Research Paper

Efficacy of Oxaliplatin, Fluorouracil and Calcium Folinate in Advanced Primary Liver Cancer

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This study seeks to elucidate the efficacy of oxaliplatin, fluorouracil and calcium folinate combined with hepatic arterial infusion chemotherapy, in patients with advanced primary liver cancer. In this study, 156 advanced primary liver cancer individuals who were treated in our hospital between July 2018 and July 2021 were selected among which 70 patients who received folinic acid/calcium folinate, fluorouracil and oxaliplatin regimen *via* conventional intravenous infusion were assigned as control group and 86 patients who received hepatic arterial infusion chemotherapy using the folinic acid/calcium folinate, fluorouracil and oxaliplatin regimen were included in the research group. The two groups were compared with respect to their curative effects, complication rate (nausea and vomiting, fatigue, fever, abnormal liver function and thrombocytopenia) and improvement of health status using Karnofsky performance scores. Similarly serum indices such as vascular endothelial growth factor, alpha-fetoprotein, cancer antigen 19-9 and 1 y overall survival were also evaluated. Significantly higher overall effectiveness, better improvement of health status (high Karnofsky performance scores) and fewer complications were found in the research group when compared with the control group; the post-treatment vascular endothelial growth factor, alpha-fetoprotein, cancer antigen 19-9 of the research group reduced statistically and were lower compared with the control group. Notably higher 1 y overall survival was determined in the research group. Therefore, hepatic arterial infusion chemotherapy using the folinic acid/calcium folinate, fluorouracil and oxaliplatin regimen is beneficial to improve the clinical outcomes of advanced primary liver cancer patients with a good preventive effect on the occurrence of complications, which can not only significantly improve patients' health status, inhibit vascular endothelial growth factor, alpha-fetoprotein, cancer antigen 19-9 levels, but also significantly increase the 1 y overall survival of patients.

Key words: Oxaliplatin, fluorouracil, calcium folinate, hepatic arterial infusion chemotherapy, advanced primary liver cancer

Primary Liver Cancer (PLC), one of the common fatal tumors in the world, is etiologically closely linked to alcoholism, obesity, metabolic syndrome, type 2 diabetes and nonalcoholic fatty liver disease besides Hepatitis B Virus (HBV) and HCV infections[1]. According to the relevant epidemiological data, Hepatocellular Carcinoma (HCC) is the major pathological type of PLC, accounting for up to 90 % of the total cases. The global mortality rate of HCC is about 8.5 out of 100 000 people and the incidence is also rising highly[2,3]. Early HCC is primarily treated by radical treatment such as surgical resection, local ablation and liver transplantation, which contributes to a median survival exceeding 5 y[4,5]. However, the median survival time will drop to about 2 y in PLC cases diagnosed in the middle and late stages, when the above treatment options are not suitable[6]. Although the Folinic acid/calcium folinate, Fluorouracil and Oxaliplatin (FOLFOX) chemotherapy regimen can be used to treat advanced HCC, conventional intravenous infusion may limit therapeutic effectiveness due to the low concentration of the drug at the tumor site[7]. In addition, the high side effects associated with this therapy may also

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make it difficult for patients to tolerate[8]. Therefore, this study sought to explore a better treatment strategy for patients with advanced HCC based on FOLFOX chemotherapy regimen to improve the clinical outcome of patients.

The FOLFOX regimen is composed of Oxaliplatin (OXA), Fluorouracil (FU), and Calcium Folinate (CF), among which OXA, as a Deoxyribonucleic Acid (DNA) synthesis inhibitor superior to cisplatin, is also effective in the treatment of HCC patients with a diameter >10 cm when used in continuous Hepatic Arterial Infusion Chemotherapy (HAIC)[9]. It can also play a synergistic role with FU and CF in the treatment of HCC, which helps to improve the survival outcome of advanced HCC patients to a certain extent[10]. FOLFOX regimen has been shown to be more effective and safe in patients with large unresectable HCC and is superior to Transcatheter Arterial Chemoembolization (TACE) alone[11]. In addition, modified FOLFOX regimen with HAIC as an implementation mode can be used as an alternative treatment strategy for advanced HCC when TACE is ineffective or inappropriate[12]. At present, the research on the clinical advantages of FOLFOX-HAIC regimen for advanced PLC is still limited.

This study attempts to analyze the influence of FOLFOX (OXA+FU+CF)-HAIC regimen on clinical outcomes of advanced PLC patients, in order to provide new clues for the treatment and prognosis improvement of such patients.

