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ORIGINAL ARTICLE

Short-term efficacy of oral low-dose Tegafur chemotherapy after transarterial chemoembolization in primary hepatic carcinoma

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Summary

Purpose: *To observe the short-term efficacy of oral low-dose Tegafur chemotherapy after transarterial chemoembolization (TACE) in primary hepatic carcinoma (PHC).*

Methods: *120 PHC patients undergoing TACE treatment for the first were randomly divided into the Tegafur group and the TACE group. Patients in TACE group received TACE only, whereas those in the Tegafur group received TACE and postoperative oral low-dose Tegafur chemotherapy. All patients were followed up for 4 to 20 months. Clinical efficacy, liver function changes, progression-free survival (PFS), and adverse reactions were compared between the two groups.*

Results: *The disease control rate (DCR) and clinical benefit rate (CBR) of the Tegafur group were significantly higher than those of TACE group ($p<0.05$). Moreover, higher PFS was found in the Tegafur group than that of the TACE group after 18 months of follow-up ($p<0.05$). Before treatment, serum levels of ALT, AST, TBIL and DBIL in the two groups were not statistically significant ($p>0.05$). After treatment, the above-mentioned indicators were remarkably increased in both groups. In particular, the indicators were lower in the Tegafur group than those of the TACE group ($p<0.05$).*

Conclusions: *TACE combined with low-dose Tegafur for treating PHC can slow down the tumor progression and prolong the PFS. This approach is safe and effective.*

Key words: *curative effect, hepatoma, tegafur, transarterial chemoembolization*

Introduction

Primary hepatic carcinoma (PHC) includes hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (CC). PHC is a malignant tumor that occurs in liver cells or intrahepatic bile duct epithelial cells. Globally, about 250,000 people die of PHC each year, and men are more frequently affected than women [1,2]. The etiology and pathogenesis of PHC have not been completely clarified. Various factors are related to PHC development, such as viral hepatitis, cirrhosis, and drinking contaminated water [3]. At present, hepatectomy is the most effective treatment for PHC. However, PHC patients are often in middle or advanced stages when first diagnosed since the insidious symptoms [4]. Surgical resection and liver transplantation are the main treatment methods for PHC. However, only 9-29% of PHC patients are clinically eligible for surgical resection [5].

Non-surgical therapies are suitable for most PHC patients. TACE is the most preferred choice for non-surgical treatment of PHC [6,7]. TACE can effectively block the blood supply of hepatoma from the hepatic artery. It continuously releases chemotherapeutic substances to reduce tumor size,

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thereafter leading to ischemia and even necrosis of tumors. At present, iodinated oil chemotherapeutic drugs are frequently used in clinical practice. They are injected into the hepatic artery to exert long-lasting anti-tumor effects [8]. Repeated TACE treatment can reduce the tumor invasion for the following surgical resection. TACE can also be performed after surgical resection to remove residual cancer cells and reduce the recurrence rate. However, TACE efficacy varies a lot because of large individual differences, which still cannot effectively eliminate tumor lesions and control disease progression [9-11].

As a new type of fluorouracil oral drug, Tegafur is a relatively new compound containing Tegafur, Gimeracil, and Potassium oxonate. Tegafur is converted into 5-fluorouracil (5-FU) by liver enzymes to suppress tumor. Gimeracil reduces the activity of dihydropyrimidine dehydrogenase (DPD) and increases 5-FU concentration. Potassium oxonate binds to orotate phosphoribosyltransferase and blocks the conversion of 5-FU to 5-FUMP. It has a great effect on increasing 5-FU concentration in the body and prolonging duration of action [12-14]. Studies have shown that continuous use of low-dose Tegafur inhibits VEGF expression and upregulates thrombospondin-sensitive protein, thereby inhibiting tumor angiogenesis and accelerating tumor cell apoptosis. Low-dose Tegafur chemotherapy can also inhibit tumor-induced autoimmune function resistance and enhance proliferation of natural killer (NK) cells. It can increase the immune function of tumor patients and kill cancer cells indirectly [15,16].

