Clinical Efficacy of Chemotherapy Combined with Vascular Targeted Agents in Advanced Liver Cancer Treatment

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This study aims to assess the clinical efficacy of combining chemotherapy with vascular targeted agents in managing advanced liver cancer. A total of 86 patients diagnosed with advanced liver cancer between March 2020 and August 2022 were enrolled in this study. They were randomly divided into an observation group (n=43) receiving chemotherapy combined with vascular targeted agents and a control group (n=43) receiving chemotherapy alone. The study compared treatment outcomes, tumor marker levels, inflammatory cytokine profiles, quality of life, and adverse reactions between the two groups. Prior to treatment, no significant differences were observed in the levels of alpha-fetoprotein, vascular endothelial growth factor, fibroblast growth factor, and carcinoembryonic antigen between the observation and control groups ($p>0.05$). Post-treatment, the observation group exhibited significantly lower alpha-fetoprotein, vascular endothelial growth factor, fibroblast growth factor, and carcinoembryonic antigen levels compared to the control group ($p<0.05$). Pre-treatment, there were no noteworthy differences in interleukin-6, interleukin-10, and tumor necrosis factor-alpha levels between the two groups ($p>0.05$). Post-treatment, interleukin-6 and tumor necrosis factor-alpha levels decreased in the observation group, while interleukin-10 levels increased in comparison to the control group ($p<0.05$). Before treatment, there were no significant disparities in quality of life scores between the groups ($p>0.05$). However, post-treatment, the observation group showed higher quality of life scores than the control group ($p<0.05$). The incidence of adverse reactions did not significantly differ between the observation and control groups ($p>0.05$). Combining chemotherapy with vascular targeted agents for treating advanced liver cancer is associated with notable reductions in tumor marker levels, modulation of immune function, and enhanced patient quality of life. This combined approach is both safe and reliable, warranting its consideration for wider clinical application and promotion.

Key words: Advanced liver cancer, vascular targeting drugs, alpha-fetoprotein, immune function, quality of life

Liver cancer is a prevalent malignancy characterized by challenges in prevention and treatment, high invasiveness, and low survival rates. Incidence and mortality rates are greater in males and suburban regions compared to females and urban areas[1]. Currently, primary treatment methods for liver cancer encompass surgery, chemotherapy, targeted drugs, intervention, and immunotherapy. Nevertheless, the challenging early diagnosis of liver cancer often leads to the detection of advanced-stage cases in the majority of patients[2,3], and only 30 % of these patients meets surgical indications. Thus, the treatment for advanced liver cancer is mainly chemotherapy, which uses chemical drugs to kill tumor cells, but when chemical drugs kill tumor cells, they will also affect normal cells[4-6]. Research indicates that targeted drugs can selectively eliminate tumor cells, concentrating at tumor sites to enhance drug effectiveness while mitigating toxic side effects. This approach minimizes harm to healthy tissues and cells. Lenvatinib is a multi-target drug that can inhibit the kinase activity of vascular endothelial factor receptor, thereby inhibiting the pathological angiogenesis of tumors, and is often used in the treatment of patients with advanced liver cancer[7]. Building upon Lenvatinib's functionality, this study employed a combination

