treatment of patients with advanced primary hepatocellular carcinoma with apatinib mesylate can improve clinical outcomes, reduce the incidence of adverse reactions, and extend patient survival. The effect is promising and worth promoting.

Keywords: Apatinib Mesylate; Advanced Primary Hepatocellular Carcinoma; Clinical Efficacy; Adverse Reactions.

1. Introduction

According to a statistic: In 2018, the incidence rate of primary liver cancer in China was close to 10%, with a mortality rate of 13%. The prevalence and mortality rates of this disease rank fourth and third, respectively, among all cancers worldwide. Currently, patients with primary liver cancer are generally treated with surgery. However, most patients are already in the middle or late stages of the disease at the time of diagnosis, missing the optimal time for surgery. The surgical resection rate is at most 30%. The first-choice treatment for patients with mid-to-late-stage primary liver cancer is transarterial chemoembolization (TACE). The drug-eluting beads used in drug-eluting bead transarterial chemoembolization (DEB-TACE) are a new type of vascular embolization material. They can completely block tumor blood vessels and continuously release anti-tumor drugs, thereby further increasing the local concentration in the tumor and significantly enhancing the complete necrosis rate of the tumor [1,2]. Apatinib mesylate is a targeted drug for the treatment of malignant tumors. It can inhibit the formation of new blood vessels, leading to a reduction in tumor volume. In this article, the authors selected 60 patients with late-stage primary liver cancer treated in our hospital from January 2021 to September 2022, aiming to analyze the application effect of apatinib mesylate. The following study is presented [3,4].

1.1. Materials and Methods

1.1.1. General Information

Table 1. Comparison of general information between the two groups ($\bar{x}$ ±s) [n (%)]

General Information		Observation Group (n=30)	Control Group (n=30)	X2/t	P
Gender	Male	18	17	0.069	0.793
	Female	12	13		
Age Range		43-74	42-75		
Average Age (years)		63.62±3.46	63.81±3.59	0.209	0.835
BCLC Stage	B Stage	19	17	0.278	0.598
	C Stage	11	13		
Child-Pugh Classification	Class A	16	15	0.067	0.796
	Class B	14	15		
Lesion Diameter		3-7	3-8		
Average Diameter (cm)		4.23±0.35	4.26±0.36	0.327	0.745

Sixty patients with late-stage primary liver cancer treated in our hospital from January 2021 to September 2022 were selected. They were divided into groups according to the random number table method [5,6]. The control group (n=30) underwent treatment with drug-eluting beads transarterial chemoembolization (DEB-TACE), while the observation

group (n=30) received combined treatment with apatinib mesylate based on the treatment method of the control group. A comparison of the general information between the two groups showed no significant difference (P>0.05). See Table 1.

Inclusion Criteria:

1) Diagnosed with advanced primary hepatocellular carcinoma (HCC) based on radiological and pathological examinations

2) Staged as B-C according to the Barcelona Clinic Liver Cancer (BCLC) stagingsystem

3) Classified as Class A-B using the Child-Pugh grading system

4) Expected survival duration of at least 3 months

5) Complete clinical data available

6) Informed about the study and agreed to participate.

Exclusion Criteria:

1) Severe hepatic or renal function abnormalities

2) Cardiopulmonary insufficiency

3) Active hepatitis and severe infections

4) Presence of distant metastases

5) Concurrent malignancies in other systems

6) Presence of psychiatric disorders

1.1.2. Methods

Control Group: Patients underwent drug-eluting beads transarterial chemoembolization (DEB-TACE). Local anesthesia was administered during the procedure. The Seldinger technique was used to puncture the femoral artery. Angiography of the celiac trunk and superior mesenteric artery was conducted. The tumor's location, size, number, and blood supply were verified. Using a microcatheter, superselective catheterization of the tumor-feeding artery was achieved. Under fluoroscopic guidance, one vial of 100-300μm drug-eluting beads and 40-50mg of doxorubicin was thoroughly mixed and delivered for embolization. Successful embolization was indicated by an angiographic review showing no contrast enhancement of the tumor lesions. The procedure was then concluded [7,8]. Observation Group: Based on the treatment method of the control group, apatinib mesylate was also administered. Patients took an oral dose of 500mg daily. If severe adverse reactions were identified during medication, drug administration should be stopped immediately. After symptom relief through symptomatic treatment, the dosage would be gradually increased from a half dose to the full dose [9,10].

1.1.3. Observation Indicators

Short-term Clinical Efficacy Comparison:

Complete Response (CR): Complete disappearance of tumor lesions, lasting for at least four weeks.

Partial Response (PR): At least a 50% reduction in tumor volume, maintained for at least four weeks.

Stable Disease (SD): No change in tumor lesions.

Progressive Disease (PD): At least a 25% increase in tumor size or the emergence of new lesions.

Clinical Response Rate = (CR+PR) / Total number of cases in the group × 100%.

Comparison of Adverse Reaction Incidence: This primarily includes fever, abdominal pain, nausea and vomiting, bone marrow suppression, general fatigue, hypertension, proteinuria, hand-foot syndrome, and rashes.

Comparison of pre- and post-treatment serum levels of Vascular Endothelial Growth Factor (VEGF) and Hypoxia-Inducible Factor-1α (HIF-1α): Venous blood (3ml) was drawn from fasting patients, centrifuged at 3000r/min to obtain the upper layer of serum. The enzyme-linked immunosorbent assay (ELISA) method was used to detect VEGF and HIF-1α levels. Survival Duration Comparison.

1.1.4. Statistical Analysis

SPSS 20.0 statistical analysis software was used. Count data were expressed in percentages and analyzed using the $\chi 2$ test. Measurement data were expressed as ($\bar{x}$ ±s) and analyzed using the t-test. A P-value of less than 0.05 was considered statistically significant.