Adjuvant chemotherapy after TACE in PHC patients has gradually been recognized. However, there are no recommended guidelines for specific chemotherapy regimens. In this study, we investigated the efficacy and safety of low-dose Tegafur chemotherapy for PHC patients after TACE, so as to provide a basis for TACE application.

Methods

Participants

120 PHC patients undergoing the first TACE treatment in our hospital from January 2015 to December 2015 were enrolled. This study was approved by the ethics committee of the Second Xiangya Hospital of Central South University. Signed informed consents were obtained from all participants before the study entry. Inclusion criteria were: (1) Patients were pathologically or clinically diagnosed as PHC; (2) Inability to perform surgical resection based on the AASLD Guideline for the Diagnosis and Treatment of hepatocellular carcinoma, 2010 [17]; (3) Karnofsky PS>70; (4) Liver function level with Child-Pugh A or B; (5) No obvious bone marrow suppression or impaired renal function; (6) Intrahepatic single tumor or multiple tumors which were clustered together and those with portal vein tumor thrombus (PVTT) were directly connected with the primary tumor. We excluded patients whose imaging borders were unconfirmed and those who were unable to complete the entire treatment plan. Among them, 97 patients were male and 23 were female. Eighty patients were younger than 60 and 44 were older than 60. Based on the disease condition, 59 patients were Child-Pugh Grade A and 55 Grade B. Ninety-nine cases had AFP>20 and 15 AFP ≤20. A hundred and eight patients were infected with hepatitis B and 6 with hepatitis C patients. Sixty-five patients had a single tumor and 49 had multiple tumors.

Therapeutic method

TACE was conducted in all enrolled patients. Coeliac arteriography was performed to determine the condition of the blood supply artery and tumor size, location, quantity and staining. The blood supply artery of tumor was selected for perfusion of chemotherapeutic drugs. Iodized oil was used to embolize tumor tissues that were obviously stained. The chemotherapeutic drug regimen was 0.5 mg/m^2 fluoruracil injection + epirubicin hydrochloride. Patients in the Tegafur group were additionally given postprandial Tegafur capsules containing 20 mg Tegafur, 5.8 mg Gimeracil and 19.6 mg Potassium oxonate with 40 mg/m^2, po, bid. Tegafur administration was stopped for 7 days after 14-day continuous administration. The treatment duration was 4 months.

Table 1. Solid tumors evaluation criteria (RECIST)

Therapeutic response	*Specific standard*
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Follow-up and therapeutic effect evaluation

Enhanced CT scans of the liver were performed in all patients for 1 month after surgery to evaluate tumor condition. (1) Response Evaluation Criteria in Solid Tumors (RECIST) [18] were based on the results of ultrasonic B, CT or MRI, AFP level, blood routine, liver and kidney functions 4 weeks after the treatment finished. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were recorded. The total effective rate was calculated as the total of CR and PR. Tumor pain was evaluated based on the verbal rating scale (VRS). VRS decrease ≥1 grade was considered to be remission and increase ≥1 grade was considered to be exacerbation. No significant disease change was found during 4 weeks after finishing treatment (Table 1). (2) Follow-up: Follow-up examinations were performed every 3 months after treatment, including ultrasonic B, CT or MRI, AFP level, blood routine, liver and kidney functions, for a total of 3-18 months. PFS was analyzed according to the follow-up data. The incidences of leukopenia, thrombocytopenia and gastrointestinal reactions were evaluated according to WHO grading standards for anticancer drug toxicities.

Table 2. General comparison of characteristics of the two groups of patients

Content	*Control group*	*Observation group*
	n=60	*n=60*
Gender		
Male	50	47
Female	10	13
Age, years		
>60	18	20
≤60	42	40
Child-Pugh		
A	35	32
B	25	28
AFP(μg/L)		
>20	51	47
≤20	9	10
Etiology		
HBV	55	53
HCV	5	7
Number of tumor lesions		
Single	30	34
Multiple	27	23

Statistics

SPSS 19.0 statistical software (IBM, Armonk, NY, USA) was used for statistical analyses. The measurement data were compared with Student *t*-test. The count data were compared with chi-square test or Fisher's exact test. Survival was analyzed with Kaplan-Meier method and log rank test in both groups. P<0.05 indicated statistically significant difference.