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of chemotherapy and vascular targeting drugs for advanced liver cancer patients. The evaluation encompassed treatment efficacy, tumor marker levels, quality of life, and adverse reactions. A cohort of 86 patients diagnosed with advanced liver cancer and admitted to the first affiliated Hospital of Huzhou University between March 2020 and August 2022 were chosen as subjects for this study. Patients with advanced liver cancer diagnosed by examination[8]; no history of drug allergy; in line with the indications for vascular-targeted drugs combined with chemotherapy and patients provided informed consent and actively participated in the treatment process. Exclusion criteria excludes the patients who have received other treatments before; patients with autoimmune diseases and (or) other malignant tumors and patients with mental illness. Subjects were randomly allocated into two cohorts; the observation group and the control group, with 43 cases in each. Within the observation group, 31 males and 12 females were included, aged 36 y to 67 y, and exhibiting an average age of (51.26±3.94) y. Within this group, 29 cases presented with stage III tumors, while 14 cases exhibited stage IV tumors. The control group comprised 34 males and 9 females, aged between 34 y and 66 y, and possessing an average age of (53.42±4.56) y. Within this group, 31 cases presented with stage III tumors, and 12 cases were classified as stage IV. No statistically significant distinctions were observed between the two groups in terms of fundamental characteristics ($p>0.05$), confirming their comparability. The control group underwent chemotherapy treatment. In the specific operation, puncture was made at the site of the cannulation of the right femoral artery using paracentetic needle. Subsequently, a catheter was selectively inserted into the common hepatic artery. The intrahepatic tumor staining can be seen under X-ray imaging, inject chemotherapy drugs, and use fluorouracil injection (Tianjin Jinyao Pharmaceutical Co. Ltd., China H12020959) (0.75-1.00) g, mitomycin for injection (Hanhui Pharmaceutical Co., Ltd. H19999025) (6-12) mg, pirarubicin hydrochloride for injection (Zhejiang Haizheng Pharmaceutical Co., Ltd., H20045983) (40-60) mg, and super liquefied iodized oil 30 ml. The control group underwent treatment three times, spaced 4 w apart. The observation group received additional lenvatinib mesylate capsules (Zhengda Tianqing Pharmaceutical Co., Ltd., H20213600, specifications: 4 mg×30 capsules) in combination with chemotherapy protocol used for the control group. Patients took lenvatinib mesylate capsules 8-12 mg within 1 h after meals, once a day, for a course of 3 mo. During use, pay close attention to liver and kidney levels. Laboratory assessments included Electrochemiluminescence (ECL) analysis of Alpha-Fetoprotein (AFP), Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), and Carcinoembryonic Antigen (CEA) levels. These assays utilized kits obtained from Guangzhou Ao Rui Da Biotechnology Co., Ltd. Furthermore, Enzyme-Linked Immunosorbent Assay (ELISA) was employed to measure Interleukin (IL)-6, IL-10, and Tumor Necrosis Factor-Alpha (TNF-α) levels in the patient's serum both prior to treatment and post-treatment. The ELISA kits were procured from Tianjin Keweinuo Biotechnology Co., Ltd. Patient prognosis was assessed through a quality of life scale, encompassing domains such as Physical Function (PF), Physical Role (RP), Body Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Emotional Role (RE), and Mental Health (MH). These domains have a direct positive correlation with overall quality of life. Concurrently, adverse reactions within both groups were diligently documented. Data were analyzed using Statistical Package for the Social Sciences (SPSS) 22.0 statistical software. Measurement data were presented as mean±standard deviation ($\bar{x}\pm s$). Paired t-tests were employed to compare pre- and post-treatment outcomes within each group. Independent sample t-tests were utilized to contrast intergroup differences post-treatment. For categorical data expressed as percentages (%), the Chi-square (χ^2) test was employed. A significance level of $p<0.05$ indicated statistically significant differences. Prior to treatment, the serum levels of AFP, VEGF, FGF, and CEA were compared between the two groups, yielding non-significant results ($p>0.05$). Following 3 mo of treatment, the observation group exhibited significantly lower indicators than the control group ($p<0.05$). The corresponding outcomes are summarized in Table 1. Pre-treatment, differences in IL-6, IL-10, and TNF-α levels were compared between the two groups, showing no statistically significant variation ($p>0.05$). Post 3 mo of treatment, the observation

group displayed notably reduced IL-6 and TNF-α levels in comparison to the control group ($p<0.05$), whereas IL-10 levels were significantly higher in the observation group compared to the control group ($p<0.05$). The specific results are provided in Table 2. Through the analysis of the data in various dimensions, no statistical difference in pre-treatment quality of life was evident between the groups ($p>0.05$). After 3 mo of treatment, the observation group's quality of life showed significant improvement in contrast to the control group, indicating a statistically notable distinction ($p<0.05$). The specific results are provided in Table 3. The occurrence of adverse reactions, encompassing weight loss, proteinuria, hypertension, and diarrhea, was comparatively lower in the observation group (20.93 %) in comparison to the control group (23.25 %). However, this difference did not attain statistical significance ($p>0.05$). The specific results are provided in Table 4. Primary liver cancer is categorized into Hepatocellular Carcinoma (HCC), cholangiocarcinoma, and mixed HCC-cholangiocarcinoma, among which HCC accounts for the largest proportion, reaching 75 %-85 %, followed by Cholangiocarcinoma (ICC), the proportion is 10 %-15 %, while cHCC-ICC is relatively rare[9]. Primary liver cancer stands as the 2nd most prominent cause of cancer-related death, second only lung cancer. Within China, primary liver cancer holds the 4th position among prevalent malignancies[10]. Therefore, liver cancer is a major factor that seriously threatens people's life and health, and it is particularly important to prevent and treat liver cancer. However, since patients with early liver cancer have no obvious symptoms, it is difficult to diagnose. Major symptoms of liver cancers are persistent pain in the liver area, jaundice, ascites, and emaciation[11]. Research indicates that primary contributors to liver cancer encompass excessive alcohol consumption, infection by the Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV), nonalcoholic steatohepatitis, and a family history of liver cancer[12]; therefore, the screening and monitoring of high-risk groups for liver cancer is conducive to early detection of liver cancer and timely treatment and control. Current liver cancer treatment modalities encompass surgery, chemotherapy, targeted drugs, intervention, and immunotherapy. In cases of advanced liver cancer, direct surgical resection often yields suboptimal overall survival rates[13]. However, preoperative combination therapy involving chemotherapy and targeted drugs can enhance postoperative survival rates. This combined approach has been shown to extend patient survival and enhance treatment efficacy[14,15]. Lenvatinib primarily restrains tumor growth by targeting FGF and VEGF. It has established itself as a frontline treatment for liver cancer[16]. During the treatment of patients with advanced liver cancer, the monitoring is mainly the changes in the levels of tumor markers such as AFP, VEGF, FGF, and CEA. The study outcomes reveal that following treatment, the observation group exhibited notably reduced tumor marker levels in comparison to the control group. This disparity was statistically significant ($p<0.05$), suggesting that the combination of chemotherapy and vascular-targeted drug therapy can simultaneously curtail liver cancer progression and facilitate overall recuperation. Furthermore, the incidence of adverse reactions post-treatment did not significantly differ between the two groups, signifying that the combined use of chemotherapy and lenvatinib does not exacerbate adverse reactions. The development of advanced liver cancer is intricate, accompanied by aberrant immune reactions that trigger extensive inflammatory responses in the body, leading to the release of various immune factors. Notably, IL-6 and IL-10 function as chemokines, with IL-6 stimulating B cell proliferation and differentiation to generate related antibodies, while IL-10 aids natural and specific immunity by suppressing mononuclear macrophages. Additionally, TNF-α propels T cells and other cytotoxic cells to target and eliminate tumor cells[17]. This study initially found no statistically significant differences ($p>0.05$) in IL-6, IL-10, and TNF-α levels between the observation and control groups before treatment. However, after 3 mo of treatment, the observation group exhibited lower levels of IL-6 and TNF-α than the control group, alongside higher levels of IL-10. These differences were statistically significant ($p<0.05$). This suggests that the combined approach of chemotherapy and vascular-targeted drug therapy can regulate immune functions, thus curbing disease progression. Notably, this approach also led to enhanced PF, social activities, MH, and overall quality of life in the observation group, with a

