EFFECT OF THALIDOMIDE COMBINED WITH OXALIPLATIN AND PIRARUBICIN IN THE TREATMENT OF PRIMARY LIVER CANCER ON THE LEVELS OF TK1 AND CXCL13

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ABSTRACT

***Objective**: To investigate the efficacy of thalidomide combined with oxaliplatin and pirarubicin in the treatment of unresectable primary liver cancer with arterial chemoembolization (TACE) and the effects on TK1 and CXCL13 levels.*

***Methods**: Eighty-five patients with primary liver cancer admitted to our hospital from January 2015 to January 2018 were selected. The patients were divided into the control group (43 cases) and the observation group (42 cases) according to the TACE treatment plan. The control group was treated with fluorourea combined with oxaliplatin and pirarubicin. The observation group was treated with thalidomide combined with oxaliplatin and pirarubicin.*

***Results**: The total effective rate of the observation group was 33.33%, and the disease control rate was 88.10%, which were significantly higher than those of the control group (13.95% and 65.12% ($\chi2=4.44$, $P=0.035$, $\chi2=6.24$, $P=0.013$), respectively). The incidence of adverse reactions in the observation group was 33.33%, which was significantly lower than the 58.14% incidence of the control group ($\chi2=5.27$, $P=0.022$). After treatment, the levels of TK1 and CXCL13 in the observation group were 8.40 ± 1.21 pmol/L and 45.69 ± 5.71 pmol/L, respectively, which were significantly lower than those of the control group (13.66 ± 2.71 pmol/L and 52.33 ± 8.81 pg/mL, respectively (both $P < 0.05$)).*

***Conclusion**: Thalidomide combined with oxaliplatin and pirarubicin is effective and safe in the treatment of unresectable primary liver cancer, and it can reduce the levels of TK1 and CXCL13.*

***Keywords**: Thalidomide, Oxaliplatin, Pirarubicin, Arterial embolization, Primary liver cancer, Efficacy, TK1, CXCL13.*

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Introduction

Primary liver cancer (PLC) has one of the world's worst prognoses among malignant tumours and was the sixth most common cancer in the world, with the second highest cancer-related death rate, in 2012. Nearly half of the total number of cases and the total number of deaths occurred in China[(1)]. Primary liver cancer is the fourth most common malignant tumour and the third leading cause of cancer-related death in China, posing a major threat to the lives and health of the Chinese people[(2, 3)]. Surgical removal of the liver is the main method for the treatment of liver cancer, but the lack of residual liver volume has been an important factor in the surgical resection of liver cancer. Postoperative liver failure is one of the main complications[(4)]. The mortality rate of primary liver cancer (PHC) is high. At present, the main treatment methods for unresectable PHC are radiotherapy and chemotherapy and arterial chemoembolization (TACE) therapy[(5)]. Assisted transcatheter arterial chemoembolization (TACE) may help prolong survival in high-risk liver cancer patients, including

those with larger size, multiple nodule tumours, and microvascular invasion[6, 7]. This intervention has unique treatment characteristics for unresectable liver cancer, such as high efficiency, minimal invasiveness and relatively short duration of treatment[8]). As an important interventional therapy for patients with unresectable PHC, TACE is often combined with chemotherapy drugs, including anthracyclines, platinum, and fluorouracil. The main drugs are pirarubicin, oxaliplatin, and fluorouridine. Thalidomide was originally used for sedation, also known as the reaction stop. Later, its antitumour activity was found to be multi-mechanistic, and it was effective in combination with other drugs for the treatment of malignant tumours. In this study, the clinical data of 85 patients with PHC were collected to investigate the efficacy of thalidomide combined with oxaliplatin/pirarubicin in the treatment of unresectable PHC and the effects on TK1 and CXCL13 levels.

Materials and methods

General materials

Inclusion criteria: Child-Pugh grade of liver function was A-B; estimated survival time was more than 3 months; the clinical diagnosis was PHC; this study was reviewed by our clinical ethics committee, and patients gave informed consent.

Exclusion criteria: Combined with other malignancies; Karnofsky performance score (KPS) less than 60 points; International Union Against Cancer (UICC) liver cancer TNM staging <T2.

Case selection and grouping: Eighty-five patients with PHC admitted to our hospital from January 2015 to January 2018 were divided into a control group (43 cases) and observation group (42 cases) according to different treatment plans.