Results

Comparison of basic characteristics

120 PHC patients were enrolled in this study, with 60 in each group. There were 50 males and 10 females in the Tegafur group. Among them, 42 patients were ≤ 60 years old and 18 were >60 years old. Sixty patients were in the TACE group (47 male and 13 female). Among them, 40 patients were ≤ 60 years old and 20 were >60 years old. No significant differences in gender, age liver function Child-Pugh grade, AFP level, viral hepatitis history, tumor size and tumor number were found between the two groups (p>0.05, Table 2).

Comparison of clinical efficacy

DCR (70%) and CBR (90%) in the Tegafur group were significantly higher than those of TACE group (46. and 68.3%, respectively), and the differences were statistically significant (p<0.05, Table 3).

Comparison of liver function indicators before and after treatment

No significant differences in ALT, AST, TBIL and DBIL levels before treatment were found between the two groups (p>0.05). After treatment, the above-mentioned indicators were increased in both groups. However, these indicator levels in the Tegafur group were significantly lower than those of the TACE group (p<0.05, Figure 1).

PFS comparison

Follow-up data showed that the median PFS in the Tegafur group and TACE group was 16.87 months (95% CI:15.581-16.919) and 11.75 months (95% CI:9.566-14.934), respectively (p<0.05, Figure 2).

Table 3. Comparison of the two groups were the size of a solid tumor volume change

Group	*CR(%)*	*PR(%)*	*SD(%)*	*PD(%)*	*DCR(%)*	*CBR(%)*
Observation group(n=60)	20 (33.3)	22 (36.7)	12 (20)	6 (10)	42 (70)	54 (90)
Control group(n=60)	10 (16.7)	18 (30)	22 (36.7)	19 (31.7)	28 (46.7)	41 (68.3)