MATERIALS AND METHODS

The participants were 156 advanced PLC patients from July 2018 to July 2021. Among them, 86 patients in the research group received FOLFOX-HAIC, and 70 patients in the control group received FOLFOX *via* routine intravenous infusion. The gender parity and mean age (y) of research group were 53:33 and (56.97±9.25), respectively; control group was composed of 45 males and 25 females aged (59.03±8.14) y on an average. Research and control groups were clinically comparable with no evident difference in gender, age and other baseline data. The Ethics Committee of the Third Affiliated Hospital of Anhui Medical University (No: 202107) has approved for this research study.

Inclusion criteria:

Patients diagnosed with advanced PLC[13]; patients having no contraindications to the treatment methods in this study; patients who had completed 1 y follow-up; patients whose estimated survival is ≥3 mo; patients who did not undergo any treatment intervention in recent 1 mo were included in this study.

Exclusion criteria:

Patients with other liver diseases, other malignant tumors or serious organ diseases; patients who underwent other treatments; pregnant or lactating women; patients with mental illness; patients incomplete clinical medical records were excluded from this study.

Methods:

Patients in both research and control groups received routine care and basic treatment.

Primarily the patients in control group received 85 mg/m^2 of OXA on the 1st d, 200 mg/m^2 of CF, 400 mg/m^2 of FU and 600 mg/m^2 of FU on the 1st and 2nd d. Each chemotherapy session lasted for 2 w.

Similarly patients in research group underwent hepatic artery catheterization in the Digital Subtraction Angiography (DSA) catheterization room of our hospital and femoral artery puncture using the Seldinger technique. After celiac trunk artery or hepatic artery angiography, the microcatheter was inserted superselectively to the tumor feeding artery as far as possible and the puncture point of the femoral artery was fixed externally. After the patient returned to the wards, the catheter was connected to an arterial infusion pump and received an arterial infusion of OXA (130 mg/m^2) for 1.5 h, followed by arterial infusion of CF (200 mg/m^2) for 1.5 h; bolus infusion of 400 mg/m^2 of FU was also given on the 1st d, followed by arterial infusion of 2400 mg/m^2 of FU for 46 h. After the treatment, the arterial indwelling catheter was removed and the puncture site was pressed to stop bleeding. Postoperative fluid replacement, support and symptomatic treatment were given. Patients in research group received HAIC treatment, with a cumulative treatment of 36 times.

Detection indicators:

Efficacy: Complete Response (CR) corresponds to the complete disappearance of all measurable lesions and the absence of new lesions, lasting ≥4 w. Partial Response (PR) is defined as a >50 % reduction in the total maximum length diameter of all measurable lesions, lasting for ≥4 w. Stable Disease (SD) corresponds to reduction of the issue to <50 % or

a <25 % increase in the sum of the all measurable lesions (length in diameters). Progressive Disease (PD) is defined as a >25 % increase in the total maximum length and diameter of the tumor or the appearance of new lesions.

Complication rate: We observed and counted the cases of nausea, vomiting, fatigue, fever, abnormal liver function and thrombocytopenia in the two groups and calculated the total incidence.

Improvement of health status: The improvement of patients' health status was assessed using the Karnofsky Performance Status (KPS) score; range having 0-100[14], with a post-treatment KPS score increased by >10 points, altered by ≤10 points and decreased by >10 points indicating improved, stabilized and deteriorated, respectively.

Serum indices: 5 ml of fasting cubital venous blood was collected before and after treatment and was centrifuged to isolate serum samples. Enzyme-Linked Immunosorbent Assay (ELISA) was used to determine Vascular Endothelial Growth Factor (VEGF), Alpha-Fetoprotein (AFP) and Cancer Antigen 19-9 (CA19-9). The procedure strictly followed the kit instructions.

1 y Overall Survival (OS): Patients were followed up for 1 y by means of medical records, telephone visits and outpatient visits, etc. For every 3 mo, all the patients were followed up and the 1 y OS was recorded.

Statistical analysis:

The number of cases/percentage (n/%) and the mean±Standard Error of Mean (mean±SEM) are used to represent categorical and continuous variables, respectively. Paired t-test and independent sample t-test were respectively used for intra- and inter-group comparison before and after treatment. The statistical analysis, relied upon a $p<0.05$ using Graphpad Prism version 7.0 software.

RESULTS AND DISCUSSION

Research group and control group showed no marked differences in sex, age, Child-Pugh liver function classification, tumor stage, AFP and tumor diameter ($p>0.05$), showing clinical comparability (Table 1).

The total effective rate of the research group was 70.93 %, which was significantly >42.86 % compared with the control group ($p<0.05$) (Table 2).

Complication rate of the two groups was studied. The number of cases with nausea, vomiting, fatigue, fever, abnormal liver function and thrombocytopenia in the two groups were observed and counted to calculate the incidence of corresponding complications. The statistical results identified dramatically lower incidence rates of the above complications in research group *vs.* control group ($p<0.05$) (Table 3).