significantly higher quality of life than the control group. To conclude, the combined application of chemotherapy and targeted drugs for advanced liver cancer treatment substantially diminishes tumor marker levels, modulates immune responses, enhances patient quality of life, and demonstrates strong safety credentials. This approach holds promise for widespread adoption and implementation in clinical practice.

TABLE 1: TUMOR MARKER LEVEL COMPARISON BETWEEN GROUPS (x̄±s)

Group	n	Time	AFP (ng/ml)	VEGF (ng/ml)	FGF (ng/ml)	CEA (ng/ml)
Observation	43	Before treatment	498.70±73.91	159.42±21.45	10.07±2.13	7.23±1.38
		After treatment	81.81±15.52[a]	78.09±7.88[a]	3.29±0.74[a]	2.72±0.65[a]
Control	43	Before treatment	487.26±63.95	152.42±19.79	10.79±2.69	7.60±1.34
		After treatment	198.49±37.32[b]	131.65±12.80[b]	6.16±1.35[b]	4.61±0.89[b]
t[b]			18.83	33.52	12.12	11.99
p[b]			<0.001	<0.001	<0.001	<0.001

Note: Compared before and after treatment within group, [a]p<0.05 and compared between group after treatment, [b]p<0.05

TABLE 2: INFLAMMATORY FACTOR LEVEL COMPARISON BETWEEN GROUPS (x̄±s, ng/l)

Group	n	Time	IL-6	IL-10	TNF-α
Observation	43	Before treatment	20.61±2.52	4.06±1.03	34.53±2.08
		After treatment	12.75±1.88[a]	10.78±1.74	20.32±2.57
Control	43	Before treatment	20.04±2.86	4.36±1.53	34.78±2.75
		After treatment	17.02±2.07[b]	7.48±1.63	24.16±1.83
t[b]			10.36	10.34	8.89
p[b]			<0.001	<0.001	<0.001

Note: Compared before and after treatment within group, [a]p<0.05 and compared between group after treatment, [b]p<0.05

TABLE 3: QUALITY OF LIFE COMPARISON BETWEEN GROUPS (x̄±s, points)

Group	n	Time	PF	RP	BP	CH
Observation	43	Before treatment	58.52±4.23	58.66±3.99	54.98±3.45	60.27±5.35
		After treatment	79.25±4.98[a]	80.12±4.18[a]	78.45±4.58[a]	86.74±4.52[a]
Control	43	Before treatment	59.47±4.17	57.25±4.42	55.47±4.26	61.32±4.29
		After treatment	68.68±5.05[b]	71.56±4.05[b]	67.96±4.19[b]	74.35±4.41[b]
t[b]			18.14	26.87	17.68	18.25
p[b]			<0.001	<0.001	<0.001	<0.001

Note: Compared before and after treatment within group, [a]p<0.05 and compared between group after treatment, [b]p<0.05

TABLE 4: ADVERSE REACTION COMPARISON BETWEEN GROUPS [case (%)]

Group	n	Hypertension	Proteinuria	Diarrhea	Weight loss	Total incidence
Observation	43	2 (4.65)	3 (6.98)	1 (2.32)	3 (6.98)	9 (20.93)
Control	43	1 (2.32)	1 (2.32)	4 (9.30)	4 (9.30)	10 (23.25)
χ^2						0.068
p						0.795

Conflict of interests:

The authors declared no conflict of interests.

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