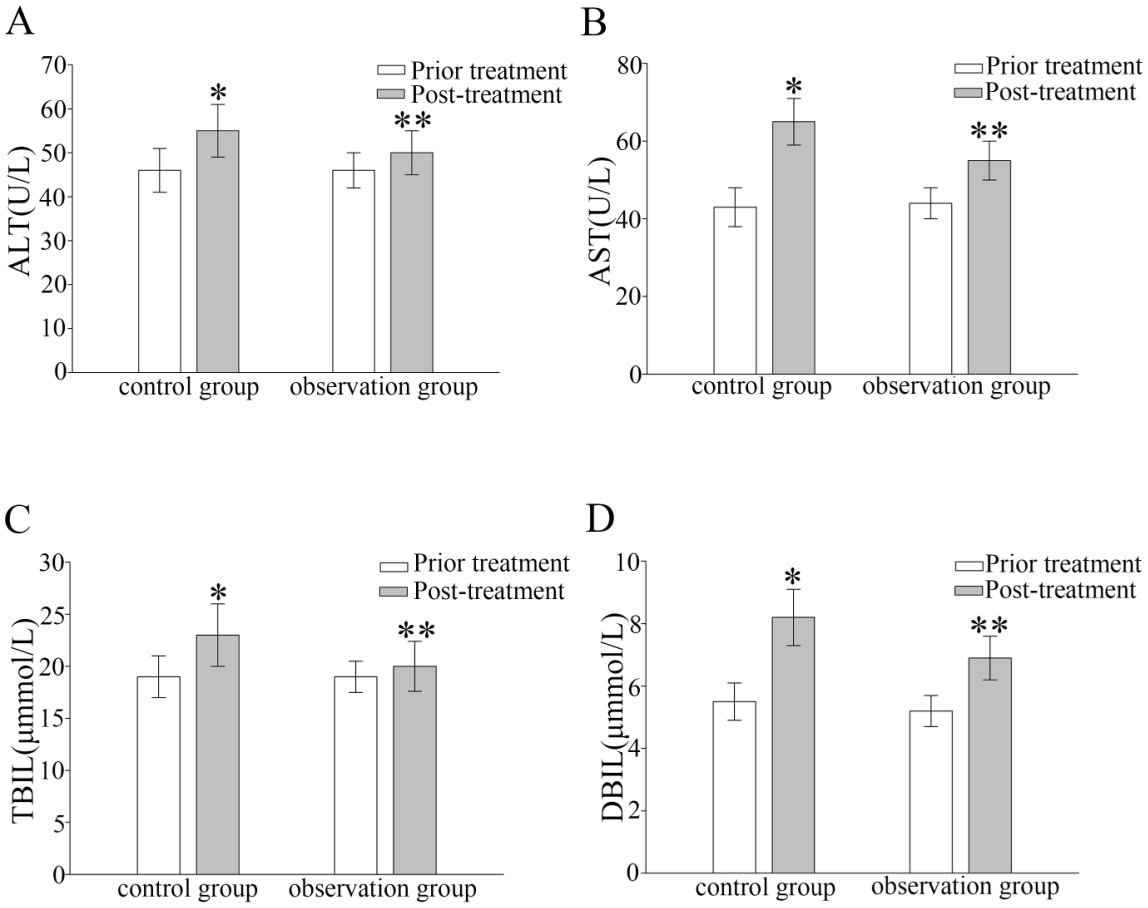

Figure 1. Comparison of liver function before and after treatment in the two groups of patients. **(A):** Changes of ALT before and after treatment in the two groups of patients. **(B):** Changes of AST before and after treatment in the two groups of patients. **(C):** Changes of TBIL before and after treatment in the two groups of patients. **(D):** Changes of DBIL before and after treatment in the two groups of patients. *p<0.05: Compared with before treatment; **p<0.05: Compared with the TACE group

Comparison of PFS in patients with different liver function grading and different tumor amounts in the Tegafur group

We compared the effects of different liver function grades and different tumor numbers on PFS of PHC patients in the Tegafur group. The median PFS of patients with Child-Pugh Grade A and B was 16.50 months (95% CI:15.761-17.187) and 16.00 months (95% CI:15.542-16.475), respectively (p=0.938, Figure 3). The median PFS of patients with single and multiple tumors was 16.80 months (95% CI:15.988-17.834) and 16.34 months (95% CI:15.549-17.152), respectively (p=0.643, Figure 4).

Adverse reactions

Adverse reactions in both groups included chemotherapy-related toxicities, such as myelosuppression, anorexia, liver function impairment, hand-foot syndrome. In the Tegafur group, the incidence of myelosuppression, digestive system reaction (nausea, vomiting, loss of appetite, etc.) and other adverse reactions was 31.25, 18.75 and 6.25%, respectively. In the TACE group, the incidence of myelosuppression was 34.78%, the digestive system reaction incidence was 15.22% and other adverse reactions incidence was 4.35%. No significant difference in adverse reactions was found between the two groups (p>0.05).

Discussion

PHC is one of the common malignancies in the digestive system. It is a malignant tumor with high morbidity and mortality worldwide [19]. The most effective treatment method is surgical resection. However, most of PHC patients are in advanced stage when diagnosed because of insidious onset. These patients could not receive surgical treatment [20]. At present, TACE has become the most applied non-surgical method for PHC treatment because of its advantages of less trauma, easier operation and repeatability [21].

However, TACE has some certain limitations. Because of the incomplete tumor embolization and the establishment of collateral vessels of tumor, TACE is often difficult to achieve complete efficacy. Meanwhile, tumor ischemia or hypoxia after TACE leads to upregulation of hypoxia-inducible factor-1 (HIF-1). HIF-1 induces overexpression of vascular endothelial growth factor (VEGF), resulting in intrahepatic tumor recurrence and distant metastasis [22-24]. In addition, decreased immunity and liver function, chemotherapeutic drug insensitivity and drug resistance after TACE all result in unsatisfactory long-term therapeutic effect. Therefore, comprehensive treatment has become a consensus for improving postoperative survival and quality of life of PHC patients. In addition, serum VEGF levels are increased in most PHC patients [25]. VEGF is a substance that regulates angiogenesis and exerts a vital role in tumor growth [26]. Serum level of VEGF in HCC patients is much higher than in normal patients [27].

