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Original Research Article

Short-term efficacy of oxaliplatin as interventional therapy for liver cancer, and its effect on serum CD163 and AFU

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Abstract

Purpose: *To investigate the short-term effectiveness of oxaliplatin in the interventional treatment of liver cancer, and its effect on serum CD163 and α-L-glucosidase (AFU).*
Methods: *Eighty liver carcinoma patients treated in The Affiliated Hospital of Shaoxing University, Shaoxing, China from January 2022 to January 2023 were allotted to 2 cohorts (each with 40 patients). Subjects in control group were treated with hepatic Transarterial Chemoembolization (TACE), while study group was treated with combination of hepatic TACE and oxaliplatin. Efficacy, serological indicators, health status and cancer-related fatigue were determined and compared between both cohorts.*
Results: *DCR was significantly higher in study group than in the control. There were significantly reduced post-treatment amounts of CYFRA21-1, CA125 and VGEF in the study cohort, relative to pre-treatment and control levels ($p < 0.05$). Post-treatment values of CD4+/CD8+ and CD4+ were significantly low, relative to levels before treatment, while CD8+ in both groups were significantly increased after treatment ($p < 0.05$). However, post-treatment T lymphocyte level was comparable in both groups. There was significantly higher post-treatment KPS score in study cohort than pre-treatment and control scores, but RPFS score was significantly reduced, relative to the corresponding pre-treatment and control scores. Post-treatment serum amounts of CD163 and AFU were significantly down-regulated in both cohorts, with lower levels in the study cohort.*
Conclusion: *The combined use of liver TACE and oxaliplatin produces good clinical outcome in the treatment of liver cancer. It is beneficial in reducing serum levels of CD163 and AFU, inhibits proliferation of tumor cells, reduces tumor volume, and improves cancer prognosis in patients.*

Keywords: *Oxaliplatin, Liver cancer, Interventional therapy, Short-term efficacy, α- L-glucosidase*

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INTRODUCTION

Liver cancer is considered the 6th most common carcinoma and the 3rd major cause of cancer-related mortality in the world [1]. Liver carcinoma development usually occurs in people with a chronic hepatic illness such as cirrhosis. In addition, the incidence of liver cancer is affected by many influences such as serum hepatitis B and hepatitis C viruses, diabetes mellitus, albumin expression, age at sustained virologic response, alcohol intake, and smoking [2]. At

present, there are no radical means of clinical treatment of patients with liver cancer. Local ablation or radical resection is mainly used in the treatment of early and middle stages of liver cancer [3]. However, this operation results in many residual liver cancer tissues which result in poor clinical curative effect. Therefore, arterial infusion chemoembolization treatment is widely used in the clinical treatment of liver cancer. The chemotherapeutic drugs used in the arterial infusion chemoembolization of liver cancer are diverse, and they include fluorouracil, alkaloids, anthracyclines, and platinum. It has been shown that these chemotherapeutic drugs produce different degrees of clinical effectiveness [4]. Oxaliplatin has been applied clinically in combined treatment with folinic acid and 5-fluorouracil (FOLFOX4) as effective therapy for severe liver cancer [5]. Oxaliplatin is a DNA interactor which generates intra-chain adducts with DNA via covalent linkages, thereby exerting anticancer effects by blocking DNA replication and transcription in cancer cells [6]. The CD137 is an important co-stimulatory molecule in T cell activation, and it enhances the antitumor effect of T cells [7].

Serum α-L-glucosidase (AFU) is a liposomal enzyme that is widely present in tissues and body fluids [8]. This study was aimed at investigating the short-term effectiveness of oxaliplatin on liver cancer, and its effect on serum concentrations of CD163 and AFU, so as to provide reference for the selection of clinical treatment methods for liver cancer.

METHODS

General information

Eighty patients with liver cancer who were treated in The Affiliated Hospital of Shaoxing University, Shaoxing, China from January 2022 to January 2023 were assigned in a random fashion to 2 cohorts, each with 40 subjects. No statistically significantly significant differences in medical data and biodata existed between both groups, as shown in Table 1. This research was permitted by the Ethical Authority of Shaoxing People's Hospital (approval no. SXPH2023006), and was carried out in line with the amended Helsinki declaration [9].