1.2. Results

1.2.1. Short-term Clinical Efficacy Comparison

The short-term clinical efficacy in the observation group was superior to that in the control group (P<0.05), as shown in Table 2.

Table 2. Comparison of Short-term Clinical Efficacy [n (%)]

Group	Sample Size	CR	PR	SD	PD	Remission Rate
Observation Group	30	1	13	9	7	14(46.7)
Control Group	30	0	6	10	14	6(20.0)
X2	-	-	-	-	-	4.800
P	-	-	-	-	-	0.028

1.2.2. Comparison of Adverse Reaction Rates

The incidence of fever, abdominal pain, nausea and vomiting, and bone marrow suppression in both groups of patients was comparable (P>0.05). The incidence of general fatigue, hypertension, proteinuria, hand-foot syndrome, and rash in the observation group was higher than that in the control group (P<0.05). See Table 3.

Table 3. Comparison of Adverse Reaction Rates [n (%)]

Adverse Reactions	Observation Group (n=30)	Control Group (n=30)	X2	P
Fever	15(50.0)	13(43.3)	0.268	0.605
Abdominal Pain	13(43.3)	12(40.0)	0.069	0.793
Nausea/Vomiting	11(36.7)	9(30.0)	0.300	0.584
Bone Marrow Suppression	6(20.0)	4(13.3)	0.480	0.488
General Fatigue	13(43.3)	5(16.7)	5.079	0.024
Hypertension	8(26.7)	1(3.3)	6.405	0.011
Proteinuria	11(36.7)	0(0.0)	13.469	0.000
Hand-Foot Syndrome	8(26.7)	0(0.0)	9.231	0.002
Rash	4(13.3)	0(0.0)	4.286	0.038

1.2.3. Comparison of Serum VEGF and HIF-1α Levels Before and After Treatment

Before treatment, there was no significant difference in VEGF and HIF-1α levels between the two groups (P>0.05). After treatment, the levels of VEGF and HIF-1α in the observation group were lower than those in the control group (P<0.05). See Table

Table 4. Comparison of Serum VEGF and HIF-1α Levels Before and After Treatment($\bar{x}$ ±s) (pg/ml)

Group	Sample Size	VEGF		HIF-1α	
		VEGF Before Treatment	VEGF After Treatment	HIF-1α Before Treatment	HIF-1α After Treatment
Observation Group	30	198.66±18.65	108.71±9.81	418.33±39.47	298.61±28.65
Control Group	30	197.44±18.59	139.54±12.96	417.91±39.40	331.44±33.07
t	-	0.254	10.389	0.041	4.110
P	-	0.801	0.000	0.967	0.000

1.2.4. Survival Time Comparison

The survival time for patients in the observation group was (11.86±1.07) months, while the survival time for patients in the control group was (7.67±0.72) months. The comparison between the two groups was statistically significant (P<0.05).

2. Discussion

Primary liver cancer is one of the malignant digestive system tumors with a relatively high incidence rate in modern clinical practice. The malignancy of this disease is relatively high, with a poor prognosis, and a five-year survival rate of only 15%. The causes of liver cancer are complex and are mainly related to excessive alcohol consumption, hepatitis B virus infection, and cirrhosis [11,12]. For patients with advanced primary liver cancer, treatment is typically administered through transarterial chemoembolization (TACE). Common embolic agents include a mixture of iodized oil and chemotherapy drugs. This type of embolic agent can enter the systemic circulation, which may increase its toxic side effects. Additionally, the tumor's surrounding collateral circulation can wash out the iodized oil, preventing complete embolization. Polyvinyl alcohol drug-loaded microspheres are a new type of embolic agent that can address these shortcomings by gradually releasing chemotherapy drugs in a controlled manner to the tumor, maintaining a sustained, effective drug concentration, and achieving more thorough tumor embolization, leading to tumor tissue hypoxia and ischemic necrosis. However, merely treating patients with drug-loaded microspheres through TACE has limitations in its anti-tumor effect. This is mainly because after treatment, the tumor microenvironment becomes ischemic and hypoxic. Under the combined influence of VEGF and HIF-1α, new tumor blood vessels form, causing tumor recurrence and disease progression. Apatinib mesylate is a new type of growth factor receptor-2 inhibitor with high selectivity. It can inhibit the phosphorylation of VEGFR-2 and competitively inhibit the binding of VEGFR-2 and VEGF, thereby suppressing the formation of new blood vessels and producing an excellent anti-tumor effect. This study found that the clinical remission rate of the observation group was higher than that of the control group [13,14]. The reason being, the good effect of drug-loaded microspheres through TACE, followed by the administration of apatinib mesylate to patients, effectively controlled the level of VEGF in the patient's body and reversed chemotherapy resistance, significantly enhancing the anti-tumor effect of chemotherapy drugs, leading to better short-term results. The growth of tumors and metastatic tumors is closely related to blood vessel formation. VEGF and HIF-1α are angiogenesis factors, which enhance blood vessel formation capability and are closely related to tumor recurrence and metastasis. This study found that the levels of VEGF and HIF-1α in patients in the observation group were lower than those in the control group. The reason is that treating patients with advanced primary liver cancer with apatinib mesylate after surgery effectively inhibits tumor blood vessel formation and progression, prevents tumor recurrence, and extends the survival time of patients. This study found that the occurrence rate of general fatigue, hypertension, proteinuria, hand-foot syndrome, and rash in patients in the observation group was higher than that in the control group. However, these adverse reactions improved after symptomatic treatment [15]. In summary, administering apatinib mesylate to patients with advanced primary liver cancer can increase the clinical remission rate but may also increase the risk of adverse reactions. Therefore, during medication, intensified monitoring is required.

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