Methods

Treatment: The Seldinger technique was used to intubate the patient's femoral artery, and celiac artery and common hepatic artery angiography were performed. The specific location, volume and blood supply of the tumour were recorded. The 2.7-F Progeal microcatheter was used to intubate the tumour-feeding artery. The perfusion chemotherapy embolization was performed according to the patient's imaging data. Patients in the observation group were treated with thalidomide in combination with oxaliplatin/pirarubicin, thalidomide at a dose of 300 mg once a night, oxaliplatin 100 mg/m^2, and pirarubicin 400 mg/m^2. Patients in the control group were treated with fluorourea combined with oxaliplatin/pirarubicin, fluorouridine 1000 mg, oxaliplatin 100 mg/m^2, and pirarubicin 400 mg/m^2. The perfusion time was no less than 20 min. After the operation, the patient routinely carried out supportive treatments such as liver protection, antiemetic, and fluid replacement, and we recorded adverse reactions such as gastrointestinal tract and high fever. On the 4th day after the operation, the fasting venous blood was taken in the morning, and the blood routine and liver and kidney function indexes were reviewed. The treatment interval was 4 to 6 weeks until the efficacy evaluation was complete remission (CR) or the patient did not tolerate it.

Test method: We collected 3-5 mL of fasting venous blood in the morning before and after treatment and used a TIS1 chemical digital imaging analyser to detect TK1 by enzyme-linked immunosorbent assay (kit from Shenzhen Huarui Tongkang Bio Co., Ltd.). The adsorption method was used to detect CXCL13 (kit purchased from R&D Systems).

Observation index and efficacy judgement criteria

Efficacy evaluation was performed according to the improved solid tumour efficacy evaluation standard (mRECIST). Complete remission (CR): lesion disappeared, effect lasted for 4 weeks, no new lesions formed; partial remission (PR): total lesion diameter decreased by ≥30%, effect maintained for 4 weeks; disease stable (SD): lesion reduced total diameter, failure to achieve PR or increase in diameter, did not reach PD; disease progression (PD): a total increase in lesion size ≥ 20% or new lesions. Total effective rate (RR) = CR + PR. Disease control rate (DCR) = CR + PR + SD. The follow-up went until April 2016 or the patient relapsed and died.

The follow-up methods included return to hospital review and telephone follow-up. We compared the disease-free progression time (PFS) between patients in the two groups, and the follow-up rate was 100.00%. The incidence of adverse reactions in the two groups, such as gastrointestinal reactions and leukopenia, were recorded and compared. The changes in the levels of TK1 and CXCL13 from before to after treatment were compared between the two groups.

Statistical processing

Analysis was performed using SPSS 18.0 statistical software. Normal measurement data are described by mean ± standard deviation and were compared between groups by the t test; count data are described by adoption rate and composition ratio and were compared by the χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Comparison of general demographic characteristics

There was no significant difference in the general data between the two groups (P>0.05). See Table 1 for details.

Groups	Gender (man/woman, cases)	Ages ($\bar{x} \pm s$, years old)	Tumour size ($\bar{x} \pm s$, cm)	Liver function grading (cases)	
				A grade	B grade
Observation (n= 42)	25/17	47.25 ± 8.73	6.85 ± 3.16	26	16
Control (n =43)	23/20	46.66 ± 9.42	7.06 ± 4.19	24	19
χ^2/t	0.31	0.30	-0.26	0.33	
P	0.575	0.765	0.795	0.568	

Table 1: Comparison of general data between the two groups of patients.

Comparison of treatment effects between the two groups

The total effective rate of the observation group was 33.33%, and the total effective rate of the control group was 13.95%. The difference between the two groups was statistically significant (χ^2=4.44, P=0.035). The disease control rate of the observation group was 88.10%, which was higher than that of the control group (χ^2=6.24, P=0.013). See Table 2 for details.

Groups	CR	PR	SD	PD	RR	DCR
Observation (n = 42)	1(2.38)	13(30.95)	23(54.76)	5(11.90)	14(33.33)	37(88.10)
Control (n =43)	0(0)	6(13.95)	22(51.16)	15(34.88)	6 (13.95)*	28 (65.12)*

Table 2: Comparison of treatment effects between the two groups of patients [cases (%)].
**Compared with the observation group, P<0.05*

Comparison of treatment adverse reactions between the two groups

The adverse reaction rate of the observation group was lower than that of the control group (χ^2=5.27, P=0.022) (Table 3).

Types	Observation group (n = 42)	Control group (n = 43)
Gastrointestinal reaction	4 (9.52)	6 (13.95)
Fever	2 (4.76)	4 (9.30)
Leukopenia degrees I–II	2 (4.76)	5 (11.63)
Anaemia	1 (2.38)	4 (9.30)
Thrombocytopenia degree I	3 (7.14)	2 (4.65)
Tired weakness	2 (4.76)	4 (9.30)
Total	14 (33.33)*	25 (58.14)

Table 3: Comparison of adverse reactions between the two groups [cases (%)].