Subjects enrolled in this research were liver cancer patients aged 18 ≤ 80 years who were expected to survive for ≥ 6 months, and those with complete medical records. Patients with abnormal coagulation function or tendency to bleed; those with a history of massive hemoptysis in the previous 3 months; patients with severe cardiac, hepatic and renal dysfunctions, and patients with other malignant tumors, were excluded from the study.

Treatments

Patients in control category received liver TACE, while those in study group were given combination of hepatic TACE and oxaliplatin. After administering TACE, a micro-pump was used to slowly and continuously pump about 50 mg of oxaliplatin (Suzhou Lixin Pharmaceutical Co. Ltd., approval no. Guoyao Zhunzi h20113144) when the patients returned to the ward.

Evaluation of parameters/indices

Serological indices

Approximately 3 mL of venous blood was taken from each subject from the two groups pre- and post-treatment, and the level of carbohydrate antigen 125 (CA125) was determined using microparticle chemiluminescence method. Carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA21-1) were assayed using chemiluminescence quantitative method. The serum amounts of CD4 + and CD8 + cells in both groups were determined with a flow cytometer (Beckman, USA), and the CD4+/CD8+ ratios were calculated. Serum levels of CD163 and AFU were determined with ELISA.

Health status and cancer-related fatigue [10]

Health condition of patients was assessed with a double-blind KPS scoring system. The scoring system comprised 20 items with a score range of 0 - 100 points.

Table 1: Clinical data of patients in both groups (n=40)

Group	Gender		Years of age	Liver function grade (n)		Pathological stage (n)	
	Male	*Female*		*Class A*	*Class B*	*III*	*IV*
Study	25	15	60.18±5.89	14	26	28	12
Control	27	13	61.33±6.23	15	25	27	13
χ^2/t	0.220		-0.848	0.054		0.058	
P-value	0.639		0.399	0.816		0.809	

The higher the score, the better the health status of the patients. A double-blind method, i.e., Piper Fatigue Scale (RPFS) was used to evaluate the degree of cancer-related fatigue in the two groups. The scale consisted of four dimensions: cognition, emotion, perception, and behavior, with a score range of 0 - 10 points. The higher the score, the more serious the cancer-related fatigue in patients.

Statistical analyses

The SPSS version 20.0 package was employed for statistics. Counted data are expressed as n, (%), and comparison was done using χ2 test. Measurement data are expressed as mean ± standard deviation (SD). Statistical comparison was performed using *t*-test and Kaplan Meier method for survival analysis. Statistical significance was assumed if $p < 0.05$.

RESULTS

Clinical treatment efficacy

As presented in Table 2, DCR was significantly higher in the study group than in control group.

Tumor markers levels

Pre-treatment concentrations of VEGF, CA125 and CYFRA21-1 were comparable in both groups. However, post-treatment concentrations of these parameters were significantly decreased in study group, relative to pre-treatment and control levels ($p < 0.05$). These data are presented in Table 3.

Levels of immune parameters

Pre-treatment T lymphocyte levels in both groups were similar. In contrast, post-treatment CD4+/CD8+ ratio and CD4+ levels were significantly reduced, relative to pre-treatment, while levels of CD8+ in both groups were significantly increased, relative to pre-treatment values ($p < 0.05$). However, post-treatment T lymphocyte level was similar in both groups. These results are presented in Table 4.

KPS and RPFS scores

Prior to drug administration, both groups had similar KPS and RPFS scores. However, post-treatment KPS score was significantly higher in study group than the pre-treatment and control scores, while post-treatment RPFS score was significantly decreased, relative to pre-treatment and control scores ($p < 0.05$). These results are presented in Table 5.