Improvement of health status in two groups was evaluated according to the KPS score. The health status was improved by 46.51 % in research group and 25.71 % in control group, with a notable difference ($p<0.05$) (Table 4).

Serum indices of the two groups were evaluated, where we performed ELISA to measure serum VEGF, AFP and CA19-9 levels. These indices did not differ much between the two groups prior to treatment ($p>0.05$), but they all showed a significant decrease after treatment ($p<0.05$), with lower post-treatment levels in research group than in control group ($p<0.05$) (fig. 1).

Finally, 1 y OS of two groups was studied and compared by drawing survival curves. 1 y OS was found to be 79.07 % in research group and 50.00 % in control group, with a statistical significance ($p<0.05$) (fig. 2).

TABLE 1: BASELINE INFORMATION OF THE PATIENTS

Indicators	Research group (n=86)	Control group (n=70)	χ^2/t	p
Gender			0.117	0.733
Male	53 (61.63)	45 (64.29)		
Female	33 (38.37)	25 (35.71)		
Age (y)	56.97±9.25	59.03±8.14	1.459	0.147
Child-Pugh liver function classification			0.864	0.353
A	62 (72.09)	55 (78.57)		
B	24 (27.91)	15 (21.43)		
Tumor stage			0.145	0.703

III	49 (56.98)	42 (60.00)		
IV	37 (43.02)	28 (40.00)		
AFP (μg/l)			0.361	0.548
<400	45 (52.33)	40 (57.14)		
≥400	41 (47.67)	30 (42.86)		
Tumor diameter (cm)			2.231	0.135
<5	68 (79.07)	48 (68.57)		
≥5	18 (20.93)	22 (31.43)		

TABLE 2: EFFICACY OF THE TWO GROUPS

Indicators	Research group (n=86)	Control group (n=70)	χ^2/t	p
CR	3 (3.49)	0 (0.00)		
PR	58 (67.44)	30 (42.86)		
SD	20 (23.26)	22 (31.43)		
PD	5 (5.81)	18 (25.71)		
Total effective rate	61 (70.93)	30 (42.86)	12.51	<0.001

TABLE 3: INCIDENCE OF COMPLICATIONS RATE IN TWO GROUPS

Indicators	Research group (n=86)	Control group (n=70)	χ^2/t	p
Nausea and vomiting	15 (17.44)	31 (44.29)	13.37	3.657
Fatigue	9 (10.47)	16 (22.86)	4.403	0.036
Fever	14 (16.28)	22 (31.43)	4.989	0.026
Abnormal liver function	5 (5.81)	14 (20.00)	7.261	0.007
Thrombocytopenia	20 (23.26)	29 (41.43)	5.915	0.015

TABLE 4: IMPROVEMENT OF HEALTH STATUS IN THE TWO GROUPS

Indicators	Research group (n=86)	Control group (n=70)	χ^2/t	p
Improved	40 (46.51)	18 (25.71)		
Stabilized	37 (43.02)	32 (45.71)		
Deteriorated	9 (10.47)	20 (28.57)		
Improvement rate	40 (46.51)	18 (25.71)	7.146	0.008

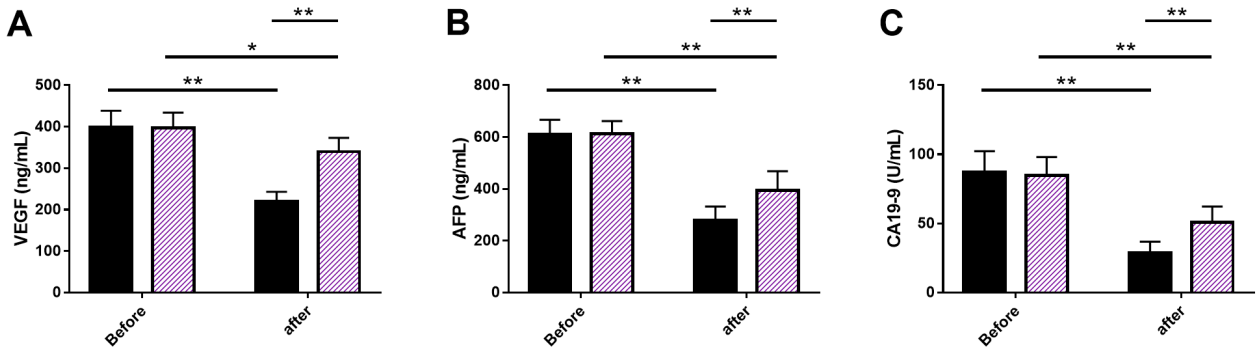

Fig. 1: Reduced levels of serum indices of the two groups before and after the treatment, (A): VEGF; (B): AFP and (C): CA19-9
Note: *p<0.05 and **p<0.01, (■): Research group and (▭): Control group