Comparison of TK1 and CXCL13 levels between the two groups

There were no differences in the level of TK1 or CXCL13 between the two groups before treatment. However, there were significant differences between the two groups in the change from before to after treatment, and the levels of TK1 and CXCL13 in the observation group were lower than those in the control group (Table 4).

Groups	Time	TK1 (pmol/L)	CXCL13 (pg/mL)
Observation group (n = 42)	Before treatment	32.85 ± 11.33	73.25 ± 14.62
	After treatment	8.40 ± 1.21	45.69± 5.71
	t	14.07	11.38
	P	< 0.001	< 0.001
Control group (n =43)	Before treatment	31.43 ± 12.14	71.42 ± 13.29
	After treatment	13.66 ± 2.71*	52.33 ± 8.81*
	t	9.36	7.85
	P	< 0.001	< 0.001

Table 4: Comparison of TK1 and CXCL13 levels between the two groups ($\bar{x} \pm s$)
**Compared with the observation group, P<0.05*

Discussion

At present, there are many clinical treatments for PHC, the most important of which is surgery. It is the first choice for clinical treatment to perform radical resection of PHC, which can enlarge the lesion of the liver and control the spread of cancer cells. However, it is necessary to find other treatments that can effectively control the progress of PHC for those

with higher stage, larger tumours or unwillingness to undergo surgery[9, 10]. Systemic intravenous infusion chemotherapy is a common method for clinical treatment of cancer patients who cannot be treated surgically. Chemotherapy drugs include cisplatin, doxorubicin and its derivatives. Single-agent chemotherapy and combination chemotherapy can be used in the selection of chemotherapy regimens. The combined interventional programme can synergize with anticancer agents to improve the therapeutic effect, as patients with PHC have scattered cancer in the liver or have a short circuit of the arteriovenous vein and portal vein-hepatic vein[11]. TACE is the main treatment for PHC in the middle and late stage. Compared with radical surgery, it inflicts less trauma on the human body. However, there is no uniform standard for the selection of combined chemotherapy drugs and high-level evidence-based medical evidence. Common types include nucleosides, anthracyclines, platinum and fluorouracils, and representative drugs are gemcitabine, pirarubicin, oxaliplatin and fluorouridine, respectively[12, 13].

Fluorouracil is the first generation of antimetabolites and is a widely used anti-pyrimidine drug in clinical practice because it has a positive effect in controlling the progress of solid cancer. However, it has strong side effects on the human body, including high incidences of bloody diarrhoea and myelosuppression[14, 15]. In this study, the incidence of adverse reactions in the control group was significantly higher than that in the observation group. Although there was no appearance of high-grade gastrointestinal or blood routine abnormalities, the fluorouridine still indicated a higher toxicity. Thalidomide, derived from glutamate derivatives, was first used in the treatment of leprosy and arthritis with sedative and immunomodulatory functions. With the advancement of clinical research, thalidomide has used for antitumour effects[16]. Compared with fluorouridine, the antitumour activity of thalidomide is multi-mechanical. The more common mechanism is manifested in two aspects: one is to regulate the expression level of some cytokines or adhesion molecules in the body, and the other is to improve immunization for the whole cells of the patient to increase antitumour activity[17, 18].

In this study, the RR, DCR, and median PFS of the observation group were significantly higher than those of the control group, confirming that thalidomide combined with oxaliplatin/pirarubicin TACE has obvious clinical advantages in controlling the progression of the disease. Some 45.5% to 53.8% of PHC patients with cirrhosis and chronic hepatitis have low tolerance to chemotherapy, and thalidomide may increase antitumour activity through multiple mechanisms[19].

As a kind of pyrimidine salvage pathway enzyme, TK mainly occurs in the form of the TK1 and TK22 isoenzymes. In normal cells, TK1 is regulated by the cell cycle, and its level is abnormally increased in the body of patients with malignant tumours. The detection of cytokine levels in lung cancer patients by microarray analysis showed that CXCL13 had the highest expression level among 84 types of factors, and its increase was positively correlated with the induction of tumour differentiation (20). The results of this study showed that TK1 and CXCL13 were significantly decreased after treatment in both groups, and the levels in the observation group were significantly lower than those in the control group. Although the relevant mechanism of action of TK1 and CXCL13 in the body of PHC patients is still unclear, the results can explain to a certain extent why thalidomide combined with oxaliplatin/pirarubicin TACE can inhibit PHC progression and metastasis.

In summary, thalidomide combined with oxaliplatin/pirarubicin in the treatment of unresectable PHC is effective and safe and can reduce the levels of TK1 and CXCL13. The number of patients in this study was small, and the follow-up time was short, so further research is needed.

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