Table 2: Clinical effectiveness in each {n = 40; (%)}

Group	Cr	PR	SD	PD	DCR
Study	8 (20.00)	16 (40.00)	11 (27.50)	5 (12.50)	35 (87.50)
Control	4 (10.00)	10 (25.00)	13 (32.50)	13 (32.50)	27 (70.00)
χ^2					4.588
P-value					0.032

Table 3: Comparison of tumor marker levels between the two groups

Group	CYFRA21-1 (μg/L)		CEA (μg/L)		CA125 (U/mL)	
	#Pre-	***Post-***	***Pre-***	***Post-***	***Pre-***	***Post-***
Study	39.87±7.51	17.58±4.08*	51.79±8.26	17.58±4.94*	88.25±11.13	41.89±8.78*
Control	40.33±7.23	24.42±5.23*	52.25±10.39	31.31±8.61*	87.75±10.71	52.21±9.21*
t	-0.279	-6.522	-0.219	-8.748	0.205	-5.129
P-value	0.781	0.000	0.827	0.001	0.838	0.000

#Pre- and post- refer to treatment periods. *$P < 0.05$, vs. pre-treatment

Table 4: Comparison of immune index levels between the two groups (n=40; %)

Group	$CD4^+$		$CD8^+$		$CD4^+/CD8^+$	
	Before	***After***	***Before***	***After***	***Before***	***After***
Study	28.13±5.85	23.37±7.42*	29.24±5.47	35.22±4.47*	0.95±0.18	0.72±0.14*
Control	28.40±5.12	22.72±4.33*	29.75±5.64	33.74±6.61*	0.94±0.16	0.67±0.12*
t	-0.220	0.479	-0.411	1.173	0.263	1.715
P-value	0.827	0.634	0.683	0.244	0.794	0.090

*$P < 0.05$, vs. patients in pre-treatment

Table 5: KPS and RPFS scores in each group (points) (n=40)

Group	KPS		RPFS	
	[#]***Pre-***	***Post-***	***Pre-***	***Post-***
Study	64.21±8.73	85.87±12.62*	5.77±1.02	4.11±0.72*
Control	65.75±10.42	76.21±11.35*	5.74±0.97	4.87±0.85*
t	-0.717	3.600	0.135	-4.315
P-value	0.476	0.001	0.893	0.000

[#]Pre- and post- refer to treatment periods. **P* < 0.05, vs. pre-treatment patients

Table 6: Serum CD163 and Afu levels

Group	CD163 (ng/mL)		AFU (µg/L)	
	Before	***After***	***Before***	***After***
Study	1943.52±189.05	522.34±91.21*	219.02±17.47	103.15±12.34*
Control	1943.48±190.94	810.81±131.14*	220.13±17.32	142.62±14.43*
t	0.001	-11.421	-0.285	-13.148
P-value	0.999	0.000	0.776	0.000

Note: **P* < 0.05, vs. pre-treatment

Serum CD163 and AFU concentrations

Table 6 shows that serum levels of CD163 and AFU were similar in both groups, prior to treatment. However, post-treatment serum concentrations of CD163 and AFU in both cohorts were significantly decreased, but the study cohort had lower levels.

DISCUSSION

Liver cancer is characterized by invasion, metastasis and frequent recurrence. Primary liver cancer accounts for 70 – 90 % of liver cancers, and it has become a major health issue worldwide [11]. In spite of advances in management of liver carcinoma, the disease prognosis is still unsatisfactory. At present, the pathogenesis and etiology of hepatocellular carcinoma are not fully understood. However, recent studies suggest that hepatocellular carcinoma may be linked to factors such as genetics, inflammation, immune defects, age and radiation [12]. At present, chemoradiotherapy and surgical resection are used in clinics for managing liver cancer. Although these strategies may cure cancer in some cases, an appreciable number of patients have late diagnosis, thereby losing the critical period for therapy. Moreover, the late-diagnosis cases are not sensitive to chemoradiotherapy, resulting in limited clinical treatment effect [13].