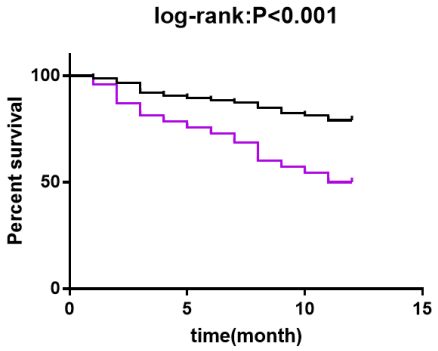

Fig. 2: 1 y OS of the two groups
Note: (—): Research group and (—): Control group

Most PLC patients are diagnosed with advanced HCC, with as many as 900 000 new cases and about 830 000 deaths worldwide annually, resulting in a great medical burden for patients and society[15,16]. In addition, patients with advanced HCC are often accompanied by typical clinical symptoms like liver pain, which has a negative impact on their daily life and work[17]. Therefore, focusing on the treatment of advanced HCC patients and providing better treatment options are of great clinical implications to improve treatment outcomes, alleviate clinical symptoms and improve quality of life.

Many researchers have provided optimized schemes for the FOLFOX regimen in the treatment of advanced PLC patients. For example, the application of FOLFOX in combination with *Astragalus* polysacharin injection which is effective in enhancing clinical efficacy, physical status and safety in patients with gastric cancer[18]. Wu *et al.*[19] reported that the FOLFOX regimen combined with recombinant human adenovirus type 5 for HCC patients was significantly beneficial in reducing the risk of metastasis and recurrence, and increasing the progression-free survival, with a favorable safety profile. Li *et al.*[20] also pointed out that HAIC with FOLFOX can significantly prolong the disease-free survival of HCC patients with microvascular invasion, and the toxicity is tolerable. Currently, there are limited analytical studies on the efficacy of FOLFOX which includes OXA, FU and CF with HAIC regimen in advanced PLC patients, so this study made a relevant attempt. The efficacy evaluation revealed an evidently higher overall effective rate in research group and control group (70.93 % *vs.* 42.86 %), suggesting a certain effect of the FOLFOX-HAIC regimen in enhancing the efficacy in advanced PLC patients and a better treatment response of this therapy compared with FOLFOX through the routine intravenous infusion, which is consistent with the research results of Si *et al.*[21]. This may be attributed to the fact that the FOLFOX-HAIC regimen may be more helpful in reducing tumor load, maintaining residual liver proliferation and preventing tumor progression in advanced PLC patients[22]. On the other hand, the therapeutic advantage of this regimen may also be related to its high anti-tumor effect under prolonged infusion during HAIC therapy[23]. As to complications, the statistics showed markedly lower incidences of nausea, vomiting, fatigue, fever, abnormal liver function and thrombocytopenia in research group compared with control group, which means that the FOLFOX-HAIC regimen has a certain preventive effect on the occurrence of complications in patients with advanced PLC. Although the extended duration of chemotherapy infusion under HAIC may elicit well-tolerated hepatotoxicity, patients receiving such treatments tend to have a lower risk of liver function decompensation and surgery-related death[24,25]. In the study of Lai *et al.*[25], the FOLFOX-HAIC regimen not only a significant antitumor therapeutic effect in patients with advanced HCC with high-risk characteristics, but also has a certain safety profile, similar to our results. After the KPS score test, the health improvement rate of research group was also confirmed to be higher than that of control group, suggesting that the FOLFOX-HAIC regimen can effectively improve the health status of advanced PLC patients. Subsequently, ELISA quantization denoted that levels of serum indices such as VEGF, AFP and CA19-9 were significantly lower in research group than in control group, indicating that the FOLFOX-HAIC regimen can significantly inhibit serum VEGF, AFP and CA19-9 levels in advanced PLC patients, thus playing a synergistic role in anti-

liver cancer to a certain extent. The survival curve analysis further determined an obviously higher 1 y OS rate in research group *vs.* control group (79.07 % *vs.* 50.00 %), which indicates that the FOLFOX-HAIC regimen is helpful to improve prognosis and OS in advanced PLC patients. In a randomized phase III trial, FOLFOX-HAIC regimen was also shown to have a significant effect in prolonging OS, similar to our findings[26]. In another study, the FOLFOX-HAIC regimen was reported to be cost-effective in patients with large unresectable HCC[27].

Conclusively, this study confirms that FOLFOX-HAIC (OXA+FU+CF) is better than TACE alone in advanced PLC patients in terms of efficacy, complications, improvement in health status, serum levels of tumor-related markers, and 1 y OS, with obvious clinical advantages in all the above dimensions, which is worthy of clinical promotion. Our findings also provide an optimized choice for the clinical management of patients with advanced PLC, which is conducive to improving the clinical outcomes of such patients.

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Conflict of interests:

The authors declared no conflict of interests.

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