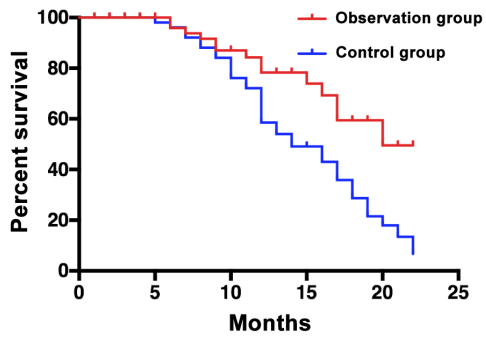

Figure 2. Comparison of disease-free survival between the two groups (p<0.05).

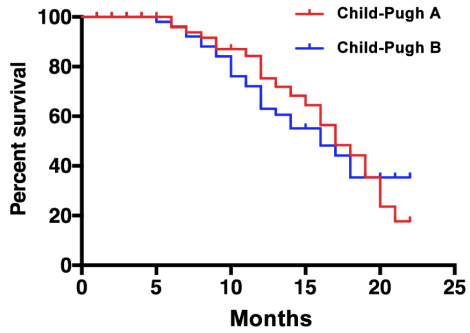

Figure 3. Comparison of disease-free survival in patients with different liver functions in the Tegafur group (p=0.938).

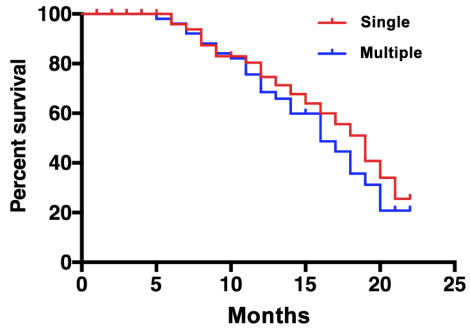

Figure 4. Comparison of disease-free survival in patients with different tumor numbers in the Tegafur group (p=0.643).

Tegafur capsule is a new generation of fluorouracil oral compound. Its active ingredients include three biological regulators, including Tegafur, Gimeracil, and Potassium oxonate. Among them, Tegafur is a precursor of 5-FU, which is converted to 5-FU to block DNA, RNA, and protein synthesis [28,29]. Gimeracil inhibits the catabolism of 5-FU transformed from Tegafur by DPD, which helps maintain the effective concentration of 5-FU in the body, especially in the tumor tissue for a long time [28,30]. Potassium oxonate has the ability to block the phosphorylation of 5-FU, which has a high concentration distribution in gastrointestinal tissues. It can reduce the toxicity and adverse reactions of 5-FU in the gastrointestinal tract [31]. Tegafur remarkably inhibits the high-level DPD in PHC cells, which exerts a better therapeutic effect than other drugs [32]. Moreover, studies also indicated that Tegafur has a good effect on primary liver malignant tumors and metastatic tumors [33,34].

In this study, we observed higher DCR and CBR in the Tegafur group than in those of the TACE group. The median PFS was also higher in the Tegafur group. Moreover, the therapeutic effect in the Tegafur group was not influenced by liver function and tumor burden. Previous *in vivo* experiments showed that body weight, leukocyte counts and hemoglobin concentrations of tumor-bearing mice with low-dose Tegafur treatment did not remarkably decreased [35]. In our study, adverse reactions mainly included anorexia, nausea, vomiting, bloating, diarrhea, etc. Most of them can be relieved by symptomatic treatment. Patients with grade 3 myelosuppression were recovered by injection of granulocyte colony-stimulating factor and interleukin-11 or recombinant human thrombopoietin.

Conclusions

TACE combined with low-dose Tegafur for treating PHC can slow down the tumor progression and prolong the PFS, and is safe and effective.

Conflict of interests

The authors declare no conflict of interests.

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