With in-depth studies on tumor genes at the molecular level, the use of tumor-targeted drugs has gradually gained acceptance in the treatment of tumor patients. The incidence, invasion and recurrence of hepatocellular carcinoma are usually high. Thus, there is need for targeted radical treatment of hepatocellular carcinoma subjects. In recent years, with the continuous advancements in medical techniques, molecular targeted therapeutics have been employed in drug treatment of liver cancer. Oxaliplatin is a frequently-used tumor-targeted drug in clinics. The drug effectively inhibits tumor growth. This study investigated the short-term effectiveness of oxaliplatin during interventional therapy of liver cancer, and its effect on serum CD163 and AFU. The results showed that this treatment method produced good clinical effectiveness. The DCR was significantly higher in study cohort than in controls. Post-treatment CD4+/CD8 + ratio and CD4+ levels were significantly reduced, relative to pre-treatment, while CD8+ levels in both cohorts were significantly increased after treatment. However, after drug exposures, T lymphocyte level was similar in both cohorts. Moreover, the post-therapy KPS score in the study cohort was significantly higher than pre-treatment and control scores, while the post-treatment RPFS score was significantly lower than the pre-treatment and control group scores. These data show that TACE-oxaliplatin combination produced good clinical treatment effectiveness on liver cancer, and it was beneficial in reducing the tumor volume and improving liver cancer prognosis in the patients.

When the body tissue is damaged by invasive tumor, CA125, a glycoprotein, is released into the blood, resulting in increasing serum contents of CA125 in patients. Thus, CA125 level may serve as an indicator of short-term effectiveness of cancer drugs [14]. An acidic glycoprotein, CEA is secreted by secretory cells of adult gastrointestinal tract. It has human embryonic antigen specificity, and it plays an important role in the evaluation of prognosis of lung cancer [15]. When tumor cells become necrotic, CYFRA21-1 which exists in the cytoplasm of epithelial cells, is released into the blood, and it serves as a serum tumor marker in NSCLC patients [16]. This

research demonstrated that after treatment, the levels of tumor markers were significantly decreased in study group, and were low, relative to control group values. These data indicate that the use of TACE in combination with oxaliplatin in the treatment of liver cancer was beneficial for inhibiting the proliferation of tumor cells and controlling liver cancer in patients. Oxaliplatin is employed as a standard chemotherapy regimen for advanced HCC in combination with 5-fluorouracil and folinic acid (FOLFOX4). Oxaliplatin is a DNA interactor. It produces intra-chain adducts through covalent bonding with DNA, thereby exerting anticancer effects by blocking DNA replication and mRNA synthesis. Studies have also found that oxaliplatin induces immunogenic cell death by regulating anti-tumor immune response in liver cancer cells [17].

Studies have shown that CD137 enhances the antitumor effect of T cells [18]. It belongs to the TNF family; it is a crucial co-stimulatory agent for T cell stimulation, and it is produced in stimulated T cells (CD4+ and CD8+). In addition, CD137 is present superficially on many types of white blood cells. Studies have found that the CD137 expression level in liver cancer tissues is up-regulated, relative to tissues from other cancers such as colon and small cell lung cancers. Moreover, CD137 is expressed in PD-1-exhausted high-CD8+ T cells. The lysosomal acid hydrolase AFU, which is present in most mammalian cells, is associated with the degradation of fucan conjugates containing fucose. Several studies have shown that serum AFU levels are increased in patients with liver cancer. However, the enzyme is usually found at low concentrations in healthy tissues [19]. Studies have found that AFU is up-regulated in hepatic carcinoma, and the sensitivity and specificity of AFU are 90 and 97.5 %, respectively [20]. In liver cancer patients, AFU activity was significantly reduced following treatment, suggesting that it may serve as an index for evaluating treatment effectiveness and prognosis. The data obtained in this study indicate that AFU is a useful serum marker for the diagnosis of liver cancer. After treatment, the serum concentrations of CD163 and AFU in both cohorts were significantly decreased, relative to values before drug exposure, with significantly lower levels in the study cohort.

Limitations of this study

The source of study sample of liver TACE used in combination with oxaliplatin for cancer treatment was limited to one hospital. Therefore, further studies will require multi-center research.

CONCLUSION

The combined use of liver TACE and oxaliplatin produce good clinical effectiveness in liver cancer treatment. It is effective in improving serum CD163 and AFU levels, inhibit tumor cell proliferation, reduce tumor volume, and improve prognosis of liver cancer in patients. A large-scale study will be required to validate the outcome of this study.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was performed by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Lin Liu designed the study, supervised the data collection, and analyzed the data. Sen Zhao interpreted the data and prepared the manuscript for publication. Liang Wang, Jiadong Xia and Lin Liu supervised the data collection, analyzed the data and reviewed the draft of the manuscript.

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